



**VIRTUAL CONFERENCE**

**The 11<sup>th</sup> Asia Pacific Paediatric  
Endocrine Society (APPEs)  
Biennial Scientific Meeting  
in conjunction with  
42<sup>nd</sup> Annual Congress of the  
Malaysian Paediatric Association  
(MPA)**

**Date: 26<sup>th</sup> – 28<sup>th</sup> November 2021**

**Theme:  
"Nurture, Educate and  
Best Practices of Care  
of Children with Endocrine  
Disorders & Diabetes"**



**eBooklet**

**Organised By:**



[www.appes2021.org](http://www.appes2021.org)

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## Message from the President of APPES



Dear Delegates,

I bid you a warm welcome to the 11<sup>th</sup> Asia Pacific Paediatric Endocrine Society (APPES) Biennial Scientific Meeting in conjunction with the 42<sup>nd</sup> Annual Congress of the Malaysian Paediatric Association (MPA).

The COVID-19 pandemic is an unprecedented global crisis, and the resulting travel restriction and social distancing requirement has severely curtailed our plans to hold this meeting which was originally scheduled for November 2020 at the Kuala Lumpur Convention Centre. The meeting was postponed to November 2021 in the hope that the pandemic will abate and we can meet in person again, but unfortunately it continued to ravage throughout the world. Under the trying circumstances, the councils of APPES and MPA decided that this joint meeting will be held as a virtual conference. Despite the ongoing pandemic we must persevere in our mission, be innovative and adapt to the circumstance in order to continue our mandate to promote and develop paediatric endocrinology in Asia Pacific in order to bring better care to the children, and to grow the influence and prominence of Asia Pacific in the global paediatric endocrinology fraternity. Our scientific meetings and fellows' schools are very important avenues to share and impart knowledge, and also to grow our paediatric endocrine community and build camaraderie. Thus it is very gratifying to see my fellow colleagues in APPES and MPA persevering to produce this virtual conference despite the challenges.

I would like to take this opportunity to congratulate and thank the scientific committee for putting together such an excellent programme. I am grateful for the partnership of MPA and on behalf of my APPES council members, I would like to express our gratitude for their friendship and collaboration.

We hope you will enjoy the experience of this virtual conference!

With best regards,

Professor LEE Yung Seng  
President, APPES

## Message from the President of MPA



Dear Friends and Colleagues,

As the president of the Malaysian Paediatric Association, it gives me great pleasure and honour to welcome you to the 42<sup>nd</sup> Annual Congress of the Malaysian Paediatric Association (MPA) held in conjunction with the 11<sup>th</sup> Asia Pacific Paediatric Endocrine Society (APPES) Biennial Scientific Meeting.

The organising committees of this congress had been observing the global Covid-19 pandemic situation and had to re-schedule this congress from the year 2020 to year 2021. Regretfully, the pandemic did not permit us to have a successful face-to face nor a hybrid congress. As such, the organising committees had reluctantly decided to re-schedule this congress for 26<sup>th</sup> – 28<sup>th</sup> November 2021, and to proceed with a full virtual congress instead of a hybrid congress that was initially planned.

The theme of the congress is “Nurture, Educate and Best Practices of Care of Children with Endocrine Disorders & Diabetes”. There are more than 40 highly respected internationally renowned speakers from the Asia Pacific region and the world to share their knowledge and best practices, and to discuss new developments and scientific advancements in Paediatric Endocrinology.

In addition, there is a general paediatric track for our non-paediatric endocrinologists and general paediatric colleagues. A sincere thank you to the scientific committee for putting together this wonderful scientific programme. Despite not being able to attend the congress in-person, I believe all of us will benefit and improve our knowledge from the various distinguished speakers, and renew or foster new friendships.

For all members of MPA, I would like to invite you to attend our MPA AGM on the 27<sup>th</sup> November 2021, Saturday at 8.45am.

On behalf of MPA, I welcome you and wish you an enjoyable and successful congress.

Thank you.

Dr HUNG Liang Choo  
President 2019-2021  
Malaysian Paediatric Association

# Message from the APPES 2021 Organising Chairman



On behalf of the organising committee, it gives me great pleasure and privilege to invite you to the 11<sup>th</sup> Asia Pacific Paediatric Endocrine Society (APPES) Biennial Scientific Meeting held in conjunction with the 42<sup>nd</sup> Annual Congress of the Malaysian Paediatric Association (MPA).

With the CoVID-19 pandemic still rampant, the organizing committee had to make a difficult decision to proceed this important meeting as a full virtual conference from 26<sup>th</sup> – 28<sup>th</sup> November 2021.

Staging APPES 2021 in Malaysia is a good opportunity for paediatric endocrinologists as well as paediatricians in general from the Asia Pacific region to come together and exchange their knowledge and expertise while sharing their experiences.

Bringing the theme of **“NURTURE, EDUCATE AND BEST PRACTICES OF CARE OF CHILDREN WITH ENDOCRINE DISORDERS & DIABETES”**, the objective of this important meeting goes hand in hand with APPES mission and vision. This theme also emphasizes our hope to improve knowledge, provide best practice and increase collaboration in the field of paediatric endocrinology among our members from Asia Pacific countries and the world.

Despite not being able to be present at site, I believe our friendships are still strong and all of you are still able to connect with friends around the globe. I hope you would have a pleasant knowledge booster during this 3-day conference.

Thank you and enjoy the scientific content of APPES & MPA Congress 2021.

Professor Dr Muhammad Yazid JALALUDIN  
Organising Chairman, APPES 2021

## Local Organising Committee

Organising Congress Chairman	Muhammad Yazid JALALUDIN
Organising Congress Vice Chairperson	Azriyanti ANUAR ZAINI
Secretary	Swee Fong TANG
Treasurer	Musa MOHD NORDIN
Scientific Chairperson	Loo Ling WU
Scientific Committee Members	Janet HONG Muhammad Yazid JALALUDIN Suhaimi HUSSAIN Thiyagar NADARAJAW
Business Development	Zulkifli ISMAIL
Publications	Noor Shafina MOHD NOR
Social Programme	Rashdan Zaki MOHAMED
Committee Members	Liang Choo HUNG Tzer Hwu TING Nalini SELVEINDRAN

## Scientific Programme Committee

Scientific Chairperson	Noriyuki NAMBA – Japan
Members	Yung Seng LEE – Singapore Muhammad Yazid JALALUDIN – Malaysia Reiko HORIKAWA – Japan Paul HOFMAN – New Zealand Ben WHEELER – New Zealand Jeerunda SANTIPRABHOB – Thailand Kenichi KASHIMADA – Japan
Appointed Positions Fellows School Convenor	Tony Huynh – Australia
Co-Opted Members	Noriyuki Namba – Japan Paul Hofman – New Zealand Jeerunda Santiprabhob – Thailand

## APPEs Fellow School Committee & Local Committee

Head	Tony HUYNH – Australia
Committee	Muhammad Yazid JALALUDIN – Malaysia Reiko HORIKAWA – Japan Sylvia ESTRADA – Philippines Maria CRAIG – Australia Fauzia MOHSIN – Bangladesh Jeerunda SANTIPRABHOB – Thailand Yan LIANG – China Jin-ho CHOI – Korea Hae Woon JUNG – Korea
Local Committee	Azriyanti ANUAR ZAINI – Malaysia Noor Shafina MOHD NOR – Malaysia

## APPES Council 2020-2022

President	Yung Seng Lee – Singapore
Immediate Past President	Muhammad Yazid JALALUDIN – Malaysia
President Elect	Maria Craig – Australia
Honorary Secretary	Junfen Fu - China
Honorary Treasurer	Reiko Horikawa – Japan
Council Members	<p>Yan Liang – China            Sylvia Estrada – Philippines            Jin-Ho Choi – South Korea            Prapai Dejkhamron - Thailand            Noriyuki Namba – Japan            Fauzia Mohsin – Bangladesh            Anju Seth – India            Mya Sander Thein - Myanmar            Muhammad Faizi hamid - Indonesia            Huynh Thi Vu Quynh – Vietnam            Azriyanti binti Anuar Zaini – Malaysia</p>
Appointed Positions Fellows School Convenor	Tony Huynh – Australia
Co-Opted Members	<p>Noriyuki Namba - Japan            Paul Hofman – New Zealand            Jeerunda Santiprabhob – Thailand</p>

## INVITED FACULTY



Akanksha Parikh  
India



Anders Juul  
Denmark



Anju Seth  
India



Ari Wassner  
United States



Asiah Kassim  
Malaysia



Atsumi Tsuji Hosokawa  
Japan



Azriyanti Anuar Zaini  
Malaysia



Ben Wheeler  
New Zealand



Cheri Deal  
Canada



Cindy Wei Li Ho  
Singapore



Clare Wall  
New Zealand



Constantine Stratakis  
United States



Craig Munns  
Australia



Daphne Gardner Tan Su Lyn  
Singapore



Elizabeth Davis  
Australia



Fauzia Mohsin  
Bangladesh



Fei Hong Luo  
China



Firdaus Mukhtar  
Malaysia



Hamid Jan Jan Mohamed  
Malaysia



Hany Ariffin  
Malaysia



Liang Choo Hung  
Malaysia



Huynh Thi Vu Quynh  
Vietnam



Jae Hyun Kim  
South Korea



Janet Yeow Hua Hong  
Malaysia



Jean Claude Carel  
France



Joanna Yuet Ling Tung  
Hong Kong



Jun Fen Fu  
China



Jeerunda Santiprabhob  
Thailand



Jin Ho Choi  
South Korea



Kenichi Kashimada  
Japan



Way Seah Lee  
Malaysia



Poi Giok Lim  
Malaysia



Louise Baur  
Australia



Yung Seng Lee  
Singapore



Margaret Zacharin  
Australia



Martin Savage  
United Kingdom



Martine Cools  
Belgium



Masanobu Kawai  
Japan



Maria Craig  
Australia



Mohamad Maghnie  
Italy



Muhammad Yazid Jalaludin  
Malaysia



Musa Mohd Nordin  
Malaysia



Mohamad Ikram Ilias  
Malaysia



Muhammad Faizi Hamid  
Indonesia



Mya Sandarthein  
Myanmar



Noor Shafina Mohd Nor  
Malaysia



Noriyuki Namba  
Japan



Ouyporn Panamonta  
Thailand



Peter Simm  
Australia



Paul Hofman  
New Zealand



Prapai Dejkhamron  
Thailand



Rachael Waring Taylor  
New Zealand



Ravi Savarirayan  
Australia



Rebecca Deans  
Australia



Rakhee Yadav Hematram Yadav  
Malaysia



Rashdan Zaki Mohamed  
Malaysia



Reiko Horikawa  
Japan



Ron Dagan  
Israel



Sonir Roberto Antonini  
Brazil



Selva Kumar Sivapunniam  
Malaysia



Sylvia Estrada  
Philippines



Suhaimi Hussain  
Malaysia



Sung Yoon Cho  
South Korea



Susana P. Padilla Campos  
Philippines



Susumu Yokoya  
Japan



Swee Fong Tang  
Malaysia



Tzer Hwu Ting  
Malaysia



Tony Huynh  
Australia



Loo Ling Wu  
Malaysia



Xiao-Ping Luo  
China



Yong Junina Fadzil  
Malaysia



Yan Liang  
China



Yong Guo Yu  
China



Zulkifli Ismail  
Malaysia



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 Biennial Scientific Meeting  
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 42<sup>nd</sup> Annual Congress of the Malaysian Paediatric Association (MPA)  
 26<sup>th</sup> - 28<sup>th</sup> November 2021 | VIRTUAL CONFERENCE

**APPEs 2021 (26<sup>th</sup>-28<sup>th</sup> November 2021)**

**Theme: NURTURE, EDUCATE AND BEST PRACTICES OF CARE FOR CHILDREN WITH ENDOCRINE DISORDERS & DIABETES**

**Day 1, Friday, 26<sup>th</sup> November 2021**

Time	Hall 1	
0830-0915	<p align="center"><b>Plenary 1: Adrenocortical Tumours</b>            Chairpersons: <a href="#">Muhammad Yazid JALALUDIN (Malaysia)</a>, <a href="#">Jin-Ho CHOI (South Korea)</a></p> <p align="center">Molecular Basis of Adrenocortical Tumours (CAT)  <a href="#">Sonir Roberto RAUBER ANTONINI (Brazil)</a></p>	
	Hall 1	Hall 2
0915-1015	<p align="center"><b>Kaichi Kida Session: Oral presentation</b></p> <p>Questioners: 1) <a href="#">Noriyuki NAMBA (Japan)</a>            2) <a href="#">Jeerunda SANTIPRABHOB (Thailand)</a>            3) <a href="#">Jin-Ho CHOI (South Korea)</a>            4) <a href="#">Reiko Horikawa (Japan)</a></p> <p>Chairpersons: 1) <a href="#">Muhammad Yazid JALALUDIN (Malaysia)</a>            2) <a href="#">Maria CRAIG (Australia)</a></p>	<p align="center"><b>MPA Young Investigator Award (YIA): Oral Presentation</b></p> <p>Judges: 1) <a href="#">HUNG Liang Choo (Malaysia)</a>            2) <a href="#">TANG Swee Fong (Malaysia)</a>            3) <a href="#">Zulkifli ISMAIL (Malaysia)</a></p> <p>Chairpersons: 1) <a href="#">Rakhee Yadav HEMATRAM YADAV (Malaysia)</a>            2) <a href="#">Selva Kumar SIVAPUNNIAM (Malaysia)</a></p>
0915-0927	KK 1 - <a href="#">Nicholas NG Beng Hui</a>	YIA 1 - <a href="#">Muhammad Muizz ABDUL MANAN</a>

0927-0939	KK 2 - Andrew SNG	YIA 2 - CHENG Hooi Peng
0939-0951	KK 3 - Anupriya GORA	YIA 3 - TING Yi Wen
0951-1003	KK 4 - Lin YANG	YIA 4 - Nur 'Aini RAMAN
1003-1015	KK 5 - Sarah MAESSEN	YIA 5 - NG VOON Swee Im
<b>Hall 1</b>		
1015-1100	<b>OPENING CEREMONY</b>	
1100-1130	Break/Poster Tour	
<b>Hall 1</b>		<b>Hall 2</b>
1130-1300	<b>Symposium 1: Thyroid</b> Chairpersons: Reiko HORIKAWA (Japan), Prapai DEJKHAMRON (Thailand)	<b>Symposium 2: Endocrinopathies In Chronic Diseases</b> Chairpersons: WU Loo Ling (Malaysia), Selva Kumar SIVAPUNNIAM (Malaysia)
1130-1200	1. Central congenital hypothyroidism <b>Ari J WASSNER (United States)</b>	1. Childhood cancer survivors (CCS) <b>Margaret ZACHARIN (Australia)</b>
1200-1230	2. Current Status of Thyroid Cancer after the Fukushima Nuclear Accident <b>Susumu YOKOYA (Japan)</b>	2. Premature development of ageing and metabolic disorders in survivors of childhood cancer <b>Hany ARIFFIN (Malaysia)</b>
1230-1300	3. Etiological Spectrum of Congenital Hypothyroidism - an Indian Perspective <b>Akanksha PARIKH (India)</b>	3. Multitransfused Thalassemia <b>Anju SETH (India)</b>
<b>Hall 2</b>		
1300-1400	<b>Satellite Symposium 2: GSK</b> Chairperson: Zulkifli ISMAIL (Malaysia)	
1300-1305	1. Opening Remarks by Chairperson	
1305-1325	2. Respiratory Infections Among Children During Current Pandemic <b>Asiah KASSIM (Malaysia)</b>	
1325-1345	3. Optimising Immunisation with Hexavalent Combinations <b>Musa Mohd NORDIN (Malaysia)</b>	
1345-1400	4. Panel QA& Closing	

	Hall 1	
1400-1445	<p align="center"><b>Plenary 2: Nutrition Diabetes</b>  Chairpersons: Yung Seng LEE (Singapore), Azriyanti ANUAR ZAINI (Malaysia)</p> <p align="center"><b>DOHAD and importance of nutrition to combat NCD (obesity and diabetes)</b>  Hamid Jan JAN MOHAMED (Malaysia)</p>	
	Hall 1	Hall 2
1445-1530	<p align="center"><b>Meet The Expert 1:</b>  Chairperson: Muhammad Yazid JALALUDIN (Malaysia)</p> <p align="center"><b>Management of Prader-Willi Syndrome</b>  Cheri DEAL (Canada)</p>	<p align="center"><b>Meet The Expert 2:</b>  Chairperson: TING Tzer Hwu (Malaysia)</p> <p align="center"><b>Practical approach to DSD</b>  LIM Poi Giok (Malaysia)</p>
1530-1615	Tea Break/Poster Tour	
Time	Hall 1	Hall 2
1615-1745	<p align="center"><b>Symposium 3: Bone</b>  Chairpersons: Anju SETH (India), Noriyuki NAMBA (Japan)</p>	<p align="center"><b>Symposium 4: Obesity &amp; Diabetes</b>  Chairpersons: Azriyanti ANUAR ZAINI (Malaysia), Rashdan Zaki MOHAMED (Malaysia)</p>
1615-1645	1. Emerging new therapies for skeletal dysplasia: changing the rules of the game Ravi SAVARIRAYAN (Australia)	1. Emerging therapies for obesity and Type 2 DM Muhammad Yazid JALALUDIN (Malaysia)
1645-1715	2. Clock genes and bone Masanobu KAWAI (Japan)	2. Child & adolescent obesity and insulin resistance in Asia Pacific: health service implications Louise BAUR (Australia)
1715-1745	3. Skeletal dysplasias, lysosomal storage diseases (Dysostosis multiplex) Sung Yoon CHO (South Korea)	3. Eat, sleep, move – the roles in childhood obesity prevention Rachael TAYLOR (New Zealand)

**Day 2, Saturday, 27<sup>th</sup> November 2021**

Time	Hall 1	
0800-0845	<p align="center"><b>Plenary 3: Pituitary Tumours, Growth</b>            Chairpersons: <a href="#">Paul HOFMAN (New Zealand)</a>, <a href="#">Yan LIANG (China)</a></p> <p align="center">X-linked acrogigantism and other causes of paediatric gigantism  <b><a href="#">Constantine STRATAKIS (United States)</a></b></p>	
	<b>Hall 1</b>	<b>Hall 2</b>
0845-0945	<b>APPEP AGM</b>	<b>MPA AGM</b>
0945-1100	Break/Poster Tour	
	<b>Hall 1</b>	<b>Hall 2</b>
1100-1230	<p align="center"><b>Symposium 5: Growth</b>            Chairpersons: <a href="#">Sylvia ESTRADA (Philippines)</a>, <a href="#">Jun Fen FU (China)</a></p>	<p align="center"><b>Symposium 6: Nutrition and Growth</b>            Chairpersons: <a href="#">Zulkifli ISMAIL (Malaysia)</a>, <a href="#">Mohamad Ikram ILIAS (Malaysia)</a></p>
1100-1130	1. The study of Phenotype Standardization and Genotype-phenotype Associations in short stature <b><a href="#">YU Yong Guo (China)</a></b>	1. The role of the gut microbiota in health and development during early childhood <b><a href="#">Clare WALL (New Zealand)</a></b>
1130-1200	2. Growth in Childhood Cancer Survivors (CCS) <b><a href="#">Cindy HO Wei Li (Singapore)</a></b>	2. Paediatric Nutrition & Catch-Up Growth: Role of Clinicians in Educating Parents <b><a href="#">LEE Way Seah (Malaysia)</a></b>
1200-1230	3. Impact of GH treatment in terms of efficacy and safety: Lessons from registries <b><a href="#">Mohamad MAGHNIE (Italy)</a></b>	3. Behavior Management for Childhood Malnutrition <b><a href="#">Firdaus MUKHTAR (Malaysia)</a></b>
1230-1300	Break/Poster Tour	
	<b>Hall 1</b>	<b>Hall 2</b>
1300-1400	<p align="center"><b>Satellite Symposium 3: KYOWA KIRIN</b>  <b>Phosphorus - The Forgotten Mineral for Strong Bone</b></p> <p>Chairperson: <a href="#">Muhammad Yazid JALALUDIN (Malaysia)</a></p>	<p align="center"><b>Satellite Symposium 4: PFIZER</b></p> <p>Chairperson: <a href="#">Yong Junina FADZIL (Malaysia)</a></p>
1300-1305	1. Introduction <b><a href="#">Muhammad Yazid JALALUDIN (Malaysia)</a></b>	1300-1400 Public health impact of pneumococcal conjugate vaccine: Assessment of pneumococcal disease burden and serotype distribution <b><a href="#">Ron DAGAN (Israel)</a></b>
1305-1320	2. Approach to the diagnosis of Hypophosphatemic rickets <b><a href="#">Muhammad Yazid JALALUDIN (Malaysia)</a></b>	
1320-1350	3. New Era of Management of X-linked hypophosphatemia <b><a href="#">Craig MUNNS (Australia)</a></b>	
1350-1400	Q & A	

	Hall 1	Hall 2
1400-1500	<p align="center"><b>Oral Presentation Session 1 Obesity and Metabolic Syndrome</b></p> <p>Chairperson: Kenichi KASHIMADA (Japan)</p>	<p align="center"><b>Oral Presentation Session 2 Growth</b></p> <p>Chairperson: Jeerunda SANTIPRABHOB (Thailand)</p>
1400-1412	FP1.1 - Ahreum KWON	FP2.1 - Liulu XIE
1412-1424	FP1.2 - YAN Ya-Qin	FP2.2 - Myeongseob Lee
1424-1436	FP1.3 - Hye Jin LEE	FP2.3 - Masanobu FUJIMOTO
1436-1448	FP1.4 - Hae Woon JUNG	FP2.4 - Min Jae KANG
1448-1500	FP1.5 - Xin YUAN	FP2.5 - Han Saem CHOI
Time	Hall 1	Hall 2
1500-1630	<p align="center"><b>Symposium 7: Adrenal/DSD</b></p> <p>Chairpersons: Tony HUYNH (Australia), Huynh Thi Vu QUYNH (Vietnam)</p>	<p align="center"><b>Symposium 8: Puberty</b></p> <p>Chairpersons: TING Tzer Hwu (Malaysia), Suhaimi HUSSAIN (Malaysia)</p>
1500-1530	1. Urogenital surgery <b>Rebecca DEANS (Australia)</b>	1. Central Precocious puberty: referrals and early identification <b>Azriyanti ANUAR ZAINI (Malaysia)</b>
1530-1600	2. The transition in DSD/Adrenal disorders <b>Martine COOLS (Belgium)</b>	2. Trends in timing of normal and precocious puberty <b>Anders JUUL (Denmark)</b>
1600-1630	3. Adrenal disorders and DSD <b>Atsumi TSUJI-HOSOKAWA (Japan)</b>	3. Deciphering the code in CPP Management <b>Jean-Claude CAREL (France)</b>
1630-1715	Tea break	
Time	Hall 1	Hall 2
1715-1800	<p align="center"><b>Meet The Expert 3:</b></p> <p>Chairperson: <b>Azriyanti ANUAR ZAINI (Malaysia)</b></p> <p align="center"><b>Endocrine emergencies</b> <b>Peter SIMM (Australia)</b></p>	<p align="center"><b>Meet The Expert 4:</b></p> <p>Chairperson: <b>Nalini SELVEINDRAN (Malaysia)</b></p> <p align="center"><b>Practical approach to short stature</b> <b>Janet HONG Yeow Hua (Malaysia)</b></p>

**Day 3, Sunday, 28<sup>th</sup> November 2021**

Time	Hall 1	Hall 2
0800-0845	<p><b>Meet The Expert 5:</b> Chairperson: <a href="#">Noor Shafina MOHD NOR (Malaysia)</a></p> <p><b>Pubertal induction regimes – current recommendations</b> <a href="#">Joanna TUNG Yuet Ling (Hong Kong)</a></p>	<p><b>Meet The Expert 6:</b> Chairperson: <a href="#">Janet HONG Yeow Hua (Malaysia)</a></p> <p><b>Interpretation of unusual thyroid function tests</b> <a href="#">Suhaimi HUSSAIN (Malaysia)</a></p>
Time	<b>Hall 1</b>	
0845-0930	<p><b>Plenary 4: Diabetes</b> Chairpersons: <a href="#">Maria CRAIG (Australia)</a>, <a href="#">Fauzia MOHSIN (Bangladesh)</a></p> <p><b>New technology in diabetes management</b> <a href="#">Elizabeth DAVIS (Australia)</a>.</p>	
0930-1030	Break/Poster Tour	
Time	Hall 1	Hall 2
1030-1130	<p><b>Oral Presentation Session 3</b> <b>Puberty</b></p> <p>Chairperson: <a href="#">Mya Sander THEIN (Myanmar)</a></p>	<p><b>Oral Presentation Session 4</b> <b>Thyroid</b></p> <p>Chairperson: <a href="#">Noriyuki NAMBA (Japan)</a></p>
1030-1042	FP3.1 - <a href="#">Yun Jeong LEE</a>	FP4.1 - <a href="#">Chunhua ZENG</a>
1042-1054	FP3.2 - <a href="#">Kristy TIAN</a>	FP4.2 - <a href="#">Divya MATHEWS</a>
1054-1106	FP3.3 - <a href="#">Dilhara Senani GAMAGE</a>	FP4.3 - <a href="#">Min Jeong JANG</a>
1106-1118	FP3.4 - <a href="#">Lan HUYNH</a>	FP4.4 - <a href="#">Khishigjargal BATJARGAL</a>
1118-1130	FP3.5 - <a href="#">Hyo-Kyoung NAM</a>	FP4.5 - <a href="#">Yun Jeong LEE</a>

Time	Hall 1	
1130-1300	<b>Symposium 9: Diabetes</b> Chairpersons: Ben Wheeler (New Zealand), Muhammad Faizi HAMID (Indonesia)	
1130-1200	1. Exercise in Diabetes – new insights <b>Elizabeth DAVIS (Australia)</b>	
1200-1230	2. Monogenic Diabetes: Finding the needle in a haystack <b>Daphne Gardner TAN Su Lyn (Singapore)</b>	
1230-1300	3. Diabetes management in a poor-resource country <b>Fauzia MOHSIN (Bangladesh)</b>	
Time	Hall 1	Hall 2
1300-1400	<b>Satellite Symposium 5: IPSEN</b> <b>Central Precocious Puberty (CPP): Decoding the patient journey to optimize treatment outcomes</b>  Chairperson: Muhammad Yazid JALALUDIN (Malaysia)	<b>Satellite Symposium 6: GENESCIENCE</b> <b>Growth Hormone Treatment in Non-GHD Patients: Result from clinical studies</b>  Chairperson: Xiao-Ping LUO (China)
1300-1305	1. Welcome remarks <b>Muhammad Yazid JALALUDIN (Malaysia)</b>	<b>1300-1320</b> 1. Growth Hormone Treatment in Idiopathic Short Stature <b>Jun-Fen FU (China)</b>
1305-1320	2. CPP: Etiologies and Diagnostic Aspects <b>Anders JUUL (Denmark)</b>	<b>1320-1340</b> 2. Long Acting Growth Hormone Treatment in Idiopathic Short Stature <b>Yan LIANG (China)</b>
1320-1335	3. Revisiting the Treatment Management of CPP <b>Martin SAVAGE (United Kingdom)</b>	<b>1340-1400</b> 3. Growth Hormone Treatment in Prader-Willi Syndrome <b>Fei-Hong LUO (China)</b>
1335-1350	4. Experience sharing: Optimizing CPP patient care with long-acting GnRHa <b>Jae-Hyun KIM (South Korea)</b>	
1350-1355	5. Panel Q & A	
1355-1400	6. Closing remarks <b>Muhammad Yazid JALALUDIN (Malaysia)</b>	
Time	Hall 2	
1400-1530	<b>Symposium 10: Thyroid</b> Chairpersons: Janet HONG Yeow Hua (Malaysia), Noor Shafina MOHD NOR (Malaysia)	
1400-1430	1. Grave disease <b>Ouyporn PANAMONTA (Thailand)</b>	
1430-1500	2. Congenital hypothyroid Screening – Can we do better? <b>WU Loo Ling (Malaysia)</b>	
1500-1530	3. Newborns of mothers with thyroid disorders – Outcome and management? <b>Susana CAMPOS (Philippines)</b>	
1530-1600	Closing Ceremony	



# Speakers' Abstract

## P1 - Molecular Basis of Adrenocortical Tumours (CAT)

Sonir ANTONINI  
The University of Sao Paulo, Brazil

### "Molecular Basis of Pediatric Adrenocortical Tumours (pACT)"

Although pediatric adrenocortical tumors (pACT) are rare (0.2-0.3 individuals younger than 14 years of age per million per year), pediatric endocrinologists frequently face the possibility of a pACT in patients presenting with precocious pubarche, with or without signs of hypercortisolism. Moreover, when investigating a patient with excessive weight gain and growth stunt, the diagnosis of a pACT also is a possibility.

pACT present distinct clinical and histopathological features from the disease in adults. Pediatric patients usually present with functional tumors and signs of excessive hormone secretion, mainly virilization. Most pACT are classified as adrenocortical carcinomas (ACC) based on histopathological findings. The only curative treatment for patients with localized disease is surgical resection. Children with completely resected tumors present a 5-year survival of around 80–90%, while those with residual or metastatic disease have a 5-year survival closer to 0–15%.

pACT display complex genomic background and lack robust prognostic and predictive biomarkers. Mutations in the *TP53* gene are frequent in pACT. The germline P53 p.R337H variant is prevalent in Southern Brazil and accounts for the high local incidence of the disease. pACT harboring this mutation and those harboring other *TP53* germline mutations display a similar genomic profile in terms of chromosomal gains and losses. Abnormal Wnt/B-catenin pathway activation, with or without beta-catenin mutations are also frequent in pACT and result in unfavorable outcomes for these patients. pACT have other molecular hallmarks, like alterations in chromosome 11p15, IGF2 overexpression, mutations in the *ATRX* gene, and errors in telomere length maintenance. However, isolated, these molecular marks do not have prognostic relevance, but once accumulated, represent a complex interplay in patients with unfavorable outcomes.

## **S1.1 - Central congenital hypothyroidism**

Ari J. WASSNER

Boston Children's Hospital, USA

Central congenital hypothyroidism (CCH) is caused by inborn disorders that impair the secretion or function of thyrotropin, leading to insufficient thyroid hormone production. Although it was thought in past decades to be very rare and generally mild, CCH has been revealed by recent studies to be both more common (up to 1 in 13,000 infants) and more severe than previously appreciated. Etiologies of CCH can be categorized broadly as defects of hypothalamic or pituitary development—which are usually associated with additional pituitary hormone deficits—or as isolated CCH. In recent years, the identification of new causative genes for isolated CCH has broadened our understanding of this disorder and has provided insights into the regulation of the hypothalamic-pituitary thyroid axis. Given the importance of thyroid hormone for normal neurodevelopment, prompt diagnosis and adequate treatment of CCH are vital for optimal outcome. However, diagnosis may be complicated by the design of newborn screening programs and/or their suboptimal sensitivity for detecting CCH. Developmental outcomes generally are favorable for children with isolated CCH but are less certain for children with combined pituitary hormone deficiency.

## **S1.2 - Current Status of Thyroid Cancer among Young Residents after the Fukushima Accident**

YOKOYA Susumu  
Fukushima Medical University, Japan

After the accident of Fukushima Daiichi Nuclear Power Plant caused by the Great East Japan Earthquake and the tsunami on March 11, 2011, the Thyroid Ultrasound Examination (TUE) program as a part of the Fukushima Health Management Survey was initiated among subjects aged  $\leq 18$  years at the time of the accident in order to support residents of Fukushima Prefecture and to analyze the health effects of the released radionuclides.

The first-round survey of the TUE program was undertaken between 2011 and 2013 to obtain baseline data, the second-round during 2014-15 and succeeding rounds every two years thereafter. The TUE program consisted of ultrasonographic examinations in both the primary and the secondary confirmatory examinations and, if indicated, fine needle aspiration cytology. In the first-round survey the rates of thyroid cancer or its suspicion were reported to be much higher than those documented in the cancer registries of Japan. As of June 30, 2021 a total of 266 individuals was found to have thyroid cancer or suspected thyroid cancer cytologically and at least 222 among them underwent surgical treatment.

Regarding the effects of radiation most investigators have found no statistically significant increases of thyroid cancer with increased exposure level. This view has also been supported by smaller amount of released radionuclides and lower thyroid exposure doses than at the Chernobyl accident, unincreased occurrence under the age of 5 years at the time of the accident and different histological and genetic findings from the Chernobyl accident. Concerning the risk of overdiagnosis, i.e. detection of thyroid cancer that would not have become clinically significant throughout life, the criteria for the TUE program were developed for its effective countermeasures.

This presentation is expected to contribute correct and exact understanding of the current situation of Fukushima.

### **S1.3 - Etiological Spectrum of Congenital Hypothyroidism - an Indian Perspective**

Akanksha PARIKH

Kokilaben Dhirubhai Ambani Hospital, India

In comparison to the West, a much higher incidence of congenital hypothyroidism (CH), as high as one in every 1130 live births being affected has been observed in India as per the national survey conducted by the Indian Council of Medical Research in 2018. In addition, dysmorphogenesis was reported as the most frequent etiology of primary CH. This high incidence has motivated some states of India to initiate universal newborn thyroid screening (NBTS), with more states to follow through soon. A large multicentred retrospective study in two southern states of India was undertaken to analyse 805 individuals who were attending the Paediatric Endocrinology clinics. The study also sought to analyse the real world use of NBTS as a tool for diagnosis. The median current age of the cohort was noted to be 10.3 years and 55.2% were females. A history of consanguinity was obtained in 18.5% of the patients. Although only 22% of the patients were diagnosed by a NBTS in this cohort, an improving trend of its use with time was evident. A majority of the NBTS was performed in babies born in private hospitals in tier 1 cities. Primary hypothyroidism accounted for 776 (96.3%), of whom 41.9% had thyroid dysgenesis, 26.5% had dysmorphogenesis and 28% remained unevaluated. Ectopic thyroid was the most common structural anomaly with suprahyoid being the most common location of the thyroid gland. The overall median age of diagnosis was 0.3 years and nearly one-third of children were diagnosed within the first month of life while the median age of diagnosis for children who had not undergone NBTS was 0.5 years. Neonatal jaundice (19%), developmental delay (27.7%) and short stature (26%) were the most common presenting symptoms which led to the diagnosis in this group. A thyroid nuclear scan was performed in 68% of the patients. In the dysmorphogenesis subgroup, the mean age of diagnosis was 3.3 years whereas in comparison, children with dysgenesis were diagnosed significantly earlier at 2.3 years ( $P = 0.006$ ) and had a significantly more number of girls affected ( $P = 0.017$ ). However, the two groups did not differ in prevalence of consanguinity, preterm birth, birth weight, as well as weight and height at presentation.

Traditionally, Western literature report structural anomalies of the thyroid gland to account for 80 – 85% of all cases of CH, particularly in the Caucasian population. Our study too revealed thyroid dysgenesis to be the most common etiology of primary hypothyroidism albeit to a much lesser extent. A higher degree of consanguinity may explain the relatively increased prevalence of dysmorphogenesis. The use of NBTS as a diagnostic tool is as yet suboptimal, particularly in the public setup and calls for a national policy for addressing the issue.

## **S2.1 - Childhood cancer survivors (CCS)**

Margaret ZACHARIN

Royal Children's Hospital, Melbourne, Australia

### Long term effects of childhood cancer

Overall survival after childhood cancer has increased to between 80-90% for some conditions but at a cost of increasing cumulative incidence of endocrine abnormalities across the lifespan, with high risks for thyroid cancer, hypothyroidism, impaired fertility, metabolic syndrome and type 2 diabetes mellitus. Endocrine late effects of irradiation and chemotherapy can be direct, resulting in endocrine gland hypofunction or indirect via metaplasia and malignant transformation of exposed tissues and via altered bone growth. Adequate surveillance and planning strategies are essential, to reduce morbidity and to improve quality of life. Recognition of major global effects on learning, short term memory impairment and memory processing is necessary, to understand complex management needs. One in eight survivors after CSXRT will have a symptomatic stroke by age 45 secondary to radiation induced cerebral arteritis.

Hypothalamic pituitary axis deficits occur after radiation exposure in a dose related fashion with evolution of losses up to 20+ years. Replacement of losses is essential to optimize growth and to reduce morbidity. Acquisition of optimal peak bone mass and maintenance of bone quality in adulthood is compromised by alterations in pubertal and growth cascades.

Altered timing and tempo of puberty after CXRT or total body irradiation, evolving to hypogonadism, requires in depth understanding, to provide treatment appropriate to current status. Specific losses of gonadal function vary, depending on sex, age, type and amount of gonadotoxin. For boys, loss of germinal epithelium occurs with low dose radiation exposure, with Leydig cell damage at higher doses. Germ cell loss with chemotherapy, particularly alkylating agents, requires semen collection or attempted germ cell salvage before puberty as an experimental option for male fertility preservation. For girls, reduction in the oocyte pool occurs at any age, following both radiation and chemotherapy, late recovery being possible even after alkylators. Ovum salvage is should be offered prior to gonadotoxin exposure.

Thyroid nodularity and differentiated carcinoma is common after scatter or direct radiation. Risk continues for 40 years, requiring mandatory ultrasound surveillance every second year.

Future planning should involve risk-based screening and surveillance, targeted education for risk reduction and healthcare delivered by clinicians familiar with issues and risks.

## **S2.2 - Premature development of ageing and metabolic disorders in survivors of childhood cancer**

Hany ARIFFIN  
University of Malaya, Malaysia

Long-term survivors of childhood cancer (CCS) have a disproportionate increase in chronic age-related health problems compared to the general population. Survivorship studies have shown that CCS are in an increased pro-inflammatory state with shortened leucocyte telomere length and perturbations of the microbiome. CCS also develop poor muscle strength and increased fatigue, i.e. components of frailty, two to three decades earlier than their peers. Causes of the underlying biologic mechanisms for premature ageing in CCS is an area of active research to identify frontiers where either preventive or therapeutic measures can be instituted.

### **S2.3 - Multitransfused Thalassemia**

Anju SETH  
Lady Hardinge Medical College, India

#### Endocrinopathies in multi-transfused thalassemia

Beginning second decade of life, multi-transfused patients with thalassemia are vulnerable to develop multiple endocrinopathies. The onset and severity of endocrine involvement is primarily dependent on the iron overload. While all endocrine glands are susceptible, the commonest endocrine issues seen in these patients include short stature and pubertal delay/failure, followed by disturbances of glucose metabolism. Thus, management of a child with thalassemia requires regular growth monitoring, assessment for pubertal development and annual endocrine screening after 9 years of age. Early identification and prompt management of the endocrine complications reduces morbidity and improves quality of life in patients with thalassemia. The annual endocrine screening includes assessment of free T4 and TSH, fasting glucose, oral glucose tolerance test (in case of impaired fasting glucose), serum calcium, phosphate and ALP, vitamin D and PTH (in suspected hypoparathyroidism), and bone age. The LH, FSH, and sex steroids are evaluated in the adolescents with delayed/arrested puberty. A baseline DXA scan followed by annual/once in 2 years screening of bone mineral density is also recommended. Other endocrine testing is undertaken on clinical suspicion.

Evidence indicates institution of intensive chelation may retard progression/ reverse early endocrine involvement. However, prevention continues to be the best approach. Thus, preventing anemia through a regular transfusion schedule, optimum chelation to keep serum ferritin level under control, maintaining an adequate nutritional status and regular physical exercise would help prevent/delay endocrine involvement.

## **SS2.2 - Respiratory Infections Among Children During Current Pandemic**

Asiah KASSIM

Hospital Tunku Azizah Kuala Lumpur, Malaysia

The pandemic has changed the way we live, and this has impacted the pattern of respiratory illnesses in children in Malaysia. Pneumonia however still remains the number one cause of hospital admission and prevention of pneumonia is paramount through vaccination.

### **SS2.3 - Optimising Immunisation with Hexavalent Combinations**

Musa Mohd NORDIN  
KPJ Damansara Specialist Hospital, Malaysia

The hexavalent combination vaccine was introduced into the Malaysian National Immunisation Programme in 2020. This presentation highlights the burden of these diseases impacting young children and evidence of the hexavalent vaccine over the years.

## **P2 - DOHAD and importance of nutrition to combat NCD (obesity and diabetes)**

Hamid Jan B JAN MOHAMED  
Universiti Sains Malaysia, Malaysia

The developmental origins of health disease (DOHAD) hypothesis proposes that altered child environment or mismatch between circumstances during conception and in later life leads to metabolic dysregulation and the development of obesity and diabetes. Maternal health status and poor nutrition are widely recognised as implications in the onset of premature birth, underweight and stunting in children. The 'fetal programming' effect is also well established in animal studies and several cohort studies. This programming phenomenon is thought to affect the biochemical and physiological process during growth and development. These problems were then exaggerated with growth issues such as catch-up growth in early childhood. Many study has shown that poor nutritional status during childhood may lead to increased risk of non-communicable diseases development in later life. Stunted child may grow up as poorly as a stunted adult who may have increased risk of obesity based on the Body Mass Index formula. Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes. There is an established evidence that in obese individuals, adipose tissue releases increased amount of chemicals such as non-esterified fatty acids, hormones and pro-inflammatory cytokines that are involved in the development of insulin. It is clear now that NCD prevention strategies should start as early as possible. Identifying and supporting women at risk of poor pregnancy outcome is very important. Intervention on women before and during first 1000 days may help prevent children with poor growth and development and ensuring a healthy generation free from NCD's.

## MTE1 - Management of Prader-Willi Syndrome

Cheri DEAL  
University of Montreal, Canada

Prader-Willi Syndrome is a rare (birth incidence 1 in 10,000-30,000), complex and clinically heterogeneous genetic condition with mean age of death at 30 y. The challenges to management are multiple because PWS affects cognition, which raises multiple ethical and social concerns. The clinical goals of the endocrinologist may be at odds with patient/caregiver needs: hyperphagia, management of behavioral and psychiatric issues and independent living being the top unmet needs voiced by families, while physicians have been focused on growth, body composition and metabolic outcomes. Despite all these difficulties, the life of our patients with PWS has changed markedly over the last 20 years, and this is due to 1) a better genetic, molecular, and clinical understanding of PWS, 2) our caregiver-healthcare team partnerships and 3) better management guidelines.

Care requires multiple specialists because of the large number of co-morbidities that may vary and/or evolve throughout the lifespan. These include hypotonia and developmental delay, early feeding issues, viscous saliva with tooth decay, speech articulation defects, estropia/myopia, skin picking, scoliosis, sleep disturbances and sleep apnea, metabolic syndrome and T2D, epilepsy, autism-like symptoms, anxiousness and distress, temper outbursts, obsessive-compulsive traits leading to repetitive and ritualistic behavior and other psychiatric symptoms including psychotic episodes. Coordinating care and keeping healthcare teams harmonized in their approach, as well as up to date with the clinical care guidelines, is a significant challenge. All these factors place a tremendous burden on caregivers.

Today I will focus on the current recommendations for diagnosis and suggested anticipatory guidance for caregivers. We will address the early nutritional interventions and prevention measures that need to be in place as the infant moves from the hypotonic and failure to thrive nutritional phase (birth to 9 months, phase 1a) through to the hyperphagic phase with some satiety (4.5 to 8 y, phase 2b) to an insatiable appetite (8 y to adulthood, phase 3). We will briefly discuss some of the therapies to manage hyperphagia that have been tested in small case series or larger clinical trials (Liraglutide/semaglutide -GLP-1 agonists; Livoletide -unacylated ghrelin analog; GLWL-01 -inhibitor of ghrelin acylation; topiramate -Na/Ca channel blocker; DCCR/diazoxide choline controlled-release - KATP channel agonist; Carbetocin -oxytocin analog). However, to date there are no approved treatments for hyperphagia judged to be efficacious and safe. Most of the trials have had limited numbers of pediatric subjects and even larger trials must contend with many within subject confounders and protocol limitations (weight and BMI SDS inappropriate primary endpoints, lack of biomarkers, questionnaires relying on caregiver observations - to name a few), making statistical significance difficult to achieve. Bariatric surgery is, in general, felt to be contraindicated.

Guidelines for replacement therapy for the multiple endocrinopathies of hypothalamic and/or end organ origin will be reviewed, including GH deficiency, LH/FSH/sex steroid deficiencies and occasionally TSH and ACTH with consideration of clinical goals and side effect profiles. The recent demonstration of prohormone convertase 1 deficiency in pluripotent stem cell neurons for subjects with PWS is of interest, since not only are PC1 gene (*PCSK1*) mutations associated with an obesity phenotype, but lack of this important hormone can potentially explain the pleiotropic and widespread hormone deficiencies seen in PWS because of inadequate prohormone processing. Future management will likely require multiple therapies not only because of this, but also because of the complex and interconnected neural and hormonal networks regulating hunger, satiety, energy expenditure and behavior.

## **MTE2 - Practical approach to DSD**

LIM Poi Giok  
Hospital Tunku Azizah, Malaysia

Disorder/Differences of Sex Development classification system was adopted as an umbrella expression to describe 'congenital conditions in which the development of chromosomal, gonadal or anatomical sex is atypical'. They are a complex condition with regard to diagnosis, management and sequelae thereby posing a significant challenge to the healthcare providers. It is mainly caused by a disruption in a complex network of gene regulation responsible for the development of testes, ovaries and genital tracts in the embryo.

Patients with DSD can present at any age to Paediatricians but often as a 'medical emergency' in a neonatal unit with ambiguous genitalia. The evaluation and management with neonates with ambiguous genitalia need to be dealt with great sensitivity, accuracy, and efficiency. The approach to these neonates/DSD patients need a coordinated care of a multidisciplinary team comprising of paediatric surgery/urology, neonatology, endocrinology, genetics, gynaecologist and psychiatry/psychologist. This is especially difficult during covid pandemic when there are barriers to access to healthcare and elective surgeries. Early identification of the molecular cause of a DSD can help clinicians in their management and treatment of the patient and counselling of the family but unfortunately these diagnostic tests remain out of reach to many.

This lecture summarises the normal development of the urogenital system, the genetics involved and provides a framework for a practical approach to reach a clinical diagnosis in patients with DSD.

### **S3.1 - Emerging new therapies for skeletal dysplasia: changing the rules of the game**

Ravi SAVARIRAYAN

University of Melbourne, Australia

Skeletal dysplasia are a group of conditions caused by abnormalities in the development, growth or maintenance of the human skeleton. Many of these conditions have had their molecular basis revealed over the past 20 years and, recently, several potential precision therapies have emerged for these conditions.

This talk will overview new emerging therapies for achondroplasia and Schmid metaphyseal dysplasia as examples of this new paradigm, and discuss the clinical trials that are evaluating the safety and effectiveness of these new treatments.

### **S3.2 - Clock genes and bone**

Masanobu KAWAI

Osaka Women's and Children's Hospital, Japan

Circadian clock system is an evolutionarily conserved system, by which organisms adapt their metabolic activities to environmental inputs including nutrient availability. The master pacemaker of the clock system is located in the suprachiasmatic nucleus (SCN) in the hypothalamus. The neurons in the SCN are entrained by the signals from the light through the retinal-hypothalamic tract and the light-dark cycle of the environment creates the rhythmic patterning of behavioral and physiological rhythmicity. In addition to the central pacemaker, peripheral tissues also possess their own circadian network and synchronize with the central clock system through hormonal and neuronal signals. Organisms utilize this system to maximize the efficiency of time-of-day-dependent utilization of ingested nutrients by optimizing the metabolic processes in peripheral tissues; therefore, the disruption of this system has been pathogenically linked to the disintegration of metabolic homeostasis including skeletal metabolism. These findings point to the important role of circadian clock system as a nodal point to link nutrient availability and metabolism. Calcium is a critical nutrient involved in skeletal metabolism, and circulating calcium levels are known to have daily rhythms in human, indicating that calcium homeostasis is under the regulation of circadian clock system; however, this has not been well studied so far. Based on this background, the speaker has been investigating the role for circadian clock system in calcium homeostasis using a mouse model in which intestinal circadian clock system is disrupted, and found that intestinal clock network regulates calcium absorption in a time dependent manner, which results in the disintegration of skeletal homeostasis. In this talk, the speaker would like to present current findings how calcium homeostasis is regulated by circadian clock system and its influence on skeletal metabolism.

### **S3.3 - Skeletal dysplasias, lysosomal storage diseases (Dysostosis multiplex)**

Sung Yoon CHO  
Samsung Medical Center, Korea

Inborn errors of metabolism encompass a wide spectrum of disorders, frequently affecting bone. Conditions affecting skeletal growth and development are mainly the lysosomal storage disorders, in particular the mucopolysaccharidoses (MPS) and mucopolipidosis (ML). In these disorders skeletal abnormalities are often the presenting symptom and early recognition and intervention improves outcome.

The typical symptoms of MPS include organomegaly, dysostosis multiplex, mental retardation and developmental delay. Definitive diagnosis is usually possible through enzymatic assays of the defective enzyme in cultured fibroblasts or leukocytes. MPS patients frequently exhibit failures of endochondral ossification during postnatal growth leading to skeletal deformity and short stature. With reference to the skeletal system, most important radiological findings include multiplex dysostosis, which is represented by several bone malformations found in the skull, hands, legs, arms and spine. The pathophysiology of skeletal disease involves direct substrate storage, inflammation and other complex alterations of cartilage and bone metabolism. Current treatments of MPS are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation. ERT is available for MPS I, II, IVA, VI and VII. ERT is effective in reducing urinary glycosaminoglycans and liver and spleen volume, while heart and joints outcomes are variable in different studies. Effectiveness on cardiac valves, trachea, hearing and eyes is definitely poor, probably due to limited penetration in the specific tissues. ERT does not cross the blood–brain barrier, with the consequence that the central nervous system is not cured by intravenously injected ERT. Effects of these interventions on skeletal disease manifestations are less well established and outcomes are limited. Recombinant human growth hormone appears to have effectively reverted the growth deceleration in a few MPS patients diagnosed with growth hormone deficiency.

Newborns with ML II can present with radiographic and biochemical signs of hyperparathyroidism. Awareness of this phenomenon may help in establishing a proper diagnosis and therapy. As the ML disease progresses, the variety in bone pain increases, promoting the management of the pain by surgical procedures. ML patients suffer from severe osteopenia, the form hyper-resorption of the bone. Bisphosphonate counteracts this by inhibiting osteoclasts and ultimately preventing bone resorption. ML patients with a significant skeletal disease and a decrease in bone mineral density can be considered to be managed with this form of therapy.

It is now clear that adjunctive treatments that target skeletal disease are needed and should be part of future research.

#### **S4.1 - Emerging therapies for obesity and Type 2 DM**

Muhammad Yazid JALALUDIN  
University Malaya, Malaysia

Type 2 diabetes mellitus (T2DM), once considered an illness of older adults is increasingly affecting more children. Sedentary lifestyles, unhealthy eating, obesity and insulin resistance contribute to an explosive increase in the incidence. Children with T2DM have the risk of developing complications in early adulthood, which would place a significant burden on the family and society.

Type 2 DM in children most often occurs during the second decade of life, with a mean age of diagnosis of ~13.5 years which coincides with the peak physiologic pubertal insulin resistance. It affects mainly obese children of all races but at a much greater prevalence in those of non-white European descent such as African, native North American, Hispanic, Asian, South Asian (Indian Peninsula) and Native Pacific Islanders.

Treatment options in paediatric obesity and T2DM is limited, with lifestyle and behavior modifications as the mainstay of management. For decades, the only FDA approved drugs for T2DM are metformin and insulin. Recently, FDA has approved the use of liraglutide for T2DM children aged 10-17 years (July 2019) and obese adolescents aged 12-17 years (December 2020). Few other drugs for use in paediatric T2DM population are currently under research, although these drugs have been proven to be effective and safe in adults.

## **S4.2 - Child & adolescent obesity and insulin resistance in Asia Pacific: health service implications**

Louise A BAUR

University of Sydney and Children's Hospitals Network, Australia

Child and adolescent obesity is a major health issue within the Asia Pacific region. By 2030 there will be 254 million children aged 5-19 years living with obesity (1). Of the "top 42" countries in terms of absolute numbers of affected children, 35 are low and middle income countries and 10 are in Asia. In terms of childhood obesity prevalence, then the "top ten" countries (>30%) are Pacific Island nations. The high prevalence of type 2 diabetes in adults in many Asian and Pacific countries is strongly linked to the rising prevalence of obesity. This is very likely the case for adolescents as well.

Given the high prevalence of paediatric obesity, then multi-point and multi-sectoral prevention strategies are needed. However, effective treatment services are also required.

There is strong evidence that treatment of paediatric obesity leads to some improvements in BMI as well as obesity-related complications. However, resourcing constraints prevent such interventions from being accessible and deliverable, at scale, in most health systems. A 2019/2019 survey of health professionals and other interest groups in 68 countries identified challenges for health systems in providing obesity treatment for both adults and children (2): a) while many countries have professional guidelines for obesity treatment, there is a lack of adequate services, especially in lower income countries, and in rural areas of most countries; b) there are very few clinical care pathways from primary care to secondary services; c) secondary level care services are absent or limited in some regions; d) there is a lack of training in obesity management for health care professionals; e) patients experience high costs; f) waiting lists for bariatric surgery are very long; and g) weight-based stigma is very common within health care services. In addition, there have been concerns that self-initiated dieting may inadvertently trigger an eating disorder, although the evidence for professionally run weight management services is reassuring (3).

Following are some personal recommendations for health service delivery within such an environment: a) provide various types of short, accessible training on the recognition and management of paediatric obesity for primary and secondary level care paediatric health care professionals; b) harmonise basic treatment and health promotion messaging around healthy eating and activity across the health system; c) disseminate, and train all paediatric staff in the use of, BMI for age charts; d) tackle weight-based stigma throughout the health system; e) provide a range of accessible behavioural change treatment programs, with clear referral pathways related to age and severity; f) integrate obesity treatment into the management of type 2 diabetes. Specifically for adolescents with moderate to severe obesity, consider a) pathways for accessible and affordable bariatric surgery; b) the use of more intensive dietary interventions (eg VLEDs); and c) use of appropriate drug therapies when available for this age group e.g. GLP1 receptor agonists.

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### **S4.3 - Eat, sleep, move – the roles in childhood obesity prevention**

Rachael TAYLOR  
University of Otago, New Zealand

Eat, move, sleep, repeat – the role of each behaviour in obesity prevention in children

Diet and physical activity have long been the cornerstones of weight management across all age groups. However, while these behaviours are clearly critical for good health, maintaining changes long-term is notoriously difficult. Our relative inability to both prevent and manage child obesity around the world indicates that alternative approaches should therefore be investigated. Sleep may offer one such approach. Not receiving sufficient good quality sleep has been consistently related to an increased risk of obesity in children in a wide range of observational studies. However, the mechanisms underlying short sleep leading to weight gain are not clear. Nor have many intervention trials determined the effectiveness of sleep manipulation as a good obesity prevention tool. Current observational evidence would suggest that short sleep is related more to increased energy intake or poorer dietary choices, than changes in energy expenditure behaviours, but good quality data, including experimental trials are lacking. This talk will cover the role of sleep in effective weight management in children, what we know, what we don't know, and suggestions for future research.

### **P3 - X-linked acrogigantism and other causes of paediatric gigantism**

Constantine A. STRATAKIS  
National Institutes of Health, USA

Gigantism and acromegaly are rare clinical entities caused by growth hormone (GH) hypersecretion. Their main difference is the status of the epiphyseal growth plates at the time of the GH hypersecretion; gigantism occurs during childhood when growth plates are not yet fused and acromegaly occurs after epiphyseal fusion. The most common cause of both gigantism and acromegaly is a benign GH-secreting pituitary tumor (somatotroph tumor) that occurs sporadically. However, both disorders can occur in the setting of known genetic syndromes, including familial isolated pituitary adenoma, X-linked acrogigantism, Carney complex, Multiple endocrine neoplasia type 1, McCune Albright syndrome, paraganglioma, pheochromocytoma and pituitary adenoma association and neurofibromatosis type 1. Typical clinical features include coarse facial characteristics with frontal bossing and prognathism, excessive sweating, and enlargement of the hands and feet. Clinical manifestations can be broadly categorized into local effects from the pituitary tumor and systemic effects of the GH/IGF1 excess. Measurement of serum IGF-1 is the best screening test for gigantism and acromegaly. Diagnosis is confirmed by failure of suppression of GH to less than 1 µg/L after a standardized oral glucose load. The goal of treatment is normalize GH secretion and correct clinical symptoms while preserving anterior pituitary function. Surgery is the first line of therapy for patients with a distinct pituitary micro- or macroadenoma. Medical treatment consists of three different classes of medications: somatostatin analogues, dopamine agonists and growth hormone receptor antagonist. Radiotherapy may be used as an adjuvant therapy when surgery and medical therapy are unsuccessful.

## **S5.1 - The study of Phenotype Standardization and Genotype-phenotype Associations in short stature**

Yongguo YU  
Xinhua Hospital, China

Idiopathic short stature (ISS), which is considered when height is more than two standard deviations below the mean height for a given age, sex, and population without evidence of a systemic disorder, nutritional, psychological or chromosomal disorder, or over hormonal abnormalities, is a common medical concern in the world. Nowadays, it is generally accepted that patients with idiopathic short stature, are more likely to be caused by the pathogenic effect of rare mutations in a single major gene, and thus genetic testing is often used to explore the cause of idiopathic short stature.

As for the detection methods, next-generation sequencing, especially whole-exome sequencing, has been rapidly adopted in the clinical diagnosis of idiopathic short stature due to its ability to simultaneously analyze several genes or gene regions. However, our previous research had indicated that the positive rate of next-generation sequencing was low for simple short stature while the patients with specific facial features or skeletal abnormalities were more likely to find genetic causes through high-throughput molecular detection technology. With our in-depth survey, we concluded several reasons that may lead to this dilemma, including no standardized describing system for short stature as well as no accurate correspondence between phenotype and genotype.

So how to figure out these limitations is an urgent problem needed to be solved. To this end, we conduct the study of Phenotype Standardization and Genotype-phenotype Associations in short stature. We first complemented detailed phenotypic information linked to variants by case analysis and then integrated known relationships from public databases. After completing these basic works, we collected more than 600 cases from over 50 units around China, trying to discover new relationships by GWAS. In addition, to discover solid phenotypic-genotypic relationships and further develop special auto-interpretation tools for short stature, we need standardized terms of idiopathic short stature (what we call short stature ontology). In this process, domain experts, users, and ontology/knowledge engineers primarily design the ontology, and then we establish a control board and revise ontology according to the users' feedback. In view of the fact that phenotype and genotype are too much to be included at once, users can update ontology at any time. As the ultimate aim of this research is to establish a special auto-interpretation model in short stature, we have researched and evaluated previous auto-interpretation tools and are combining them with integrating related resources based on short stature ontology in our study. All in all, we hope our study could help the etiologic diagnosis of the short stature.

## **S5.2 - Growth in Childhood Cancer Survivors (CCS)**

Cindy HO Wei Li  
National University Hospital, Singapore

Advances in cancer treatment meant improved long-term survival for patients diagnosed with cancer and increasing number of adults who are childhood cancer survivors. Many factors have been associated with the observed height impairments, apart from the cancer itself. They include the use of cranial irradiation with its risk of growth hormone deficiency and precocious puberty, spinal irradiation, intensive chemotherapeutic regimen including use of glucocorticoids, pubertal arrest due to gonadal failure, episodes of infection, malnutrition and occurrence of vertebral compression fractures. The loss of height can be associated with a poorer quality of life in the cancer survivor and hence it is paramount that paediatric endocrinologists be aware of and help to make a timely diagnosis of these conditions that are amendable to treatment to maximise the final adult height of our childhood cancer survivors.

### **S5.3 - Impact of GH treatment in terms of efficacy and safety: Lessons from registries**

Mohamad MAGHNIE  
University of Genova, Italy

In 1985, recombinant human GH (rhGH) was approved by the US Food and Drug Administration (FDA) and the availability of an unlimited supply of rhGH improved access to therapy for children with GHD. The increased supply of rhGH allowed investigation into treatment of multiple conditions associated with short stature not associated with GHD leading to FDA approval for treatment of children with growth failure associated with chronic renal insufficiency, Turner syndrome, Prader-Willi Syndrome, small for gestational age without adequate catch-up growth, idiopathic short stature, short stature homeobox (SHOX) deficiency, and Noonan syndrome.

Since then GH registries (postmarketing studies), originally mandated by the FDA in 1985, have been an invaluable resource for determining the safety and efficacy of GH treatment. Huge amounts of data were generated and the volume of real-world data overcomes several limitations. A variety of disease states were monitored helping to the understanding and management of pediatric GHD and other conditions treated with rhGH. The data were highly generalizable to the clinical practice setting.

The goals of the presentation are to provide a summary of the main published data with relevant impact on efficacy and safety findings from all patients, and to illustrate the value and utility of long-term registry for future studies. GH resulted to be efficacious with a good safety profile. A state of the art about the results of SAGHE studies will be given.

## **S6.1 - The role of the gut microbiota in health and development during early childhood**

Clare WALL

University of Auckland, New Zealand

The early stages of gut microbiome development are marked by unique temporal microbe uptake, colonisation, and selection, all of which have variable functional characteristics throughout time. This carefully managed microbial sequence begins at birth and continues until the microbiome acquires an adult-like makeup and function around 3 years of age. These many stages of microbiome development are increasingly becoming recognised as critical periods for immune and metabolic development which can impact on long term health. There have been several publications which have indicated age suitable microbiome development and specific microbiome characteristics which have been associated with later health issues.

Early life nutrition has been shown to be the most important modulator of the microbiome with breastmilk seeding and modulating the microbiome with beneficial bacteria. The introduction of solid foods which are largely influenced by physiological development, culture and tradition has a significant impact on the change and development of the gut microbial diversity. There is a growing body of research on early life and child nutrition on the development of the microbiome and subsequent immunological and metabolic competence. However, there is still a significant knowledge gap, to enable us to provide suitable nutritional recommendations in order to maintain an age-appropriate microbiome for long-term health.

## **S6.2 - Paediatric Nutrition & Catch-Up Growth: Role of Clinicians in Educating Parents**

LEE Way Seah  
University Malaya, Malaysia.

Provision of adequate nutrition in the first few years of life is essential for growth and development. Children grow fastest physically and undergo rapid neurocognitive development during the first 2–3 years of life. Inadequate nutrition during this critical period affects both mental development and physical growth. Most children with faltering growth do not have an underlying organic disease but rather due to non-organic faltering growth. This is usually observed when the growth of a child begins to slow down in late infancy and subsequently declines markedly until about 18 to 19 months. The most important cause of non-organic growth faltering is due to inadequate nutritional intake. It is estimated that at least 1 in 3 children < 5 years is undernourished or overweight and 1 in 2 children have hidden hunger, undermining the capacity of millions of children to achieve adequate growth to fulfil their growth potential. If parental attitude, knowledges and health behaviours can be modified via education or directed interventions, the potential for success in changing the behaviour of children should be greater. Parent-taught intervention has been found to be effective in stimulating attitude, knowledge, and food choice behaviour changes by parents while a school-based curriculum has less impact on parents. Paediatricians are in a unique position to partner with families/parents and children to influence key components of the broader strategy of developing community support. Paediatricians often follow up children longitudinally, sometimes from infancy through adolescence. Different prevention strategies can be tailored at different period of childhood. In addition, paediatricians are also often regarded by families as a reliable source of health advice and as experts in promoting developmentally appropriate, behaviour-change agent and advocate for healthful lifestyles

### **S6.3 - Behavior Management for Childhood Malnutrition**

Firdaus MUKHTAR  
Universiti Putra Malaysia, Malaysia

Child malnutrition may be defined as a pathological state resulting from inadequate nutrition, including undernutrition due to insufficient intake of energy and other nutrients; overnutrition due to excessive consumption of energy and other nutrients; deficiency diseases due to insufficient intake of one or more specific nutrients such as vitamins or minerals. Behavioural Management strategies are the mainstay for the management of children malnutrition and are designed to reinforce positive behaviours and minimize maladaptive behaviours. These strategies include a combination of modification of mealtime scheduling, meal duration, and mealtime transitions, as well as positive reinforcement and discrimination training. It is important that parents work alongside with other medical and allied health professionals in order to understand the range of possible strategies and apply the suitable type of behavioural intervention.

### **SS3.2 - Approach to the diagnosis of Hypophosphatemic rickets**

Muhammad Yazid JALALUDIN  
University Malaya, Malaysia

X-linked hypophosphatemia (XLH) is a rare inherited cause of hypophosphatemic rickets and osteomalacia. It is caused by mutations in the phosphate-regulating endopeptidase homolog, X-linked (PHEX). This results in increased plasma fibroblast growth factor-23 (FGF23), which leads to loss of renal sodium-phosphate co-transporter expression leading to chronic renal phosphate excretion. Raised plasma FGF23 also suppresses the production of 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), resulting in impaired intestinal phosphate absorption.

Chronic hypophosphatemia in XLH leads to impaired endochondral mineralization of the growth plates of long bones with bony deformities. Children with XLH develop genu varum or valgum upon weight-bearing, widening of ends of long bones, abnormal head shape due to craniosynostosis, progressive and disproportionate decline in linear growth, muscle weakness, bone pain, and dental abscesses due to impaired mineralization of enamel and dentine.

XLH is the most frequent inherited cause of phosphopenic rickets/osteomalacia. As hypophosphatemia is also found in calcipenic rickets/osteomalacia as a result of secondary hyperparathyroidism, it is very important to get a detailed medical, including the family history, auxology, and musculoskeletal examination, and appropriate investigation (radiology, biochemistry, and genetic studies) in the course of establishing the XLH diagnosis. This approach can help to exclude other causes of phosphopenic and calcipenic rickets/osteomalacia.

### SS3.3 - New Era of Management of X-linked hypophosphatemia

Craig F MUNNS

The Children's Hospital at Westmead, Sydney, Australia

X-linked hypophosphataemic rickets (XLH) is a rare congenital bone condition caused by inactivating mutations in the PHEX gene, which leads to upregulation of FGF23 and hypophosphatemia. Clinical features include rachitic features, limb deformity, abnormal skull shape, craniosynostosis and Chiari malformation (1).

Treatment of XLH has involved supplementation with calcitriol and phosphate. Burosumab, an anti-FGF23 antibody, is a recent treatment for XLH that targets the chronic upregulation of FGF23. A 64-week phase 3 randomised, active-control, open-label trial of Burosumab in children aged 1-12 years was recently published (2). This study showed that Burosumab was associated with a significant improvement in rickets, lower limb bowing, serum ALP, serum phosphate and growth.

It remains to be determined for which patients the clinical outcome would be sufficient with conventional therapy and which adults or children would benefit the most from Burosumab (1).

1. Imel EA, Biggin A, Schindeler A, Munns CF. FGF23, Hypophosphatemia, and Emerging Treatments. *JBMR Plus*, 2019. In press.
2. Imel EA, Glorieux FH, Whyte MP, Munns CF, Ward LM, Nilsson O, Simmons JH, Padidela R, Namba N, Cheong HI, Pitukcheewanont P, Sochett E, Högler W, Muroya K, Tanaka H, Gottesman GS, Biggin A, Perwad F, Mao M, Chen CY, Skrinar A, San Martin J, Portale AA. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet*, 2019 Jun 15;393(10189):2416-2427

## **SS4.1 - Public health impact of pneumococcal conjugate vaccine: Assessment of pneumococcal disease burden and serotype distribution**

Ron DAGAN

Ben-Gurion University of the Negev, Israel

During the last two decades, several pneumococcal conjugate vaccines (PCVs) have been introduced to most populations in the world and contain from 7 to 13 serotypes. Further development is about to occur with 15- and 20-valent PCVs. The impact of PCVs on the various disease outcomes is diverse, and depends much on vaccine uptake, but also on vaccine serotype content and the effect on nasopharyngeal carriage in the recipient (usually infants and toddlers), accounting for both direct and indirect (herd) protection. We have learned that what seems to be only a small difference in serotype distribution of the PCV content, could result in significant differences in impact on disease, although all PCVs have an important impact on invasive diseases, pneumonia, and otitis media. The serotype replacement phenomenon is a necessary result of PCV widespread administration. All currently used vaccines show significant replacement, depending on the serotypes absent from the vaccine, and virulence and prevalence of the remaining serotypes. Thus, the new generation vaccines can improve the already dramatic impact, by further reducing disease caused by some of the remaining and

## **S7.1 - Urogenital surgery**

Rebecca DEANS

The Royal Hospital for Women and Sydney Children's Hospital, Australia

Patients with disorders of sexual development (DSD) requiring vaginal reconstruction are complex and varied in their presentation.

Enlargement procedures for vaginal hypoplasia include self-dilatation therapy or surgical vaginoplasty. These interventions are offered to improve psychological and sexual outcomes. The concept of surgery for DSD conditions has become increasingly controversial in the last decade. Vaginal dilatation therapy is the first line treatment for vaginal hypoplasia due to the absence of surgical risk, but success depends on the motivation of the patient, and underlying anatomy. Concomitant psychological support improves outcomes. Surgical vaginoplasty methods depend on the genital configuration, previous attempts at genital surgery and surgeon's personal expertise and preference. There are many vaginoplasty techniques described: tension via an external traction device, peritoneal, buccal and amnion, skin, and bowel grafting, as well as muscle and skin flaps. Each method has different risks and benefits. The surgical risks include malignancy, contracture leading to introital stenosis or loss of vaginal length, vaginal prolapse, dry vagina or excessive vaginal discharge. There is a lack evidence to inform management regarding the optimum surgical technique to use, and long-term data on success is lacking, particularly with respect to sexual function. Regardless of the vaginal reconstruction technique, patients should be managed in a multidisciplinary team where there is adequate emotional and psychological support available.

## **S7.2 - The transition in DSD/Adrenal disorders**

Martine COOLS

Ghent University and Ghent University Hospital, Belgium

Both individuals who have a difference/disorder of sex development (DSD) or an adrenal disorder (AD) require life-long medical and psychosocial care, with age-specific accents. Transition from the paediatric to the adult clinic is a crucial event in the medical history of many adolescents, which can greatly influence their long-term outcome.

Whereas adult endocrinologists traditionally see far more patients with ADs, paediatric endocrinologists are much more familiar with the management of DSDs. Exchange of expertise is extremely motivating and interesting for both specialties and is crucial for our patients. Especially within the field of DSD, there has recently been a very strong focus on patient autonomy, and many medical decisions that used to be taken by the parents, are now deferred to an age where adolescents are at the core of the decision-making team. This poses new challenges for patients but also for adult endocrinologists, who are often unfamiliar with e.g. surveillance of gonads in situ, or the management of vaginal hypoplasia. Formal transition protocols can be a great way of shared learning on these topics.

The goals of the transition process are to ensure that adolescents are fully informed on all aspects of their past medical history and to jointly design a clear plan that addresses their future medical needs in a context of shared decision-making. It is crucial that adolescents feel fully comfortable with the adult endocrinologist and other specialists who will follow them further on and that they are equipped with all the skills they need to organise and comply with the (often complex) care for their condition autonomously.

Questions that will be addressed in this presentation are: Why is a formal transition protocol important? When to start the transition process? What are the topics to be discussed? How to assess transition readiness? These questions will be illustrated with some examples from our clinical practice.

### S7.3 - Adrenal disorders and DSD

Atsumi TSUJI-HOSOKAWA

National Research Institute for Child Health and Development, Japan

The thirty-year lesson from the newborn screening for congenital adrenal hyperplasia in Tokyo

Congenital adrenal hyperplasia (CAH) is an inherited disorder caused by impairment of steroidogenic enzymes involved in cortisol biosynthesis. More than 90 percent of cases result from 21-hydroxylase deficiency (21OHD). To prevent life-threatening adrenal crisis and to help perform appropriate sex assignments for affected female patients, newborn screening (NBS) programs for CAH have been introduced in numerous countries. In Japan, the NBS for CAH was introduced in 1989. Although the basis of the NBS system are identical in all local governments, the NBS in Japan was introduced individually into the prefectural administration. Tokyo is the largest city with more than ten million people, and to date, more than two million neonates have been screened. In this presentation, we aim to summarize the experience of the past 30 years of the NBS for CAH in Tokyo.

The incidence of 21OHD was approximately 1:19,000, and the mean age at diagnosis of 21OHD was 7.6 days. All the cases with 46,XX DSD was reared as female, and no false negative cases were reported. Further analysis revealed two concerns of the CAH screening, limited impact of stratified cut-off values for reducing high false positive rate and development of severe salt wasting at diagnosis in substantial number of patients.

Although the Tokyo screening program is conducted with cutoff points stratified by birth weight and gestational age which improved positive predictive value (PPV) of 25.6%, PPV for preterm infants ( $\leq 36$  weeks of gestational age) remained low of 2%, suggesting the efficiency of stratified cutoff points are limited. A major cause of false positive in preterm infants are a cross reaction to non 17 $\alpha$ OHP steroids synthesized from fetal adrenal gland in ELISA measurement. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been recommended as the best option for the screening, and from April 2021, LC-MS/MS was introduced to the CAH screening in Tokyo. Our pilot study demonstrated LC-MS/MS would remarkably increase PPV.

Based on our follow-up survey, 37.4% of 21OHD patients displayed severe salt wasting ( $\text{Na} < 130\text{mEq/L}$  or  $\text{K} > 7.0\text{mEq/L}$ ) at diagnosis. Serum sodium and serum potassium was linearly deteriorated with age in days, and the intervention must be started ideally during the first week of life. Hence, earlier sampling can be discussed for the prevention of severe salt wasting. In line with this, timeline of the NBS becomes earlier worldwide as the inborn metabolic disease were added to screening panel recently. However, we must consider the evidence of false negatives associated with the earlier sampling. Additionally, our survey revealed changes in body weight was a useful index for triaging neonates with positive CAH screening. The cases showing decrease of body weight from birth are likely to have classical 21OHD, and even in cases of 21OHD, the possibility of developing severe salt wasting is extremely low without loss of body weight during their second week of life.

The NBS for CAH was efficient and provided important insights. Continuous evaluation of the NBS and long-term follow up of the patients must be considered for further improvement in the practice of CAH.

## **S8.1 - Central Precocious puberty: referrals and early identification**

Azriyanti ANUAR ZAINI  
University Malaya, Malaysia

Central precocious puberty is diagnosed when puberty starts earlier than the norm. By definition, breast development before 8 years old in girls and testicular enlargement before 9 years old in boys. CPP is likely idiopathic in 80-90% of girls and pathogenic in 80-90% of boys. Although the secular trend is showing earlier breast development in girls worldwide, the age of menarche hasn't change much in the past decade. Having said that more data is needed in Malaysia to see if our children are showing similar trend. Early recognition and identification of this condition is necessary for assessment and treatment should it cause a concern. CPP is associated with initial height and growth spurt but eventually will end up short as adults. And apart from that early physical change and menarche may cause anxiety and psychosocial concerns in children as well as parents.

This lecture will cover a general approach on CPP and discussion on how early identification and treatment may help with the outcome. Causes and a few cases will be discussed for better illustration and understanding.

## **S8.2 - Trends in timing of normal and precocious puberty**

Anders JUUL

University of Copenhagen, Denmark

Puberty marks the transition from the childhood phase to the attainment of full adult reproductive capacity. Timing of puberty shows wide interindividual variation, of which 60% can be explained by genetic factors as evidenced from twin- and mother-daughter studies. The remaining 40% of variation is explained by lifestyle and environmental factors.

Age at pubertal onset in girls is classically observed when breast gland tissue starts to develop. A worldwide decline in age at breast development (helarche) has been demonstrated, and this trend appears to be ongoing. This worrying trend in the general population has occurred over just a few decades and must be explained by environmental (non-genetic) factors. It is paralleled by increasing number of girls referred to be evaluated for very early signs of puberty (precocious puberty). Thus, nation-wide registerbased studies from Denmark and South-Korea report marked increases in girls registered with a diagnosis of central precocious puberty.

### **MTE3 - Endocrine emergencies**

Peter SIMM

Royal Children's Hospital Melbourne, Australia

This session will be presented as a series of case vignettes to highlight different areas of Endocrinology where more pressing clinical attention may be required. Topics to be covered include sodium management post neurosurgical procedures/cerebral trauma, calcium disorders in infancy, profound hypothyroidism, neonatal Grave's disease and thyroid storm. For sodium management, the importance of accurate fluid balance and assessment of hydration state will be highlighted. The triphasic response post neurosurgery will be addressed, as will the management of cerebral salt wasting. The differential diagnosis of hypercalcaemia in infancy will be discussed, along with its management. The importance of calcium assessment with seizure presentation will be flagged, as will the recommendation to treat hypocalcaemia with oral therapy wherever possible due to the risks of intravenous calcium. Finally three thyroid cases will be presented, highlighting different aspects of acute thyroid management, such as the need to be vigilant in infants of mothers with Grave's disease, and the management of the rare condition of thyroid storm.

## **MTE4 - Practical approach to short stature**

Janet YH HONG  
Hospital Putrajaya, Malaysia

Normal growth patterns are the gold standard indicating health and well-being of children. Slow growth or short stature raises the possibility of an underlying pathological condition.

Though short stature in children beyond the first 2 years of life can be due to non pathological variants of growth, it is important to evaluate a short child systematically to detect pathological causes of growth failure (primary growth disorders, systemic disorders, endocrine disorders). Short stature can be the only presenting feature in a girl with Turner syndrome while some girls with Turner display subtle dysmorphic feature. Children born small for gestational age who do not experience catch up growth may benefit from growth hormone therapy. Therefore, accurate measurement of growth parameters and carefully plotting them on appropriate growth chart serially should be done for all children for early detection of poor growth and for timely intervention. A decreasing height velocity SDS or height crossing 2 percentile lines in the height chart indicates growth failure and this may occur long before severe short stature become obvious.

Rate of linear growth changes during different phases of growth and variations occurs with differences in the onset of puberty. Available growth charts include the World Health Organization standards and Centers for Disease Control and Prevention charts. In a 2019 publication by Bradley S. Miller et al, it is reported that Tanner Staging Age Height charts may be useful to assess linear growth for US children with pubertal timing variations in clinical management and research setting.

Detailed personal, family, social history followed by a thorough physical examination is needed before planning for laboratory or radiological investigations. Family history with informations on longitudinal growth patterns, adult height and pubertal onset helps to detect certain familial conditions and helps differentiating variants of normal growth.

With the advancement in genetic testing (though still not that easily available locally), it may be considered in certain cases after getting a multidisciplinary input including a consult with the geneticist and endocrinologist. A good example can be seen in some healthy children with a diagnosis of familial short stature whom were found to have heterozygous variant in genes involved in growth plate development.

Early identification of abnormal growth patterns allows specialise care to be offered timely to the children to improve their final adult height besides treating the underlying conditions to improve overall clinical outcomes. 2 clinical short cases will be presented.

## **MTE5 - Pubertal induction regimes – current recommendations**

Joanna Yuet-ling TUNG

Hong Kong Children's Hospital, Hong Kong

Puberty is the period to attain adult secondary sexual characteristics and reproductive capability. It involves the reactivation of pulsatile hypothalamic gonadotropin-releasing hormone secretion from its relative dormancy in childhood, on the background of an intact hypothalamic-pituitary-gonadal axis.

Both primary gonadal dysfunction and abnormalities of the hypothalamic-pituitary axis result in hypogonadism and delayed puberty. With better treatment in childhood cancers and other chronic conditions, the survival has improved dramatically. However, many of them suffer from various endocrine late effects including deficits in gonadal function, related to the underlying condition or its treatment. As a result, the number of patients requiring pubertal induction has also increased.

The goal of pubertal induction is to mimic the normal timing and progression of physical and social development at different pubertal stages, while minimizing risks. Treatment strategies should aim to achieve adequate feminization for girls or virilization for boys, to optimize pubertal growth spurt, and to attain normal body composition with optimal bone mass accrual. Implication on future fertility should also be considered. All these should be balanced with age-appropriate psychosocial and emotional maturity. Nowadays, a wide range of treatment options are available. In this session, we will discuss the merits and disadvantages of the different options, based on currently available evidence.

## **MTE6 - Interpretation of unusual thyroid function tests**

Suhaimi HUSSAIN

Universiti Sains Malaysia, Malaysia

Unusual thyroid function test (TFT) is defined as TFT result that is incompatible with the normal physiological relationship between thyroid hormone and TSH/TRH from anterior pituitary and hypothalamus. It can also be defined by discordant between hormonal and clinical status of patient for example persistently high FT4 but yet the patient is otherwise well with no clinical signs of thyrotoxicosis. Unusual TFT is categorized into 4 broad categories such as normal FT4 with high TSH, normal FT4 with suppression of TSH, high FT4 with high TSH and low FT4 with low TSH. In this lecture I will be sharing some of the cases to illustrate unusual TFT.

## **P4 - New technology in diabetes management**

Elizabeth DAVIS  
Perth Children's Hospital, Australia

100 years from the discovery of insulin it is timely to stop and consider the considerable advances in care for children and adolescents living with diabetes. The advances in technology have improved not only the lives of young people living with diabetes but also the workplace of health care professionals caring for them.

From the patient's perspective the main technological advances have been in blood glucose monitoring, new methods of insulin delivery, online advisors and apps. The pump technology has increased in functionality, improved user experience and increasingly been tested in niche groups such as the very young.

For the health care professional there has been a steep increase in the learning needed to support young people using these new technologies. Together with this, HCPs have had to upskill in the new reporting software, advisors and in some cases the technology that supports databases that facilitate benchmarking and

The region represented by APPES has a broad range in both the penetration and the choice of technologies. This presentation will review the latest technology in paediatric diabetes care for blood glucose monitoring, insulin delivery, closed loop systems and DIY , but also focus on practical suggestions of how to integrate the education and management of constantly changing technology into clinical services.

## **S9.1 - Exercise in Diabetes – new insights**

Elizabeth DAVIS  
Perth Children's Hospital, Australia

Activity requirements for children and adolescents with diabetes are the same as for those without diabetes. Meeting the physical activity recommendations helps to improve glycaemic control, reduce cardiovascular risk and support a better sense of wellbeing. However, there are a number of factors which make achieving adequate levels of exercise challenging for people living with diabetes.

Health care professionals (HCP) can assist young people living with diabetes to optimise their activity levels by having a good understanding of both the physiology and the complexities of exercise and diabetes. There are a number of barriers to exercising successfully including fear of hypoglycaemia, the varying impact on BGL with different types of exercise, the challenges of carbohydrate intake, timely insulin adjustment, and what BGL is best to maximise performance. Furthermore, many school environments and sports coaches are inadequately equipped to support children with diabetes to exercise safely and optimally.

Some of the burden of these challenges with exercise have been reduced with technologies such as pumps and CGM, but these are not available to all children living with diabetes and it is important the HCP can assist to develop a safe and effective exercise plan.

This presentation will aim to increase the confidence and knowledge of HCP assisting children living with diabetes to increase their activity safely and effectively.

## **S9.2 - Monogenic Diabetes: Finding the needle in a haystack**

Daphne Gardner TAN Su Lyn  
Singapore General Hospital, Singapore

Monogenic Diabetes is rare but is an important diagnosis to make since it informs optimum treatment choice, prognostication and risk stratification to immediate family members. Traditionally, detecting monogenic diabetes requires selecting the individual with atypical diabetes (neither Type 1 or Type 2 Diabetes) before selecting the candidate gene for sequencing. More recently, sequencing technology has advanced beyond single candidate gene testing towards targeted high throughput panels, allowing simultaneous assessment of multiple candidate genes in one sample run. The focus of the physician then shifts towards understanding the diabetes phenotype pertinent to different ethnicities to select those with a high pre-test probability of monogenic diabetes for gene sequencing.

### **S9.3 - Diabetes management in a poor-resource country**

Fauzia MOHSIN

BIRDEM General Hospital, Bangladesh

An estimated 463.0 million adults aged 20–79 years worldwide have diabetes, nearly 80% of whom live in low- and middle-income countries. The incidence of Type 1 diabetes in children and adolescents is increasing worldwide, with an overall annual increase of 3%. Although the reported incidence rates of many low and middle income countries are low, their T1D burden is large given their population size. Overweight and obesity rates along with prevalence of type 2 diabetes in children and adolescents are rising. Difficulties in the management of children and adolescents with diabetes in resource-poor countries are multiple. Lack of awareness among health professionals and families about diabetes in children, lack of diagnostic facilities can often lead to delay in diagnosis/ misdiagnosis with fatal consequences. Lack of affordable insulin and other essential medical supplies are significant problems coupled with the dearth of accessible and trained medical personnel. Glucose meters and strips are not affordable by the majority. Other serious problems include the lack of refrigeration for insulin storage, social stigma, gender bias, poor support at school. Inability to manage common complications e.g. hypoglycaemia, sick day management, drop out from the clinic (which may be due to lack of motivation, long distance or extra cost involved in travel), psychological issues are other common problems. Organizing effective diabetes care in a low resource setting is challenging. Strategies such as sustainable government policy, epidemiological data, trained healthcare workers, public-private partnership, proactive diabetes associations are important. The use of telehealth can be very helpful. In spite of the above limitations there are encouraging example of diabetes health care delivery in resource poor setting. An example of such an effort is the Diabetic association Bangladesh (BADAS) which through BIRDEM and its 61 affiliated associations and projects is providing integrated diabetes care throughout the country. Changing Diabetes in Children (CDiC) and the Life for a Child (LFAC) have been assisting BADAS to provide free comprehensive outpatient service to underprivileged children and adolescents with diabetes in Bangladesh.

## **SS5.2 - Central Precocious Puberty (CPP) Etiologies and Diagnostic Aspects**

Anders JUUL

University of Copenhagen, Denmark, Europe

Central precocious puberty (CPP) denotes a specific disease entity defined as premature development of secondary sexual characteristics in a girl (< 8 yrs) or boy (< 9 yrs) with activation of the hypothalamo-pituitary-gonadal (HPG) hormone axis. Such a GnRH-dependent precocious puberty are diagnosed as a combination of clinical characteristics including growth acceleration and pubertal signs, as well as advanced boneage and biochemical signs of CPP. The latter may include measurement of reproductive hormones and a pubertal response to a GnRH test. In girls with CPP a brain MRI should rule out CNS pathologies. Controversies regarding diagnostic aspects as well as the appropriate age cut-off for brain MRI will be discussed

### **SS5.3 - Revisiting the Treatment Management of CPP**

Martin O SAVAGE

University of London, UK

Puberty is occurring earlier, probably related to an increase in BMI globally. This means that more children, particularly girls will be referred with early puberty. It is important to distinguish CPP from early normal puberty and this is done from two key parameters; the tempo or progression of puberty and evidence of LH secretion. Both are identifiable in girls with CPP. Clinical skills are needed to take a careful history and to examine the child and document stages of puberty. The phenomenon of adrenarche should be explained to parents. If GnRH agonist therapy is indicated, this treatment should be initiated when definite precocious LH secretion is documented and the child has documented progression of pubertal signs before the age of 8 years. The key objective of GnRHa therapy is to suppress LH-dependent features, such as breast development and menstruation. Adult height gain is an added bonus and depends on the ability to reduce bone age advance. This is most effective in children <6 years of age. GnRHa therapy is safe and effective, but should continue for at least 2 years to fulfil its aims

#### **SS5.4 - Experience sharing: Optimizing CPP patient care with long-acting GnRHa**

Jae Hyun KIM

Seoul National University Bundang Hospital, South Korea

For the treatment of central precocious puberty (CPP), depot formulation of GnRH agonist (GnRHa) has been widely used as a standard treatment. In Korea, mainstay of GnRHa treatment for CPP has been monthly depot formulation. However, recent approval of 3-month and 6-month depot formulation of GnRHa in Korea showed a gradual increase in use of these agents for patient with CPP. Many clinical research showed that longer-acting GnRHa could effectively suppress the hypothalamic-pituitary-gonadal axis and gonadotropin secretion in children with CPP. The clinical benefits also have been reported such as regression of pubertal progression, delayed maturation of bone age and increased adult height. Moreover, recent Korean studies showed that clinical efficacy of 3-month depot formulation of GnRHa for CPP. There was no difference between 1- and 3- month depot formulation in terms of switching during treatment. One-year efficacy of 1- and 3-month formulation showed comparable results. Because longer-acting GnRHa offers improved convenience and compliance, especially in a pandemic period, these could be an alternative and viable strategy for treatment of CPP.

## **SS6.1 - Growth Hormone Treatment in Idiopathic Short Stature**

FU Jun-fen

The Children's Hospital, Zhejiang University School of Medicine, China

FU Jun-fen will report the clinical trial of daily GH treatment in children with idiopathic short stature (ISS). This study aimed to evaluate the efficacy and safety of daily GH treatment, as well as to determine the optimal dose of Jintropin® AQ in ISS children. Prepubertal children from 11 hospitals who were diagnosed as ISS were enrolled in this phase III study. Eligible patients were randomized 2:1 into the study group (Jintropin® AQ 0.05 mg/kg/d, n=362) and the control group (no intervention, n=119) for 52 weeks. The primary endpoint was the change of height standard deviation score (HT-SDS) from baseline. The results showed that Jintropin® AQ at a dose of 0.05mg/kg/d was effective and showed great safety profiles in ISS treatment. There was a significantly greater improvement in growth parameters in the 0.05mg/kg/d group compared to untreated subjects. Further extension phase will evaluate the long-term efficacy and safety of Jintropin AQ treatment in ISS.

## **SS6.2 - Long Acting Growth Hormone Treatment in Idiopathic Short Stature**

LIANG Yan  
Tongji Hospital, China

LIANG Yan will introduce the long-acting growth hormone treatment in children with idiopathic short stature (ISS). Pegylated human growth hormone (PEG-rhGH) --Jintrolong® has a longer half-life and requires less frequent dosing than daily rhGH. This study aimed to evaluate the safety of PEG-rhGH and determine the optimal dose in ISS children. 360 eligible ISS children from 12 hospitals in China were randomized 1:1:1 to 3 groups—high dose group (Jintrolong® 0.2 mg/kg/w, n=120), low-dose group (Jintrolong® 0.1 mg/kg/w, n=120) and control group (no intervention, n=120) for 52 weeks. The primary endpoint was the height standard deviation score (HT-SDS) at week 52. Other growth parameters such as height, growth rate, bone maturity, and serum concentrations of blood insulin-like growth factor-1 (IGF-1) were measured. Jintrolong® at a dose of either 0.1 mg/kg/w or 0.2 mg/kg/w for 52 weeks was effective and well-tolerated in children with ISS. There was a significantly greater improvement in HT-SDS at 0.2 mg/kg/w. This study supports further investigation of Jintrolong® at 0.2 mg/kg/w in children with ISS.

### **SS6.3 - Growth Hormone Treatment in Prader-Willi Syndrome**

LUO Fei-hong

Children's Hospital of Fudan University, China

LUO Fei-hong will report a single-arm, self-controlled study of recombinant human growth hormone (Jintropin® AQ) treatment in children with Prader-Willi syndrome (PWS). This study aimed to assess the efficacy of Jintropin® AQ on motor development, mental development, retarded growth, and safety profiles in children with PWS. A total of 35 PWS children in China were enrolled to receive 0.5mg/m<sup>2</sup>/d Jintropin® AQ at first 4 weeks. Then the dose increased to 1.0 mg/m<sup>2</sup>/d from week 4 to week 52. The results demonstrated that treatment with 1.0 mg/m<sup>2</sup>/d Jintropin® AQ showed great improvement in growth parameters, including normalizing Ht SDS, BW SDS, BMI SDS and bone maturity, as well as mental development. Daily Jintropin® AQ administered subcutaneously for 52 weeks showed good safety profiles.

## **S10.1 - Grave disease**

Ouyporn PANAMONTA  
Khon Kaen University, Thailand

Graves disease (GD) is the most common cause of hyperthyroidism in children and adolescents. Three treatment options are available in pediatric GD. These treatment options include antithyroid drugs (ATD) therapy with methimazole, radioiodine (RAI) therapy and surgery or thyroidectomy. Only 30% of patients achieved remission with ATD therapy. Relapse of GD during treatment and after remission are frequently found and need longer duration of ATD treatment for euthyroidism. Acquired hypothyroidism with life-long thyroxine replacement commonly found following RAI therapy and surgery. The choices for modalities of treatment are individualized, depend on age of patients, severity of GD, goiter size, and parental preference.

## S10.2 - Congenital hypothyroid Screening – Can we do better?

WU Loo Ling  
Subang Medical Centre, Malaysia

Thyroid hormones play a critical role in neurogenesis and myelination of the nervous system during the foetal and postnatal period. Congenital deficiency of thyroid hormones leads to permanent neurological damage and mental retardation in children. Early diagnosis and treatment had been shown to prevent neurological damage and restore normal IQ. Hence biochemical screening of all newborns is crucial, as signs and symptoms of congenital hypothyroidism are not apparent at birth until months later. Newborn screening for congenital hypothyroidism was implemented in Malaysia in 2003. Since inception, there had been much challenges including variation in interpretation of thyroid function, criteria for diagnosis and management of the condition. Special categories of babies such as the preterm, low birth weight and sick newborns where the thyroid physiology is different have not been appropriately addressed. Management from screening to post-screening has been very much dependent on the understanding and experience of the attending doctor. Hence the standard of care is very variable.

A working group consisting of paediatric endocrinologists was initiated to develop a national consensus guidelines based on scientific evidence taking into account the Malaysian demographics, limited resources, technology and paucity of local data. This guidelines provides a comprehensive, step-by-step approach and recommendations from screening through diagnosis to management of congenital hypothyroidism.

We recommend primary TSH with supplementary FT4 as the screening strategy, on cordblood collected at birth. As 99.6% of all deliveries in Malaysia are conducted in the hospitals, screening using cordblood is probably the most effective way to ensure complete coverage of all deliveries in the country. A cut-off TSH of  $>60$  mU/L is used to recall babies for confirmatory re-testing. Babies with borderline TSH  $>20$  to  $<60$  mU/L are also recalled if concomitant FT4 is  $\leq 15$  pmol/L. These cut-off values are derived from previous small local studies and consensus expert opinion. Recall is done on Day 4-6, at least 72 hours after birth to avoid the period of physiologic TSH surge. At recall venous blood is taken for re-testing of TSH and FT4. Results are usually confirmatory in most cases. Elevated TSH is the primary determinant for diagnosis and initiation of treatment. In babies with borderline TSH, concomitant FT4 would be the determining factor. We emphasize the importance of taking into consideration all TSH and FT4 values and their trends in our decision to treat or to monitor. It is not unreasonable to err toward treatment before confirmatory results are available for families with logistic or socioeconomic issues. This guidelines give details on initiation of treatment and follow-up to avoid under or over treatment. Re-evaluation is done at 3 years, to identify those with permanent congenital hypothyroidism who need continuation of LT4 for life. Thyroid scintigraphy and thyroid ultrasound may be considered for these patients to determine the aetiology. A special categories of babies are highlighted. Post-screening strategies are recommended for this group of babies.

### **S10.3 - Newborns of mothers with thyroid disorders – Outcome and management?**

Susana P. PADILLA-CAMPOS  
Makati Medical Center, Philippines

Maternal thyroid adaptation to pregnancy, the placental enzymatic regulation of passage of thyroid hormones, and the ontogeny and physiology of the fetal hypothalamic-pituitary-thyroid axis will be reviewed.

Maternal gestational hypothyroidism and hyperthyroidism, both overt and subclinical, are common during pregnancy with collective incidence variously reported to range from 10% to 30%. That maternal gestational hypothyroxinemia results in impaired neurodevelopmental outcome of the newborn, is well recognized. The impact of maternal iodine deficiency on neonatal thyroid function will be highlighted. Maternal gestational hyperthyroxinemia on the other hand, is associated with increased risk for prematurity, low birth weight and small for gestational age newborns. It is imperative therefore that maternal thyroid disorders be evaluated, diagnosed and treated prior to pregnancy, with adjustments in needed medications to maintain a maternal euthyroid state throughout gestation.

The importance of close coordination and cooperation with our colleagues in Obstetrics, to ensure careful and continued assessment of maternal gestational thyroid status, to avert preventable adverse outcomes of maternal hypothyroidism and hyperthyroidism in the newborn, can not be over-emphasized.



# Oral Presentation

**KAICHI KIDA**

KK 1

Nicholas Beng Hui NG

**CREB REGULATED TRANSCRIPTION COACTIVATOR 3 (CRT3) AS A NOVEL PREDICTOR OF METABOLIC RISK IN SEVERELY OBESE CHILDREN**

KK 2

Andrew SNG

**VISCERAL ADIPOSITY INDEX TO PREDICT ADVERSE METABOLIC HEALTH IN SEVERELY OBESE ASIAN CHILDREN**

KK 3

Anupriya GORA

**DAILY VERSUS MONTHLY ORAL VITAMIN D IN EQUIVALENT DOSES FOR TREATMENT OF SYMPTOMATIC VITAMIN D DEFICIENCY IN INFANTS: A RANDOMISED CONTROLLED TRIAL**

KK 4

Lin YANG

**CLINICAL SEVERITY PREDICTION IN CHILDREN WITH OSTEOGENESIS IMPERFECTA CAUSED BY COL1A1/2 DEFECTS**

KK 5

Sarah MAESSEN

**REDUCTION IN SMOKING IN PREGANCY A KEY CONTRIBUTOR TO REDUCTION IN PRESCHOOL OBESITY IN NEW ZEALAND**

## CREB REGULATED TRANSCRIPTION COACTIVATOR 3 (CRTC3) AS A NOVEL PREDICTOR OF METABOLIC RISK IN SEVERELY OBESE CHILDREN

Nicholas Beng Hui Ng  
National University Hospital, Singapore

### Background

The prevalence of childhood obesity and its related metabolic complications is on an upward rise globally. The pathogenesis of obesity involves complex genetic-environmental interplay. Over time, obesity-susceptibility genes are increasingly being discovered. Recently, the CREB-regulated transcription coactivator 3 (*CRTC3*), a protein secreted by adipocytes into the circulation, has been implicated in its role in obesity and metabolic complications.<sup>1</sup> High levels of plasma *CRTC3* have been associated with adverse cardio-metabolic profile.<sup>2,3</sup> The 2 aims of our study was (1) to evaluate the association between *CRTC3* promoter gene polymorphisms, plasma *CRTC3* levels and cardio-metabolic parameters in our cohort of severely obese children, and (2) to functionally characterise common *CRTC3* promoter polymorphisms identified in our cohort.

### Methods

Two-hundred and fifty children with early onset obesity were recruited. Anthropometric, clinical and biochemical data for all participants were collected. The cohort was divided into those with and without metabolic syndrome according to the International Diabetes Federation (IDF) consensus definition. Polymerase chain reaction followed by Sanger sequencing were conducted on patient DNA samples to screen for *CRTC3* promoter polymorphisms which were functionally characterized using dual-luciferase assay (DLA) and electrophoretic mobility shift assay (EMSA). Plasma *CRTC3* levels were assayed using ELISA kits. Statistical analyses were performed to study associations between *CRTC3* promoter polymorphisms, plasma *CRTC3* levels and the various cardio-metabolic parameters.

### Results

Plasma *CRTC3* significantly correlated with BMI ( $r=0.431$ ,  $p=0.002$ ), fasting triglyceride ( $r=0.285$ ,  $p=0.032$ ) and fasting glucose ( $r=0.301$ ,  $p=0.041$ ) in our cohort of severely obese children. Moreover, obese children with metabolic syndrome had higher plasma *CRTC3* levels ( $312\pm 46$ pg/ml vs.  $221\pm 33$ ,  $p=0.038$ ) compared to those without metabolic syndrome.

Seventeen SNPs of the *CRTC3* promoter region were identified, 4 of which were novel SNPs (mean allele frequency [MAF]: 0.00625 to 0.05), with the remaining SNPs having MAF between 0.00625 and 0.825. Two of the identified common SNPs correlated significantly with cardio-metabolic parameters:

- rs62019401 (c.-1449C>T) was associated with higher plasma *CRTC3*, total cholesterol and LDL
- rs11635252 (c.-1530T>C) was associated with higher waist to hip ratio

Functional characterization of these common variants through DLA showed that the c.-1449C>T promoter variant had a 1.47 fold increase ( $p<0.0005$ ) in transcriptional activity ( $2.43\pm 0.25$  vs.  $1.65\pm 0.04$ ) as compared to wild-type *CRTC3* promoter. There was no difference between the transcriptional activity for the c.-1530T>C promoter variant and the wild-type *CRTC3* promoter ( $1.47\pm 0.25$  vs.  $1.65\pm 0.04$ ,  $p=0.652$ ). EMSA performed showed that the c.-1449C>T promoter variant had significantly increased binding affinity with nuclear protein as compared to wild-type ( $p=0.01$ ); there was no difference observed between the c.-1530T>C promoter variant and the wild-type *CRTC3* promoter.

### Conclusion

Plasma *CRTC3* and *CRTC3* promoter polymorphisms were associated with adverse metabolic risk factors and may contribute to the genetic risk of early onset severe obesity. We demonstrated functionally that a common *CRTC3* promoter polymorphism can lead to increased gene transcription resulting in higher plasma *CRTC3* levels. Plasma *CRTC3* may serve as a novel predictor of metabolic risk in obese children.

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## **VISCERAL ADIPOSITY INDEX TO PREDICT ADVERSE METABOLIC HEALTH IN SEVERELY OBESE ASIAN CHILDREN**

Andrew Sng  
National University Health System

### **Background**

The prevalence of childhood obesity has been increasing exponentially in many countries in recent decades, including Singapore<sup>1</sup>. Very often, obesity is accompanied by increased risk of developing metabolic complications such as insulin resistance, hypertension and dyslipidemia<sup>2</sup>. However, there is a subgroup of obese subjects who are protected from the metabolic and cardiovascular complications associated with obesity, and these subjects are described as “metabolically healthy obese (MHO)”<sup>3</sup>. Conventional anthropometric measurements such as body mass index (BMI), waist circumference (WC) and hip circumference (HC) that focus on adiposity as an indication of metabolic health may not be able to discern the difference between MHO and metabolically unhealthy obese (MUO)<sup>4,5</sup>. Thus, it is important to examine novel anthropometric indices that can identify high-risk children and optimize prevention and treatment strategies to compact cardio-metabolic diseases. This study aims to compare the performance of conventional and novel anthropometric indices in predicting metabolic syndrome (MetS) in our local cohort of severely obese children.

### **Methodology**

Four hundred and six children with early onset obesity of BMI for age  $\geq$  97<sup>th</sup> percentile were recruited from Health Promotion Board and National University Hospital, Singapore. The subjects were classified into MHO and MUO according to the criteria of the International Diabetes Federation (IDF). Conventional anthropometric measurements including BMI, WC, HC and skinfolds, and blood biochemistry were obtained. Novel anthropometric indicators such as a body shape index (ABSI), abdominal volume index (AVI), body adiposity index (BAI), body surface area (BSA) and visceral adiposity index (VAI) were calculated.

Differences between MHO and MUO were analysed using Student's t test. Spearman's correlation was performed to determine relationship between anthropometric indices and metabolic outcomes. Predictive performance of anthropometric indices was described through multivariate logistic regression analysis and Receiver Operating Characteristic (ROC) curves.

### **Results**

The prevalence of MUO is 36.5% in our cohort of severely obese children. There were no significant differences in conventional anthropometric indices including BMI, body fat percentage by bioimpedance, waist circumference, hip circumference, waist hip ratio and skinfold measurements between MHO and MUO children. However, MUO showed significantly higher BSA ( $2.16 \pm 0.26$  vs.  $2.09 \pm 0.35$ ) and VAI ( $2.72 \pm 1.58$  vs.  $1.50 \pm 0.72$ ) as compared to MHO.

There were more significant correlations between novel anthropometric indices and metabolic outcomes as compared to correlations between conventional anthropometric indices and metabolic outcomes. In particular, VAI was significantly correlated with systolic blood pressure ( $r=0.113$ ), diastolic blood pressure ( $r=0.218$ ), HOMA-IR ( $r=0.228$ ) and liver enzymes. Multivariate logistic regression and ROC showed that VAI is a strong predictor of MUO phenotype (OR: 3.79, 95%CI: 2.65-5.36, AUC: 0.797,  $p<0.05$ ) while conventional anthropometric indices (AUC: 0.454-0.546) perform poorly in the prediction of MetS among the obese children.

### **Conclusion**

A novel anthropometric index, VAI, is a better indicator for metabolic health in severely obese children as compared to traditional anthropometric indices such as BMI and WC. VAI may be used as a predictive marker to identify obese subjects at risk of developing metabolic syndrome and can therefore be applied clinically to direct obesity-related prevention and treatment strategies

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**KK 3**

**DAILY VERSUS MONTHLY ORAL VITAMIN D IN EQUIVALENT DOSES FOR TREATMENT OF SYMPTOMATIC VITAMIN D DEFICIENCY IN INFANTS: A RANDOMISED CONTROLLED TRIAL**

Anupriya Gora, Anju Seth, Ekta Debnath\*, Preeti Singh  
Departments of Pediatrics and \*Biochemistry, Lady Hardinge Medical College, New Delhi

**Background:**

Efficacy and safety of bolus doses of oral vitamin D in treatment of vitamin D deficiency in infants is not established.

**Objective:**

To compare the efficacy and safety of daily versus monthly oral vitamin D3 in treatment of symptomatic vitamin D deficiency in infants aged 1-12 months

**Methods:**

In this RCT, 111 infants with symptomatic vitamin D deficiency and serum 25OHD<20 ng/ml were randomised in two groups. Group A received 2000 IU/day vitamin D3 orally for 3 months and group B, 60,000 IU vitamin D3 orally bolus dose monthly for 3 months. Both groups received calcium 500 mg per day. Serum 25(OH)D, calcium, phosphate, alkaline phosphatase, PTH, urine Ca:Cr ratio and radiological score were assessed at baseline, 4 and 12 weeks. At the end of 12 weeks, 78 infants were available for final evaluation. Efficacy of two regimes was assessed comparing the proportion of subjects with complete normalisation of radiological score and normalisation of biochemical parameters. The safety of therapy was estimated by measuring frequency of hypercalcemia, hypercalciuria and hypervitaminosis D.

**Results:**

Both groups showed a significant rise in 25OHD levels from baseline to 4 and 12 weeks ( $P<0.001$  for both groups, both points of time). Subjects in group A had significantly higher levels as compared to group B at both 4 ( $p=0.012$ ) and 12 weeks ( $p<0.001$ ). Both regimens led to a significant increase in serum calcium and phosphate levels and a significant fall in serum ALP and PTH levels from baseline to 4 weeks and 12 weeks. There was no significant inter-group difference in these parameters at any assessment. By 12 weeks all patients had normalised the levels of these parameters. Eight patients (6 in group A, and 2 in group B) developed mild hypercalcemia without hypercalciuria at 12 weeks of treatment without any clinical symptoms which corrected spontaneously within a week.

**Conclusions:**

Both daily and monthly regimes of vitamin D3 are equally efficacious and safe for treatment of symptomatic vitamin D deficiency in infants. Daily therapy causes a more robust rise in serum 25OHD levels as compared to monthly dosing. Considering cost of therapy, and ease of administration, monthly regimen is a good option for treating vitamin D deficiency during infancy.

**KK 4**

## **CLINICAL SEVERITY PREDICTION IN CHILDREN WITH OSTEOGENESIS IMPERFECTA CAUSED BY COL1A1/2 DEFECTS**

Lin Yang, Feihong Luo  
Children's Hospital of Fudan University Children's Hospital of Fudan University

### **Introduction:**

Ninety percent of Osteogenesis imperfecta (OI) cases are caused by pathogenic variants in the COL1A1/COL1A2 gene. The Sillence classification describes four OI types with variable clinical features ranging from mild symptoms to lethal and progressively deforming symptoms.

### **Methods:**

We established a prediction model of the clinical severity of OI based on the random forest model with a training set was obtained from the Human Gene Mutation Database, including 790 records of the COL1A1/COL1A2 genes. The features used in the prediction model were respectively based on variant type features only and the optimized features.

### **Results:**

With the training set, the prediction results showed that the area under the receiver operating characteristic curve (AUC) for predicting lethal to severe OI or mild to moderate OI were 0.767 and 0.902 respectively when using variant type features only and optimized features for COL1A1 defects, 0.545 and 0.731 respectively for COL1A2 defects. For the 17 patients from our hospital, prediction accuracy for the patient with the COL1A1 and COL1A2 defects were 76.5% (95%CI: 50.1%-93.2%) and 88.2% (95%CI: 63.6%-98.5%), respectively.

### **Conclusion:**

We established an OI severity prediction model depending on multiple features of the specific variants in COL1A1/2 genes, with a prediction accuracy of 76% - 88%. This prediction algorithm is a promising alternative that could prove to be valuable in clinical practice.

## **REDUCTION IN SMOKING IN PREGNANCY A KEY CONTRIBUTOR TO REDUCTION IN PRESCHOOL OBESITY IN NEW ZEALAND**

Sarah Maessen, Wayne Cutfield, Jose Derraik, Barry Milne  
A Better Start National Science Challenge and Liggins Institute, University of Auckland

### **Background:**

In New Zealand one in three preschool children (<5 years of age) are overweight or obese, escalating to 54% in Pasifika children. Despite alarming rates of preschool obesity, remarkably in recent years we have shown this rate has progressively declined across the country for 10 years, which has not been reported in any other country<sup>1</sup>. This has occurred across all ethnicities, socioeconomic classes and regions in NZ<sup>2,3</sup>. This reduction in preschool obesity began between 2000 and 2010. The key question is what has occurred in NZ at a national level that led to this change. From the early 2000's NZ launched a strong anti-smoking campaign that included progressive tobacco taxation and from 2005 graphic hard-hitting anti-smoking TV advertisements.

### **Hypothesis:**

New Zealand's anti-smoking campaign is associated with a reduction in smoking in pregnancy which is associated with a reduction in preschool obesity.

### **Methods:**

The New Zealand Government's 22 national datasets are now all integrated (the Integrated Data Infrastructure). Data from four of these datasets were linked and analysed; national smoking records, the maternity health records, birth records and the Before School Health Check (4-5 year old children). Tobacco smoking data in pregnancy and lactation, birth weight, gestation, ethnicity and birth weight, together with BMI at 4-5 years of age were collected. BMI expressed as BMI SDS. Birth and childhood BMIs were adjusted for maternal BMI and childhood BMI for birth weight.

### **Results:**

Data was collected on 312,000 mother and child pairs nationwide. Smoking in pregnancy and lactation is still common in NZ. In Māori women 37% and in Pasifika 18% smoked in pregnancy compared to 9% in Europeans. In addition, smoking is more common in less affluent women. Importantly, there has been a dramatic reduction in smoking in NZ women of childbearing age between 2006-2018, most notably between 2006-2013 when the campaign was most active. Between 2006-2018 there was a major reduction in the percentage of regular smokers in women aged 15-39 years, from 53.5% in 2006 down to 14.8% in 2018. This reduction occurred across all ethnicities, most markedly in Māori and Pasifika women.

Smoking during pregnancy was associated with an increased risk of small for gestational age (birth weight <-2 SDS) newborns with risks for light (ORadjusted 3.2) medium (ORadjusted 4.2) and heavy smoking (ORadjusted 4.7). Evaluation of women who smoked in pregnancy only and postnatally only showed independent effects of SGA with ORadjusted of 2.3 and 2.6 respectively.

Smoking during pregnancy was associated with an increased risk of childhood obesity at 4-5 years of age with risks for light (ORadjusted 1.38) medium (ORadjusted 1.49) and heavy smoking (ORadjusted 1.6). Evaluation of women who smoked in pregnancy only and postnatally only showed independent effects of childhood obesity with ORadjusted of 1.35 and 1.44 respectively.

### **Conclusions:**

There has been reduction in smoking during pregnancy and lactation, both associated with a reduction in preschool overweight/obesity in NZ children. We speculate that the reduction in smoking in pregnancy has contributed to the fall in preschool obesity in NZ.

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## **YOUNG INVESTIGATOR AWARD**

YIA 1

Muhammad Muizz ABDUL MANAN

**PREVALENCE AND OUTCOME OF UNDER-NUTRITION IN CHILDREN REQUIRING HOSPITALIZATION IN MALAYSIA**

YIA 2

Hooi Peng CHENG

**OBESITY, METABOLIC SYNDROME AND BODY COMPOSITION AMONG CHILDREN AND ADOLESCENTS WITH CLASSIC CONGENITAL ADRENAL HYPERPLASIA IN MALAYSIA**

YIA 3

Yi Wen TING

**TRIGLYCERIDE TO HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO IS AN INDEPENDENT PREDICTOR OF LIVER FIBROSIS AMONG PAEDIATRICS NON-ALCOHOLIC FATTY LIVER DISEASE**

YIA 4

Nur 'Aini RAMAN

**HEALTH-RELATED QUALITY OF LIFE AMONG SURVIVORS OF CHILDHOOD CENTRAL NERVOUS SYSTEM TUMOUR FROM A SINGLE TERTIARY CENTER IN MALAYSIA**

YIA 5

Swee Im Ng VOON

**THE ACCEPTANCE AND USEFULNESS OF ADVANCED CARE PLAN DISCUSSION AMONG MALAYSIAN PARENTS OF CHILDREN WITH CEREBRAL PALSY**

## PREVALENCE AND OUTCOME OF UNDER-NUTRITION IN CHILDREN REQUIRING HOSPITALIZATION IN MALAYSIA

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<sup>b</sup>Department of Paediatrics, Faculty of Medicine, University Malaya, Kuala Lumpur.

### Background:

Undernutrition in hospitalized children, often leads to adverse outcome, is commonly under-recognized. Knowledge on the prevalence and outcome of undernutrition in hospitalized children in Malaysia is limited. We aimed to determine the prevalence and predisposing factors contributing to under-nutrition in children requiring hospitalization and the relationship between nutritional status on admission and outcome of hospitalization in Malaysia. We also analyzed the usefulness of STRONGkids tool in predicting the nutritional status in children requiring hospital care.

### Methods:

We conducted a prospective study in Hospital Tunku Azizah, Kuala Lumpur from August to November 2020. Anthropometric data were collected using a standardized protocol and compared with WHO growth standards for weight-for-age (WFA), weight-for-height (WFH)/BMI and height-for-age (HFA) z-scores. Malnutrition was defined based on WHO criteria of <-2 standard deviation score (SDS), acute malnutrition as z-score <-2 SDS for WFH/BMI, chronic malnutrition as HFA z-score < -2 SDS and underweight as z-score <-2 SDS for WFA. Patients were followed up during hospitalization to determine the following outcome: duration of stay, weight loss during hospitalization, admission to intensive care unit, discharged alive or death. Nutritional risk was assessed using STRONGkids tool on admission (score 0 to 5; a score of 4 and 5 considered high nutritional risk).

### Results:

Of the 406 children (age 6 months-5 years; median [IQR]: 36 [16,72] months) enrolled, overall prevalence of acute malnutrition, chronic malnutrition and underweight were 19% (n=77), 26.7% (n=109) and 27.9% (n=113), respectively. A younger age, Malay ethnicity, lower level of father's education, household income of ≤ RM 1500 and patients with an underlying chronic illness were significantly associated with malnutrition, while breastfeeding during infancy protected against malnutrition. Patients with chronic malnutrition and underweight were 14% and 10% more likely to stay 4 days in hospital, respectively. STRONGkids tool showed positive correlation ( $p < 0.01$ ) with acute malnutrition, chronic malnutrition and underweight. Patients with high nutritional risk score (4 or 5) had an 88% risk of having acute malnutrition and 82% risk of underweight and were more likely to stay longer (OR 3.69, 95% CI 2.12–6.42) and experienced weight loss (OR 3.72, 95% CI 1.27–10.89) in the hospital as well as more likely to require intensive care (OR 1.07, 95% CI 1.04 –1.1).

### Conclusions:

Malnutrition remains common in Malaysian children requiring hospital care. A younger age, Malay ethnicity, lower level of paternal education, low household income and presence of an underlying chronic illness were risk factors associated with malnutrition while breastfeeding protected against malnutrition. Children with chronic malnutrition and underweight stayed longer. STRONGkids tool correlated well with patient's nutritional status and outcome of hospitalization. We recommend the use of STRONGkids tool for early identification of children with undernutrition and to prevent complications associated with adverse outcome following hospitalization.

Keyword: Hospital Malnutrition, Malnutrition, STRONGKIDS tool.

## **OBESITY, METABOLIC SYNDROME AND BODY COMPOSITION AMONG CHILDREN AND ADOLESCENTS WITH CLASSIC CONGENITAL ADRENAL HYPERPLASIA IN MALAYSIA**

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### **Introduction:**

Children and adolescents with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency have been reported to be at higher risk of obesity (1). However, there are few studies which actively look into this or include analysis of body composition (2,3).

### **Objective:**

To analyse the incidence of obesity, dyslipidaemia, insulin resistance and hypertension in children and adolescents with CAH and its associated contributing factors. As the traditional surrogate to determine excess body fat by determining body mass index (BMI) has its limitation, bioelectrical impedance analysis (BIA) was used to assess body composition.

### **Method:**

A prospective study over 1 year was conducted in children and adolescents aged 6-18 years old with CAH. Anthropometric measurements was taken, followed by BIA measurement using Inbody 720. Metabolic screening including oral glucose tolerance test (OGTT) was performed on obese patients or age >10 years. Hypertension was defined using AAP 2017 guideline (4).

### **Results:**

46 patients (21 males, 45.7%, mean chronological age  $9.69 \pm 2.78$  years old) were recruited. There was no difference in mean hydrocortisone dosage in patients with salt-wasting (SW) and simple virilisers (SV) ( $14.14 \pm 1.86$  vs  $14.26 \pm 2.90$  mg/m<sup>2</sup>/day, p-value 0.868). 65.2% of the patients were in puberty (20 SW, 10 SV). Median serum 17-OHP level was 46.05nmol/L (range 4.68-244.48nmol/L).

The mean BMI of the whole group was  $19.77 \pm 4.05$ kg/m<sup>2</sup> ( $0.95 \pm 1.40$  SDS). 41.3% of patients (16 SW and 3 SV) was obese, which indicated a higher frequency of obesity among patients than reported for normal population (15.2%) in Malaysia (5). Another 6 patients (13%) were overweight. BMI SDS correlated with waist circumference (WC), hip circumference (HC), body-fat percentage (BFP), low-density lipoprotein (LDL) level, serum renin, bone age to chronological age ratio.

Through BIA, 19 patients were identified to have obesity based on BFP criterion of  $\geq 95$ th centile, of which 5 (26%) had normal BMI. Increased adiposity correlated with age, gender, duration of treatment, BMI SDS, WC, HC, total cholesterol, LDL level and bone age. All patients had high lean muscle mass, which correlated with the testosterone level ( $r = 0.589$ , p-value  $< 0.001$ ) and BMI SDS ( $r = 0.576$ , p-value  $< 0.001$ ).

3 (7%) patients had impaired glucose tolerance and 7(15%) dyslipidaemia. 10 (9 SW, 1 SV) (22%) were hypertensive and 11 (24%) were pre-hypertensive (8 SW, 3 SV). One patient fulfilled the criteria of metabolic syndrome. The youngest age of impaired glucose tolerance and dyslipidaemia were 7.8 and 8 years. There is a positive association between BFP and total cholesterol ( $r = 0.609$ , p-value 0.003), as well as BFP and LDL level ( $r = 0.672$ , p-value 0.001). There was no correlation found between hydrocortisone dose with BMI SDS, BFP, HOMA-IR or hypertension. This could be limited by the sample size.

### **Conclusion:**

The incidence of obesity, risk of metabolic syndrome and increased adiposity was high among children and adolescents with CAH. Metabolic impairments in CAH could begin at a young age. Healthy lifestyle interventions should be incorporated early in the management of all patients with CAH.

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## TRIGLYCERIDE TO HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO IS AN INDEPENDENT PREDICTOR OF LIVER FIBROSIS AMONG PAEDIATRICS NON-ALCOHOLIC FATTY LIVER DISEASE

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### Background:

Insulin resistance (IR), one of the key components of the metabolic syndrome, is recognised as the pathophysiological hallmark of non-alcoholic fatty liver disease (NAFLD) (1). Triglyceride to high-density lipoprotein cholesterol ratio (TG: HDL-C) has been validated as a promising surrogate of IR in various clinical studies (2-3). This study aims to investigate the relationship between surrogate markers of IR and the severity of NAFLD among overweight or obese children.

### Methods:

A total of 56 consecutive children aged 6 to 18 years old were recruited from the paediatric obesity and diabetes clinic in University Malaya Medical Centre (UMMC) from 2016 to 2019. Data on anthropometric measurements, clinical components of metabolic syndrome and fasting serum insulin were collected. Triglyceride to high-density lipoprotein cholesterol ratio (TG: HDL-C), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Single Point Insulin Sensitivity Estimator (SPISE) were calculated. The study population were stratified to three TG: HDL-C ratio tertile groups. Transient elastography was performed with hepatic steatosis and liver fibrosis assessed by controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), respectively.

### Results:

The mean age of our subjects was 13 years old. Sixty percent were males and 64.9% were ethnic Malays. A total of 44 children (78.6%) had liver steatosis and presence of significant liver fibrosis (stage F<sub>≥2</sub>) was detected in 20 children (35.7%). Majority (89.3%) are obese and 22 children (39.3%) were diagnosed with metabolic syndrome. Fourteen children (25%) were stratified to the first and third tertile group of TG: HDL-C ratio respectively, whereas 50% belongs to the second tertile group of TG: HDL-C ratio. Higher number of children with diabetes mellitus, metabolic syndrome and significant liver fibrosis were associated with higher tertiles of TG: HDL-C ratio ( $p < 0.05$ ). Top tertile of TG: HDL-C ratio was an independent predictor of liver fibrosis (OR = 8.14, 95% CI: 1.24 – 53.36,  $p = 0.029$ ). ROC analysis showed that the area under the curve (AUC) of HOMA-IR (0.77) and TG: HDL-C ratio (0.71) were greater than that of metabolic syndrome (0.69) and SPISE (0.22). The optimal cut-off values of HOMA-IR and TG: HDL-C ratio for detecting liver fibrosis among obese children with NAFLD are 5.20 and 1.58, respectively.

### Conclusion:

Obese children with NAFLD and higher TG: HDL-C ratio are more likely to have liver fibrosis. TG: HDL-C ratio is a promising tool to risk stratify those who are at risk of developing advanced liver disease.

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## HEALTH-RELATED QUALITY OF LIFE AMONG SURVIVORS OF CHILDHOOD CENTRAL NERVOUS SYSTEM TUMOUR FROM A SINGLE TERTIARY CENTER IN MALAYSIA

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### Introduction:

Survivors of childhood central nervous system (CNS) tumour experience significant late effects affecting their health-related quality of life (HRQOL) despite improvement in their survival rate. The current study aimed to 1) evaluate HRQOL among Malaysian childhood CNS tumour survivors, 2) determine socio-demographic, disease or treatment-related and behavioural factors that could affect the HRQOL of Malaysian childhood CNS tumour survivors.

### Methods:

Comparative cross-sectional study was conducted over 12 months (February 2020 - January 2021) on 46 survivors of childhood CNS tumour aged 5-18 years and 90 (age and gender-matched) survivors of childhood acute lymphoblastic leukaemia (ALL) who had completed treatment for at least one year were recruited at University Malaya Medical Centre. HRQOL was assessed using the Pediatric Quality of Life Inventory (PedsQL V4.0 and PedsQL Cancer Module V3.0). The PedsQL V4.0 scores were compared to scores from a previous cohort of healthy Malaysian children. Parents also completed questionnaires on child behaviour using Child Behaviour Checklist (CBCL). Multiple regression analysis was used to determine factors associated with low HRQOL.

### Results:

The mean PedsQL V4.0 total scale, physical health summary and psychosocial health summary scores of the CNS tumour survivors were 69.0 (SD 20.3), 68.7 (SD 27.9) and 69.2 (SD 19.2), respectively. The mean PedsQL V4.0 scores were significantly lower among CNS tumour survivors in all domains ( $p < 0.05$ ) especially teenagers compared with healthy children and ALL survivors. The median PedsQL Cancer Module V3.0 score of CNS tumour survivors was significantly lower than ALL survivors in total scale, cognitive problem and communication ( $p < 0.05$ ). Special education need was associated with lower total PedsQL V4.0 score (OR -22.91, 95% CI = -36.37 to -9.45,  $p = 0.001$ ), lower physical health summary score (OR -34.55, 95% CI = -55.09 to -14.00,  $p = 0.002$ ) and lower psychosocial health summary score (OR -16.83, 95% CI = -28.82 to -4.84,  $p = 0.007$ ). Physical impairment was associated with lower total PedsQL V4.0 score (OR -14.70, 95% CI = -24.93 to -4.47,  $p = 0.006$ ), lower physical health summary score (OR -18.86, 95% CI = -35.24 to -2.48,  $p = 0.025$ ) and lower psychosocial health summary score (OR -12.54, 95% CI = -21.65 to -3.43,  $p = 0.008$ ). Abnormal internalising CBCL score was associated with lower psychosocial health summary score (OR - 16.62, 95% CI = -28.32 to -4.92,  $p = 0.007$ ).

### Conclusions:

CNS tumour survivors in Malaysia reported lower HRQOL than ALL survivors and healthy children. Teenagers had significantly lower HRQOL compared to other age groups. Special education need, physical impairment, and internalising behavioural problems were associated with lower HRQOL. Clinicians need to be vigilant of HRQOL needs among CNS tumour survivors, especially those with special education need, physical impairment, and internalising behavioural difficulties. Physical and psychosocial interventions tailored to individual patient are essential to improve the HRQOL.

Key words: Central nervous system tumour, acute lymphoblastic leukaemia, survivors, quality of life

## YIA 5

### THE ACCEPTANCE AND USEFULNESS OF ADVANCED CARE PLAN DISCUSSION AMONG MALAYSIAN PARENTS OF CHILDREN WITH CEREBRAL PALSY

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#### Aims:

Advanced care plan (ACP) discussion is a process of discussion with the child and family to make early planning in anticipation of future medical needs of the child. The objectives of our study were to determine if parents of children with quadriplegic cerebral palsy (CP) can accept ACP discussions and evaluate possible factors that may influence parental acceptability to ACP; and if parents of children with quadriplegic CP perceive ACP discussions to be useful.

#### Methods:

Prospective pre- and post- ACP discussion questionnaire study for Malaysian parents of children with quadriplegic CP with Gross Motor Function Classification System (GMFCS) level 4 and 5 seen at 2 tertiary hospitals in Malaysia.

#### Results:

Sixty-nine patients with quadriplegic CP with GMFCS 4 and 5 were recruited into the study with 40 (58%) patients had at least one additional comorbidity. The median age of children recruited was 7.9 years (IQR: 5.1-11.5). Fifty-seven (82.6%) parents found the ACP discussion acceptable, and majority (88.4%-97.1%) of parents also found the ACP discussion useful. On multivariate analysis, parents who were comfortable to discuss about end-of-life care plans were more likely to find the ACP discussion acceptable (OR: 27.78, CI 2.9-265.1, p=0.004).

#### Conclusions:

The majority of Malaysian parents of children with quadriplegic CP found ACP discussion both acceptable and useful to them. Our study shows that parents need to be comfortable to discuss end-of-life plans for their child to enable the ACP discussion to be an acceptable experience. We recommend that ACP discussion should be part of the standards of care for children with quadriplegic CP.

## **OBESITY & METABOLIC SYNDROME**

FP 1.1

Ahreum KWON

**SLEEP TIMING IS ONE OF THE RISK FOR OBESITY IN ADOLESCENTS: KOREAN NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY VII**

FP 1.2

YAN Yaqin

**GUT MICROBIOTA MEDIATES INSULIN RESISTANCE OF CATCH-UP GROWTH IUGR RATS**

FP 1.3

Hye Jin LEE

**RELATIONSHIP OF THE BISPHENOL A SUBSTITUTES, BISPHENOL F AND BISPHENOL S, WITH ADIPONECTIN/LEPTIN RATIO AMONG SCHOOL-AGE CHILDREN; FROM THE ENVIRONMENT AND DEVELOPMENT OF CHILDREN (EDC) COHORT**

FP 1.4

Hae Woon JUNG

**THE RELATIONSHIP OF EARLY ADIPOSITY REBOUND WITH ACCELERATED BONE AGE AND BREAST DEVELOPMENT IN GIRLS: A PROSPECTIVE COHORT STUDY**

FP 1.5

Xin YUAN

**THE CHARACTERISTICS OF GUT MICROBIOTA OF OBESE CHILDREN WITH DIFFERENT DEGREES AND ITS CORRELATION WITH GLUCOSE METABOLISM INDEXES**

## FP 1.1

### **SLEEP TIMING IS ONE OF THE RISK FOR OBESITY IN ADOLESCENTS: KOREAN NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY VII**

Ahreum KWON

Junghwan Suh HyunwookChaeHae InLeeMyeongseob Lee Ho-Seong Kim

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#### **Background:**

Short sleep duration is an important factor for obesity and metabolic diseases. However, there is few research on the link between bedtime and obesity, although short sleep duration is related to late bedtime. In this study, we investigate whether bedtime is associated with obesity in adolescents.

#### **Participants:**

Subjects were 1,257 adolescents, aged 12-18 years old, who participated in the Korean National Health and Nutrition Examination Survey VII, conducted between 2016 and 2018.

#### **Measurements and Results:**

Subjective sleep time and rise time were evaluated as a risk factor for obesity. Bedtime and wake-up time were self-reported. Anthropometric measurements, a questionnaire about lifestyle including food intake and physical activity, and biochemical laboratory measurements were conducted. The subjects were classified by gender, middle and high school students. Mean bedtime and wake-up time were 23:42 and 06:24, respectively. According to the analysis of the obesity rate by dividing the bedtime by one hour, the later the bedtime, the higher the obesity rate in boys and high school girls overall. Especially, the risk of obesity increased by 10.37 times if they went to bed after 24:00, based on sleeping between 22:00 to 23:00 in middle school boys, and it also increased by 8.47 times if the bed time is after 01:00 based on sleeping between 23:00 to 24:00 in high school girls. However, in middle school girls, obesity rate decreased as they went to bed late, although it increased again when the bedtime was after 1:00 a.m.

#### **Conclusions:**

**Late bedtime increases the risk for obesity in adolescents. Therefore, it is important to go to bed early for adolescent health.**

## GUT MICROBIOTA MEDIATES INSULIN RESISTANCE OF CATCH-UP GROWTH IUGR RATS

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### Objective:

Catch-up growth intrauterine growth retardation (CG-IUGR) individuals have a higher risk developing insulin resistance, T2DM and metabolic syndrome. Gut microbiota exerts significant influence on metabolic functions of human. The aim of the paper was to explore whether gut microbiota participate in CG-IUGR rats insulin resistance and its possible treatment.

### Methods:

CG-IUGR rats model was established and body weight was measured weekly. At 8 weeks, the feces were collected and microbiota analysis was performed by 16S rRNA gene sequencing. Glucose tolerance test (GTT) and insulin tolerance test (ITT) were carried out by intraperitoneal glucose injection (2g/kg of weight) and insulin (0.75U/kg of weight) respectively to assess insulin sensitivity. Then, faecal microbiota transplantation (FMT) was performed to detect the role of gut microbiota in CG-IUGR rats insulin resistance.

### Results:

Compared with the control pups, the birth weight of IUGR pups was decreased ( $P < 0.001$ ). There was no significant difference in body weight between control and IUGR at 3 weeks. Then, the weights of CG-IUGR pups were significantly higher than those of control. At 8 weeks, GTT shown the glucose levels at 15min and 30min were higher in CG-IUGR, and the area of under curve (AUC) of GTT in CG-IUGR rats was significantly higher than in control rats ( $P < 0.001$ ). ITT demonstrated the glucose levels at 90min and 120min were higher in IUGR and the AUC of ITT in CG-IUGR rats was significantly higher ( $P < 0.05$ ). CG-IUGR rats shown lower Chao1 index and Shannon index ( $P < 0.05$ ) in comparison with the control rats. PCoA analysis shown an apparent cluster of the gut microbiota structures between groups. At the phylum level, compared with the control group, CG-IUGR rats shown decreased relative abundance of Bacteroidetes ( $P < 0.05$ ) and increased relative abundance of Proteobacteria ( $P < 0.05$ ). At the genus level, the relative abundance of the dominant taxa *Alloprevotella* in CG-IUGR rats was decreased compared with control rats ( $P < 0.05$ ). After FMT, there were four groups including control-FMT-control, control-FMT-IUGR, IUGR-FMT-control and IUGR-FMT-IUGR. GTT demonstrated control-FMT-IUGR rats glucose levels at 30min and 60min were higher than those in control-FMT-control rats and the AUC of GTT was higher in control-FMT-IUGR rats ( $P < 0.001$ ); similarly, the glucose levels at 90min and 120min in IUGR-FMT-IUGR rats were higher than those in IUGR-FMT-control rats and the AUC of GTT was higher in IUGR-FMT-IUGR rats ( $P < 0.05$ ). Besides, the AUC of ITT in control-FMT-IUGR rats was significantly higher than in control-FMT-control rats ( $P < 0.05$ ) and the glucose levels at 90min and 120min in IUGR-FMT-IUGR rats were higher than those in IUGR-FMT-control rats and the AUC of ITT was higher in IUGR-FMT-IUGR rats ( $P < 0.05$ ).

### Conclusion:

Gut microbiota might regulate insulin resistance in CG-IUGR rats and FMT can improve insulin sensitivity of CG-IUGR rats.

**RELATIONSHIP OF THE BISPHENOL A SUBSTITUTES, BISPHENOL F AND BISPHENOL S, WITH ADIPONECTIN/LEPTIN RATIO AMONG SCHOOL-AGE CHILDREN; FROM THE ENVIRONMENT AND DEVELOPMENT OF CHILDREN (EDC) COHORT**

Hye Jin Lee, Yun-Chul Hong, Yun JeongLee, Hwa YoungKim, Youn-Hee Lim, Bung-Nyun Kim, Johanna Inhyang Kim, Choong Ho Shin, Young Ah Lee  
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**Background:**

Bisphenol A (BPA) is known as a possible obesogenic endocrine disruptor. Bisphenol S (BPS) and bisphenol F (BPF) are BPA substitutes that recently replaced BPA because of its adverse health effects. Previous studies suggest that BPA is related to adipokines such as adiponectin and leptin. However, data on BPA and adipokines in children are limited and there are no reports of the relationship between BPS or BPF with adipokines. We aimed to investigate the association between urine bisphenols (BPA, BPS and BPF) with adiposity and serum adiponectin, leptin, and adiponectin/leptin ratio (A/L ratio) in 6 and 8-year-old children.

**Methods:**

In this cross-sectional study, data of the 6- and 8-year-old children from the Environmental and Development of Children cohort study were used. A total of 561 children (482 children aged 6 years and 516 children aged 8 years) who visited during 2015-2019 were included. Urinary BPA levels were log-transformed, BPS levels were categorized into three groups (non-detected, lower half, higher half of detected) and BPF levels were categorized into two groups (non-detected and detected). The associations between urinary BPA, BPS and BPF with obesity, BMI z-score, fat mass (%), serum adiponectin, leptin, and A/L ratio were analyzed by repeated-measure analysis using linear mixed models.

**Results:**

Urinary BPS higher half group had higher fat mass (%) ( $\beta = 0.055$ ,  $P < .001$ ), lower adiponectin concentration ( $\beta = -0.102$ ,  $P < .001$ ) and lower A/L ratio ( $\beta = -0.107$ ,  $P < .001$ ) compared with the non-detected group. Urinary BPF detected group had lower serum adiponectin concentration ( $\beta = -0.135$ ,  $P < .001$ ) and A/L ratio ( $\beta = -0.155$ ,  $P < .001$ ) compared with the non-detected group. BPA did not show significant association with BMI Z-score, body fat, or adipokines.

**Conclusion:**

Potential adverse health effects of BPS and BPF on adipokines are found. Urine BPS level is associated with fat mass, BPS and BPF detection is associated with lower serum adiponectin concentrations and A/L ratio in 6 and 8-year-old children.

## FP 1.4

### THE RELATIONSHIP OF EARLY ADIPOSITY REBOUND WITH ACCELERATED BONE AGE AND BREAST DEVELOPMENT IN GIRLS: A PROSPECTIVE COHORT STUDY

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#### Introduction:

Adiposity rebound (AR) refers to the increase in body mass index (BMI) that follows the BMI nadir in childhood. Earlier AR increases the likelihood of being overweight/obese, leading to early pubertal advancement, especially in girls. We aimed to evaluate bone age (BA) progression and breast development in relation to AR timing in girls.

#### Methods:

Among 250 girls of the Environment and Development of Children cohort study, 212 girls who visited at 8 years had BMI measurements available for determination of AR timing. After excluding preterm and multiple births, 176 girls were classified into early (<3.9yrs; n=25, 14%), average (3.9-5.9yrs; n=44, 25%) or late (≥6yrs; n=107, 61%) AR groups. BA and pubertal examination at the 2, 4, 6, and 8yr visits were evaluated. Outcomes in anthropometric measures, BA, and breast development were analyzed according to AR timing, with adjustment for age, gestational age, birthweight, physical activity and diet.

#### Results:

At age 2 years, there were no differences in anthropometric measures. By age 4 years, the early AR group showed higher mean BMI z-scores (1.04) than both average (-0.24) and late (-0.24) groups (p=0.001, for both), with significant differences between all groups at 6 and 8 years. Height differences were seen after 6 years, with greater height z-scores in the early AR group compared to late AR (0.71 vs. 0.21 at 6yrs; 0.94 vs. 0.31 at 8yrs, p<0.05 for both). BA progression showed a similar pattern: the early AR group had advanced BA compared to late AR (6.9 vs. 6.6) at 6 years and both average (9.7 vs. 8.9) and late AR (9.7 vs. 8.5) at 8 years (p< 0.05, for all). The associations between AR timing and BA remained significant after adjusting for covariates (B= -6.474, P < 0.001 for 8yr BA). Breast development at age 8 years increased with earlier AR timing: late (n=16, 15%), average (n=15, 34%), early AR (n=12, 48%) (P for trend <0.001). The risk of breast development was increased in early AR (OR 5.0, 95%CI 1.6-13.5) and average AR (OR 2.6, 95%CI 1.1-6.2) groups, after adjusting for covariates.

#### Conclusions:

By 8 years of age, girls with early AR showed greater height, weight, BMI and BA than those with average or late AR. The risk for early breast development was higher with early or average AR, than late AR. AR timing may be a predictor for BA progression and onset of breast development in girls. The EDC study was supported by the Ministry of Environment through the Environmental Health Center Program of the Republic of Korea.

## THE CHARACTERISTICS OF GUT MICROBIOTA OF OBESE CHILDREN WITH DIFFERENT DEGREES AND ITS CORRELATION WITH GLUCOSE METABOLISM INDEXES

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### Objective:

Studies have shown that there may be differences in the gut microbiota of obese children with different degrees. This study aims to determine the characteristics of the gut microbiota of children with different degrees of obesity, and to explore the relationship between the gut microbiota and glucose metabolism indexes.

### Method

A total of 89 children aged 5 to 15 who were admitted to the Fuzhou Children's Hospital of Fujian Medical University from January 2017 to September 2018 were collected. According to the body composition test results, body fat content (BF%)  $\geq 30\%$  was defined as obesity, boys BF  $\geq 35\%$ , and girls BF  $\geq 40\%$  are defined as severe obesity; fasting venous blood in the morning is taken to test fasting blood glucose (FPG), fasting insulin (FINS) levels. The characteristics of gut microbiota were studied by 16S rDNA microbiome analysis. Spearman correlation was used to analyze the correlation between gut microbiota and FPG and FIN..

### Result

The age range of 89 participants was 5.5 to 14.2 years, with an average of  $9.75 \pm 1.92$  years. According to BF%, 89 subjects were divided into normal weight (NW) group ( $n = 29$ ), mild obesity group ( $n = 27$ ) and severe obesity group ( $n = 33$ ). The BMI and waist-to-height ratio (WHtR) of the severe obesity group were significantly higher than those of the mild obesity group (all  $P < 0.05$ ). LefSe analysis showed that phylum Fusobacteria, class Fusobacteriia, order Fusobacteriales and genus Alistipes in the mild obesity group were significantly higher than those in the severe obesity group. In the severe obesity group, the relative abundance of family Carnobacteriaceae, genus Granulicatella and Clostridium was significantly higher ( $p < 0.05$ ). Spearman's correlation analysis showed that for the mild obesity group, FPG was positively correlated with phylum Tenericutes, genus Alistipes, Megamonas, Oscillospira, and negatively correlated with phylum Verrucomicrobia, genus Akkermansia. FINS was negatively correlated with phylum Firmicutes, genus Fusobacterium. For severely obese people, FPG was negatively correlated with genus Gemmiger, and positively correlated with genus Paraprevotella.

### Conclusion

Different degrees of obese children have different gut microbiota, and metabolism-related bacteria may be involved in the occurrence of abnormal glucose metabolism in obese children.

## **GROWTH**

FP 2.1

Liu-Lu XIE

**ADENOHYPHYSAL HYPERFUNCTION IN CHILDREN AND ADOLESCENTS WITH MCCUNE-ALBRIGHT SYNDROME**

FP 2.2

Myeongseob LEE

**EFFICACY OF BISPHOSPHONATE TREATMENT IN PEDIATRIC PATIENTS WITH OSTEOPOROSIS DUE TO IMMOBILIZATION**

FP 2.3

Masanobu FUJIMOTO

**PAPP-A2 PARTIALLY REGULATES CORD BLOOD IGF-1, IGFBPS LEVELS, AND BODY SIZE IN NEWBORNS**

FP 2.4

Min Jae KANG

**THE CHARACTERISTICS OF DNA METHYLATION PATTERN IN CHILDREN BORN SMALL FOR GESTATIONAL AGE WHO FAILED TO CATCH-UP GROWTH**

FP 2.5

Han Saem CHOI

**EFFECT OF LONG-ACTING GROWTH HORMONE (GH) TREATMENT ON ENDOGENOUS GH SECRETION IN PREPUBERTAL PATIENTS WITH IDIOPATHIC SHORT STATURE**

## FP 2.1

### ADENOHYPOPHYSEAL HYPERFUNCTION IN CHILDREN AND ADOLESCENTS WITH MCCUNE-ALBRIGHT SYNDROME

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#### Background:

McCune-Albright Syndrome(MAS) is a rare disease caused by somatic gain-of-function mutations of the GNAS gene, presenting with fibrous dysplasia, cafe-au-lait spots and gonadotropin-independent precocious puberty, and other multiple hyperfunctioning endocrinopathies. Adenohypophyseal hyperfunction is reported uncommon but potentially severe complication of MAS.

#### Method:

A retrospective study was performed to evaluate the prevalence of the pituitary hyperfunction syndromes and the clinical characteristics as well as the treatments in children and adolescents with MAS.

Data was collected from pediatric patients diagnosed as MAS in Pediatric department of The first affiliated hospital of Sun Yet-sen University from 2002 to 2019.

#### Result:

1. From 2002 to 2019, 175 MAS cases were diagnosed in our department. all were girls, with the chief complaints of breast development, vaginal bleeding or vaginal discharge. Within these cases, 15(8.6%) patients had the pituitary hyperfunctions. The onset age was 1.83 (0.58-7.67) years of age, and the visiting age was 4.00 (0.75-8.17) years of age. In this 15 patients, 7 girls(46.6%) were typical type, 7 cases (46.6%) had cafe-au-lait spots accompanied with precocious puberty, and only 1(6.8%) just had isolated precocious puberty.

2. In the 15 patients with adenohypophyseal hyperfunction, 5 cases had GH excessive accompanied with hyperlactinemia, while 8 girls had hyperlactinemia only, and 2 had isolated excessive GH secretion. In cases with excessive GH secretions, the fasting GH levels were 1.02ug/L-22.28ug/L, and the standard deviation scores (SDS) of serum levels of IGF-1 were 2.17(-0.9-3.85SD). The GH levels after oral glucose tolerance tests were 0.97ug/L-20.56 ug/L. The serum PRL levels in girls with hyperlactinemia ranged from 42.85ng/ml-1036ng/ml. But only 3 patients were confirmed pituitary adenomas by MRI scans, in whom 2 girls were macro-adenomas, 1 was micro-adenomas. 7 patients had pituitary hyperfunctions also had other endocrinopathies: 4 had hypercortisolism and 3 had thyroid abnormalities.

3. In patients with hyperlactinemia, only 3 who accompanied with GH excess occurred lactation, and two of them had been found pituitary adenomas. The first one was typical MAS and had elevated levels of PRL since 4.5 years of age, but had lactation, over growth as well as facial asymmetric at 14.33 years of age. The second one had normal pituitary functions at the first visiting age, but had hyperlactinemia and lactation when she was 9.42 years old. The other one was non-typical MAS, had lactation but normal MRI scans of the pituitary.

4. All accepted letrozole or tamoxifen treatment for the GnRH independent precocious puberty. In the 3 patients who had lactation, Bromocriptine was combined. GH and PRL levels decreased in 2 cases after treatment but still fluctuated. In the girl who had overgrown, the PRL and GH levels remained elevated under the treatment of bromocriptine combined with Octreotide, and finally transsphenoidal pituitary tumor resection was performed, but the GH remained abnormal and octreotide therapy still needed.

#### Conclusion:

1. Adenohypophyseal hyperfunctions is not a rare complication in children or adolescents MAS, no matter symptomatic or not, and it is more common in patients with clinical trait or combined with FD.

2. Although adenomas can be found by the MRI scans, other findings includes normal or adenohypophyseal hyperplasia can also present in children or adolescents. And the status of hyperfunction can be variable, from mild to severe, along with age. Therefore, long-term follow up of the pituitary function is essential in the cases with high risk, even though no clinical manifestations presented or only negative findings by MRI scans.

3. Hyperlactinemia can be corrected by bomocriptine in children, however, in those accompanied with GH excessive, it may be less effective and other therapy may be needed.

## EFFICACY OF BISPHOSPHONATE TREATMENT IN PEDIATRIC PATIENTS WITH OSTEOPOROSIS DUE TO IMMOBILIZATION

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### Introduction:

Osteoporosis is medical condition commonly associated with immobilization in children, which can lead to a vicious cycle of disability, worsening osteoporosis, and recurrent fractures. Currently, bisphosphonates are widely used as a standard therapy in children with osteoporosis, but there are limited data on efficacy according to its dosage and duration. We aimed to evaluate efficacy of bisphosphonate treatment according to the dosage and duration in pediatric patients with osteoporosis due to immobilization.

### Method:

We reviewed medical records of pediatric patients who were diagnosed with osteoporosis due to immobilization rated as Gross Motor Function Classification System (GMFCS) grade V, and who received bisphosphonate therapy with regular check-up for at least 1 year. The dosage and duration of the treatment, biochemical laboratory measurements, data of bone densitometry, and the occurrence of side effects were collected.

### Results:

Subjects were 21 children. The average duration of bisphosphonate treatment was  $2.0 \pm 0.9$  years, and mean cumulative dose per body weight of bisphosphonate was  $7.7 \pm 2.5$  (mg/kg/year). After the treatment, mean lumbar spine bone mineral contents (BMC) significantly increased from  $14.20 \pm 8.58$  (g) to  $19.38 \pm 9.89$  (g) ( $p < 0.05$ ), lumbar spine bone mineral density (BMD) significantly increased from  $0.40 \pm 0.14$  (g/cm<sup>2</sup>) to  $0.49 \pm 0.14$  (g/cm<sup>2</sup>) ( $p < 0.05$ ), and height-adjusted lumbar spine BMD Z-score also showed improvement from  $-2.66 \pm 1.66$  to  $-1.66 \pm 1.38$  with statistical significance ( $p < 0.05$ ). The cumulative dose and the duration of treatment were not related to its efficacy, but increasing average dose per body weight in each cycle (mg/kg/cycle) showed significant effects on increasing change in height-adjusted lumbar spine BMD z-score ( $\beta = 1.065$ ,  $p < 0.05$ ).

### Discussion:

BMC, BMD, and height-adjusted BMD z-score significantly increased after bisphosphonate treatment in pediatric patient with osteoporosis due to immobilization. Independent of cumulative dosage and duration, the efficacy of bisphosphonate treatment increased significantly as average dose per body weight in each cycle increased. Further studies with sufficient number of subjects and long term follow-up observation are needed.

## FP 2.3

### **PAPP-A2 PARTIALLY REGULATES CORD BLOOD IGF-1, IGFBPS LEVELS, AND BODY SIZE IN NEWBORNS**

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#### **Background:**

Neonatal anthropometric data for gestational age provides beneficial information to estimate fetal growth and well-being. As exemplified by defects in the IGF-1 receptor (IGF1R) resulting in neonates born small for gestational age (SGA) (1), the IGF axis plays an essential role in fetal growth. While some components of this axis have been evaluated using umbilical cord blood (2), little is known about the underlying mechanisms regulating free IGF-1 via pregnancy-associated plasma protein-A2 (PAPP-A2), a metalloproteinase that cleaves IGFBP-3 and -5, in cord blood and their relation to fetal growth (3,4). We examined IGF-1, IGFBPs, and PAPP-A2 levels in cord blood and explored association among the analytes as well as birth weight (BW) and length (BL).

#### **Methods:**

Twenty-three neonates (gestational age of 32-41 weeks) born at Tottori University Hospital were recruited for this case-control study. Neonates corresponding to the following criteria were excluded: known genetic diseases, severe asphyxia, and diabetic mother on insulin. Written informed consent was obtained from the parent(s) / legal guardian(s). PAPP-A2, free and total IGF-1, intact and total IGFBP-3, and total IGFBP-5 were measured in umbilical cord blood by ELISA. Association between BW and BL and each analyte was analyzed using R. The study was reviewed and approved by the institutional review board at Tottori University Hospital.

#### **Results:**

The demographic characteristics of the 23 neonates (M/F = 12/11, 37.7 weeks of gestation (median)) were as follows: BW SDS, -0.39 [IQR; -0.86 – 0.27]; BL SDS, -0.78 [-1.31 – -0.15]; head circumference SDS, -0.06 [-0.06 – 0.06]. Of the 23 subjects, only 3 were born SGA. Throughout the gestation period, PAPP-A2 levels in cord blood consistently decreased, while intact and total IGFBP-3 levels increased. PAPP-A2 levels associated positively with percent free IGF-1 ( $r = 0.56$ ;  $P < 0.05$ ) and negatively with intact IGFBP-3, BL, and BW ( $r = -0.54, -0.40, -0.45$ ;  $P < 0.05$ ). Free IGF-1 levels associated negatively with intact / total IGFBP-3. Intact IGFBP-3 and IGFBP-5 levels associated positively with BW ( $r = 0.54, 0.44$ ,  $P < 0.05$ ).

#### **Conclusions:**

We observed a significant association between cord blood PAPP-A2 and percent free IGF-1 as well as neonate size. This suggests that PAPP-A2, by cleaving intact IGFBP-3 and increasing percent free IGF-1, may act to compensate for low free IGF-1 in growth-restricted fetuses. These findings need to be further evaluated in a setting with more subjects.

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## THE CHARACTERISTICS OF DNA METHYLATION PATTERN IN CHILDREN BORN SMALL FOR GESTATIONAL AGE WHO FAILED TO CATCH-UP GROWTH

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### Introduction:

DNA methylation is one of major mechanisms of epigenetic mutation. Differentially methylated regions (DMRs) are found in various imprinting disorders. In this pilot study, we aimed to analyze DNA methylation pattern of short stature children born small for gestational age (SGA-SS).

### Method:

SGA-SS subjects were included when all the following criteria were met: birth weight  $\leq$  3 percentile; height z-score after age 4  $\leq$  -1.881 (3 percentile); both parental heights  $>$  -1.881 (3 percentile). When the age of subjects were 4.0-7.5 years, they were sorted into SGA-SS group 1 (n=17). Normal control (NC) was age- and sex-matched to SGA-SS group 1 (n=11). NC subjects were normal birth weight ( $>$ 10 percentile) and normal stature ( $>$  10 percentile). When the height z-score after age 4  $<$  -2.5, they were sorted into SGA-SS group 2. DNA methylation patterns of IGF2, H19, PLAG1, MEG3, MEST, SGCE-PEG10, KvDMR genes were performed by pyrosequencing.

### Result:

Mean birth weight and height z-score of NC was 3.3 kg and 0.60, respectively. Mean birth weight SDS and height z-score of SGA-SS group 1 was -2.37 and -2.08, respectively. Mean birth weight SDS and height z-score of SGA-SS group 2 was -2.60 and -2.98, respectively and birth weight was not significantly different compared to that of SGA-SS group 1. Mean DNA methylation levels of IGF2/H19/PLAG1/MEG3/MEST/SGCE-PEG10/KvDMR gene were 58.0/46.8/44.4/55.0/53.2/45.4/48.7%, 55.1/38.2/45.6/53.1/50.6/42.8/47.1%, and 54.4/42.7/45.0/53.6/51.8/44.7/46.3 % in NC, SGA-SS group 1, and SGA-SS group 2, respectively. DNA methylation levels of SGA-SS group 1 were decreased in IGF2 (P=0.027), MEST (P<0.001) compared to those of NC. There was difference of DNA methylation levels of MEST between SGA-SS group 1 and SGA-SS group 2 (P=0.013).

### Conclusion:

DNA methylation levels of SGA-SS groups were different in several candidate genes related to fetal growth compared to those of NC. Although the mechanism of epigenetic mutation is diverse, DNA methylation pattern may have the role in pathophysiology and heterogeneity in SGA children.

## **EFFECT OF LONG-ACTING GROWTH HORMONE (GH) TREATMENT ON ENDOGENOUS GH SECRETION IN PREPUBERTAL PATIENTS WITH IDIOPATHIC SHORT STATURE**

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### **Background**

Since recombinant human growth hormone (GH) had been developed, the efficacy of daily GH for the treatment of short stature has been well established. However, daily GH injections may impose a heavy burden affecting compliance, long-acting GH (LAGH) preparations are currently being developed to improve adherence by decreasing the injection frequency. This study investigated the effects of LAGH on nocturnal endogenous GH secretion and metabolic consequences after 12 months of treatment in patients with ISS.

### **Methods**

This study prospectively enrolled 9 Korean prepubertal patients with ISS diagnosed at Yonsei University Severance Children's Hospital, between January 2018 and January 2019. Once-weekly LAGH (0.7 mg/kg/week, n=4) or daily GH (0.37 mg/kg/week, n=5) were administered for 12 months to the subjects. Nocturnal endogenous GH secretory profiles (mean serum GH concentrations, frequency, amplitude, interpulse interval of spontaneous GH secretory bursts, and mass of GH released per secretory burst) obtained from 12 hour blood samples at 30 min intervals were assessed at baseline and 2 weeks after the completion of GH treatment. Posttreatment changes in height velocity (HV), height SDS, metabolic parameters, and adverse events were measured.

### **Results**

Nocturnal endogenous GH secretory profiles, such as mean serum GH concentrations, frequency, amplitude, interpulse interval of spontaneous GH secretory bursts, and mass of GH released per secretory burst of the LAGH and daily GH groups were similar at baseline and after 12-month treatment. Furthermore, endogenous GH secretory profiles after GH treatment did not differ from those at baseline in both groups. The efficacy and safety after LAGH treatment for 12 months were similar to that of daily GH.

### **Conclusion**

12 months treatment with LAGH in patients with ISS does not suppress nocturnal endogenous GH secretion or lead to metabolic derangement. The efficacy and safety of LAGH are comparable to those of daily GH.

## **PUBERTY**

FP 3.1

Young Ah LEE

**CLINICAL AND GENETIC FEATURES OF FAMILIAL HYPERCHOLESTEROLEMIA IN KOREAN CHILDREN**

FP 3.2

Kristy TIAN

**APPLYING ASIAN-SPECIFIC CRITERIA TO DISTINGUISH MONOGENIC DIABETES FROM TYPE 1 AND TYPE 2 DIABETES**

FP 3.3

Gamage D S

**A RARE PRESENTATION OF PEUTZ - JEGHER SYNDROME IN CHILDREN**

FP 3.4

HUYNH Thi Chi Lan

**EFFECT OF GONADOTROPIN-RELEASING HORMONE AGONISTS TREATMENT IN VIETNAMESE CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY**

FP 3.5

Hyo-Kyoung NAM

**SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR-A LEVELS ACCORDING TO PUBERTAL STATE IN GIRLS**

## CLINICAL AND GENETIC FEATURES OF FAMILIAL HYPERCHOLESTEROLEMIA IN KOREAN CHILDREN

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### Background:

Early identification and management of familial hypercholesterolemia (FH) is warranted in childhood, however, it remains underrecognized. We investigated clinical and genetic features of FH and analyzed predictors to identify pathogenic variant-positive patients in Korean children with FH.

### Methods:

A total of 53 children (14 boys; mean 7.4 years at diagnosis) with clinical FH were enrolled between May 2020 and December 2020 from Seoul National University Children's Hospital. Data on anthropometrics, xanthoma or arcus cornealis, family history of hypercholesterolemia or atherosclerotic cardiovascular disease (ASCVD), and lipid profile were collected. Genetic analysis was performed using targeted gene sequencing including 32 genes.

### Results:

We identified pathogenic variants in 17 cases (32.1%): 13 with LDLR heterozygote, 1 with PCSK9 heterozygote, and 3 with ABCG8 compound heterozygote. At diagnosis, variant-positive group was younger (6.4 vs. 8.9 years,  $p < 0.001$ ) and had lower body mass index z-scores (-0.9 vs. 0.1,  $p = 0.019$ ) compared to variant-negative group. Tendon xanthoma was found in 4 (7.5%), who were all variant-positive group. None had arcus cornealis. Family history of premature ASCVD was more frequently detected in variant-positive group (41.2 % vs. 5.6%,  $p = 0.003$ ). Variant-positive group had higher total cholesterol (291 vs. 228 mg/dL,  $p < 0.001$ ) and LDL-cholesterol (LDLC) levels (226 vs. 161 mg/dL,  $p < 0.001$ ) than variant-negative group at diagnosis. There were no differences in triglyceride, HDL-cholesterol, or lipoprotein(a) levels. Lipid-lowering therapy was prescribed in 24 (45.3%; 18 with statin, 3 with ezetimibe, and 3 with cholestyramine), with higher prevalence in variant-positive group (76.5% vs. 30.6%,  $p = 0.005$ ). When multivariate logistic regression analysis was performed, LDLC levels at diagnosis was an independent predictor to identify pathogenic variants (OR=1.03,  $p = 0.014$ ). The optimal cutoff value of LDLC to identify pathogenic variant carriers was 192 mg/dL with area under the receiver operating characteristics curve as 0.850.

### Conclusion:

Pathogenic variants were found in 32.1% of Korean children with clinical FH, and LDLR mutation was most common. LDLC level at diagnosis was an independent predictor to identify pathogenic variant-positive children, and the best LDLC threshold was 192 mg/dL.

## FP 3.2

### APPLYING ASIAN-SPECIFIC CRITERIA TO DISTINGUISH MONOGENIC DIABETES FROM TYPE 1 AND TYPE 2 DIABETES

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#### Background

Monogenic diabetes (MD) is a rare heterogeneous group of autosomal dominant disorders resulting in beta-cell dysfunction. Selecting individuals for MD testing in Caucasian populations is based on age of onset of diabetes (<35 years old), need for insulin within 6 months, parental history of diabetes, and body mass index (BMI) (Shields et al., 2012). Yet thresholds should differ between populations (Misra et al., 2016), given the lower age and lower BMI at onset of type 2 diabetes (T2D), the high percentage of parental history of T2D in Asians (Rama Chandran et al., 2018), and the much lower incidence of type 1 diabetes (T1D) (Atkinson, Eisenbarth & Michels, 2014; Lee, 2000). In this pilot study, we aimed to look at the yield from applying Asian-specific criteria in distinguishing MD from T1D and T2D subtypes.

#### Methods

Subjects were selected from the paediatric endocrinology department in National University Hospital and endocrinology department in Singapore General Hospital using the following criteria: Diabetes diagnosed  $\leq 1$  year or  $\leq 35$  years with BMI  $\leq 23$  kg/m<sup>2</sup> and negative for GAD antibody (GADAb). DNA from 27 subjects was retrieved, and next generation gene sequencing (Illumina MiSeq) with an enriched targeted resequencing panel (Nextera rapid capture) for 30 known monogenic diabetes genes was performed. Variant annotation was performed through our in-house bioinformatics pipeline (CAP and EQA certified) and according to ACMG guidelines.

#### Results

6 of 27 (22%) individuals sequenced positive (Table 1). There was a high percentage of parental history of diabetes (85%) in the adult group. In this group, sequence-positive subjects tended to have lower BMI (18.0 vs. 20.9 kg/m<sup>2</sup>,  $p=0.01$ ) and were older at diagnosis (23.2y vs 17.1y,  $p=0.09$ ).

2 of 5 (40.0%) sequence-positive subjects and 15 of 22 (68.2%) sequence-negative subjects required insulin therapy within 12 months after diagnosis, with no significant difference in insulin use between groups ( $p>0.05$ ). Amongst insulin users in sequence-positive subjects, C-peptide was clearly present ( $>200$  pmol/l).

No.	Sex	Ethnicity	Age at diagnosis	BMI/centile (kg/m <sup>2</sup> )	HbA1c	Insulin treated	C-peptide (pmol/L)	Mutation
1	Female	Indian	18 years	16.5	5.5	Yes	774.7	<i>INS</i> exon 3 c.215delC p.Pro72fs heterozygous
2	Female	Chinese	25 years	17.7	5.9	No	ND*	<i>HNF4A</i> , Exon6, c.658G>A p.Val220Met (p.V220M)
3	Female	Chinese	18 years	18.9	6.5	No	ND	<i>HNF1A</i> exon 4, c.872.dupC, p.Gly292fs heterozygous
4	Female	Chinese	24 years	19.3	5.8	No	ND	<i>GCK</i> , Exon7, c.790G>A p.Gly264Ser (p.G264S), pathogenic
5	Female	Chinese	2 months	25-50 <sup>th</sup> centile	7.6	Yes	-	<i>KCNJ11</i> , Exon1, c.602G>A p.Arg201His (p.R201H), heterozygous

6	Male	Malay	31 years	17.8	6.2	Yes	250	<i>HNF1A</i> , exon4, c.788G>A p.Arg263His (p.R263H), heterozygous
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Table 1. Clinical demographics of n=6 subjects who harboured a pathogenic/likely pathogenic variant  
\*ND: Not done, as the subject was not on insulin.

### Conclusions

In this pilot study, applying an age threshold of either diabetes diagnosis  $\leq 1$  year or  $\leq 35$  years with a lean BMI ( $\leq 23$  kg/m<sup>2</sup>) and negative GADAb, there was a detection rate of 22% for monogenic diabetes in this South-East Asian setting.

## A RARE PRESENTATION OF PEUTZ - JEGHER SYNDROME IN CHILDREN.

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A four and half years old girl presented with gonadotrophin independent precocious puberty due to an oestrogen secreting left-sided ovarian tumour. She was diagnosed with Peutz- Jeghers Syndrome (PJS) as she fulfilled the clinical criteria and underwent left-sided salphingo-oophorectomy. The histology revealed sex cord tumor with annular tubules, a well-known entity in PJS, but very rare in the paediatric age group. Due to its rarity, the management is challenging and requires meticulous follow-up.

### Introduction

Gonadotrophin independent precocious puberty in Peutz- Jegher Syndrome (PJS) is a rare presentation in paediatric group and is due to the sex cord tumour with annular tubules (SCTAT) 1,3. Its occurrence in PJS 36% and it is mostly benign but, 20% are malignant<sup>3</sup>. In a study of 74 patients with SCTAT, only seven children were reported. Out of them two patients had PJS. Both of them had presented with gonadotrophin independent precocious puberty (GIDPP) 3. Due to its rarity, there is no standardized management established 2. The treatment for the condition is surgical excision and recurrence is not reported in children 3.

### Case report

A four and half year-old girl was referred due to 3 episodes of cyclical vaginal bleeding over a period of four months. There was gradual breast enlargement and rapid increment in height over seven months. She is the only child in the family of nonconsanguineous parents, who was born at term was healthy. There was no history of precocious puberty in the family but maternal uncle had a history of colorectal polyps needing regular surgical follow-ups.

She was averagely built girl with height and weight falling in between -1SD to median centiles. Her vital parameters were unremarkable. There were melanocytic macules on the lips without syndromic features. Her breast stage was Tanner II-III, pubic and axillary hair stage was Tanner I-II. Her bone age was advance at 6 to 7 years and Leutinizing Hormone was 0.09 IU/l with Follicular Stimulating Hormone of 0.05IU/l. Her beta hCG and alpha feto proteins were normal.

The MRI brain was normal and pituitary was compatible with the pubertal stage. The ultra sound scan of the pelvis revealed a pubertal uterus with an endometrial thickness of 10mm without ovarian lesions. We started Letrazole for the symptomatic management and followed up with ultrasound scans every 6 monthly. After one and half years, her ultrasound scan revealed a mass lesion in the left ovary. An MRI was performed which showed well defined left ovarian solid lesion with post contrast enhancement. She underwent left side salphingo-oophorectomy at which a tumour measuring 20×20×15mm was excised. It was well localised with no metastasis. The histology report revealed an ovarian SCTAT. Considering the PJS, we proceeded with upper and lower endoscopy which showed polyps in the antrum of the stomach and the duodenum. She was planned to undergo a repeat endoscopy in 10 years and regular follow-up was arranged.

### Conclusion

The SCTAT is a distinctive ovarian tumour associated with PJS<sup>1</sup> and mostly a hamatoma<sup>3</sup>. The clinical presentation is commonly with GIDPP 3. The treatment is surgical excision and recurrence in the paediatric age is not reported. However, a close follow up is needed.

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## FP 3.4

### **EFFECT OF GONADOTROPIN-RELEASING HORMONE AGONISTS TREATMENT IN VIETNAMESE CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY**

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#### **Objective:**

Gonadotropin-releasing hormone agonists (GnRHa) are the treatment of choice for central precocious puberty (CPP) and have been widely used for several decades. We aimed to determine the effect of GnRHa treatment on the auxological outcomes of children in both genders with CPP.

#### **Methods:**

This is a retrospective study. We analyzed a sample of 140 girls and 3 boys with CPP who finished treatment with triptorelin 3.75 mg from June 2011 to June 2021 in the Department of Nephrology and Endocrinology, Children Hospital number 2, Vietnam. Anthropometry, bone age, sexual maturity rating were assessed after 6 months and each year of the therapy, and predicted adult height (PAH) was calculated based on bone age and current height at the same time. We compared their eventual predicted adult height (PAH) with their initial PAH. Furthermore, we evaluated bone mineral density (BMD) and bone metabolism in these patients at the end of the treatment.

#### **Results:**

The mean chronological age (CA) and bone age (BA) of the patients with CPP at treatment initiation were  $8.0 \pm 0.7$  years and  $10.5 \pm 0.1$  years, respectively. The mean duration of treatment was  $2.4 \pm 0.6$  years. GnRH agonist therapy results in a decrease in height velocity, cessation of menses, and arrest pubertal progression after 6 months and this result was maintained until the end of the treatment. The rate of bone age advancement also declined with the difference between BA and CA reduced from  $2.4 \pm 0.1$  to  $0.8 \pm 0.3$  years ( $p < 0.05$ ). The PAH at treatment initiation was  $157.8 \pm 0.6$  cm in girls and  $172.3 \pm 2.4$  cm in boys. The PAH at treatment discontinuation ( $162.0 \pm 0.5$  cm in girls and  $176.7 \pm 2.3$  cm in boys) was significantly higher than the pre-treatment PAH ( $p < 0.05$ ). To investigate whether growth outcomes were influenced by the age at initial treatment, we divided girl patients into three groups, those treated under 6 years ( $n = 4$ ), between 6 and 8 years ( $n = 56$ ) and those treated after 8 years ( $n = 83$ ). For girls with GnRHa therapy before the age of 6 years, the treatment results in an average gain in adult height of  $10.2 \pm 3.2$  cm, whereas for those treated between 6 and 8 years, treatment results in an average gain in adult height of  $5.3 \pm 0.7$  cm. The average height gain of girls aged over 8 years was also remarkable,  $3.2 \pm 0.6$  cm. The parameters about BMD and biochemical markers of bone turnover (serum Calcium, phosphorus, vitamin D, alkaline phosphatase, parathyroid hormone) have shown no abnormality. Moreover, these benefits have been achieved in the absence of significant side effects.

#### **Conclusion:**

GnRHa is safe and effective for the treatment of CPP with the improvement of mature stature. It is noticeable that GnRHa therapy was still effective even after 8 years of age in girls with CPP.

## SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR-A LEVELS ACCORDING TO PUBERTAL STATE IN GIRLS

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Korea University College of Medicine

### Objectives:

Childhood obesity may lead to early puberty in girls, however, it remains unclear whether early thelarche in overweight girls is related to central activation of the gonadotropin releasing hormone-gonadotropin axis. Vascular endothelial growth factor-A (VEGF-A) is essential for governing angiogenesis in adipose tissue. We assessed serum VEGF-A level according to pubertal state and weight in girls.

### Patients and Methods:

Total 165 girls were classified as prepuberty (n=40), puberty with peak LH <5.0 IU/L (n=60), and puberty with peak LH ≥5.0 IU/L (n=65). Serum VEGF-A, sex hormone, gonadotropin level and bone age were analyzed according to pubertal state and overweight including obesity. We measured serum level of VEGF-A using ELISA kit.

### Results:

Their chronological age were similar (7.8±1.2, 7.9±0.8, and 8.0±0.9 years, p=0.410 in prepuberty, puberty with peak LH <5.0 IU/L, puberty with peak LH ≥5.0 IU/L, respectively). The mean VEGF-A level was higher in puberty girls (399.3±206.2, 633.5±473.0, 605.7±392.4 pg/mL, P=0.009) and was significantly correlated with Tanner stage (r=0.224, p=0.004), BMI SDS (r=0.191, p=0.014), and weight SDS (r=0.202, p=0.009). When sub-analysis with the degree of obesity, VEGF-A level (802.2±556.0 pg/mL) was highest in overweight puberty girls with peak LH <5 IU/L and was significantly correlated with peak LH (r=0.397, p=0.044) and peak LH/FSH (r=0.409, p=0.038).

### Conclusions:

Our study showed higher VEGF-A levels in overweight puberty girls. Obesity-associated VEGF-A rise may involve in the progression of precocious puberty. Further studies related to pathophysiological mechanism are needed.

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FP 4.2

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FP 4.5

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## FP4.1

### THE CLINICAL AND MOLECULAR CHARACTERISTICS OF 104 CHILDREN WITH HYPOPHOSPHATEMIC RICKETS CAUSED BY PHEX GENE MUTATION

Chunhua Zeng  
Department of Genetics and Endocrinology, Guangzhou Women and Children's Medical Center,  
Guangzhou

#### **Objective:**

To summarize the clinical and genetic characteristics of 104 pediatric patients with low phosphorus rickets caused by PHEX gene mutations.

#### **Methods:**

Through a retrospective analysis of the clinical data and genetic test results of 104 cases of children with X-linked dominant hypophosphate rickets caused by PHEX gene mutations diagnosed in the Department of Genetic Endocrinology, Guangzhou Women and Children's Medical Center from January 2010 to December 2020.

#### **Results:**

Among the 104 children, 38 were males and 66 were females. The age of onset ranged from 6 months to 6.5 years. The average age of diagnosis was 4.77 years (August-14 years and 5 months). Ninety-six children were diagnosed with skeletal deformities, and 8 children were diagnosed through family examinations. Most of the children have obvious lower limb bending around 1 year after birth, abnormal walking gait, slow height growth, and normal intelligence. Among 104 children, 64 cases of knee varus, 28 cases of knee valgus, 17 cases of pectus, and 10 cases of Rachitic rosary. The average blood phosphorus was 0.91 mmol/l (0.61-1.1), the blood calcium was normal, and the average alkaline phosphatase was 641 U/L (223-1766). All children had normal renal function at the time of diagnosis. Among 104 children, genetic testing showed that 50 cases had spontaneous mutations in the PHEX gene, 12 cases were inherited from fathers, 33 cases were inherited from mothers, and 8 cases were not genetically tested for their parents. The types of gene mutations include missense mutations, insertion and deletion mutations, and large deletions. The mothers of the two children had pathogenic mutations, but their blood phosphorus were normal, and they did not have a rickets phenotype. The father of one child had PHEX mutant germ cell mosaicism.

#### **Conclusion:**

This study expanded the understanding of X-linked dominant hypophosphate rickets caused by PHEX gene mutations, and provided a basis for early screening, diagnosis and treatment of hereditary rickets and genetic counseling.

## FP4.2

### **IODINE EXCESS, PREGNANCY AND THYROID SAFETY TO THE WOMAN AND THE OFFSPRING FOLLOWING HYSTEROSALPINGOGRAM USING IODINATED CONTRAST**

Divya Mathews, Jane Peart, Robert Sim, Neil Johnson, Susannah O'Sullivan, José Derraik, Paul Hofman  
Liggins Institute

#### **Background:**

Hysterosalpingograms (HSG) with oil-soluble contrast medium (OSCM) increase pregnancy rates in women with infertility (1-3). However, OSCM can cause marked and prolonged iodine excess, potentially impacting thyroid function (4). If pregnancy occurs, there is concern regarding fetal and neonatal hypothyroidism resulting from maternal iodine excess (5).

#### **Objectives:**

1. To determine the pattern of iodine excess in women undergoing OSCM HSGs.
2. To determine the types and pattern of thyroid function abnormalities in women undergoing OSCM hysterosalpingogram and the neonates conceived within 6 months of HSG in their mothers.

#### **Methods:**

A prospective study of 150 women who underwent HSG with OSCM was performed. The women were followed up for 6 months with serial measurements of thyroid stimulating hormone (TSH), Free thyroxine (T4) and Free triiodothyronine (T3) and urine iodine (UI). A delayed X-ray film was obtained after 45 minutes to assess the peritoneal spill and this was semi quantitatively assessed by the radiologist for OSCM retention. The offspring conceived during the study period underwent a routine newborn screening and a repeat thyroid test on the seventh day of life (6).

In addition, a retrospective analysis of newborn TSH data was undertaken for a separate cohort of 146 children who were conceived following OSCM HSG in the Auckland region from 2000-2019

#### **Results:**

1. 69/150 (46%) had biochemical pregnancy. However, there was marked falloff in pregnancy rates when mothers were > 40 years old (15%)
2. The rate of iodine deficiency was high with 45/139 (32%) deficient (urine iodine < 100 mcg/L), and 8.6% having levels < 50 mcg/L
3. There was a marked increase in average urinary iodine post HSG. This was quite variable with peak iodine excess occurring between 1 week and 3 months. Peak iodine levels were not associated with conception.
4. Semi-quantitative radiological assessment of peritoneal retention was predictive of iodine excess and those with more extensive spill had higher urinary iodine concentration ( $p < 0.0001$ )
5. As expected TSH levels increased post OSCM HSG with mean TSH levels being highest from 1 week to 2 months post OSCM exposure. TSH levels > 4 mIU/L occurred in 38% without significant change in Free T4 or Free T3, consistent with a diagnosis of subclinical hypothyroidism (SCH). TSH > 10 mIU/L occurred in 2% of the women, fulfilling American thyroid academy (ATA) criteria for thyroxine initiation. Subclinical hyperthyroidism developed in 1%, but transient with a suppressed TSH level.
6. Among the 30 infants born from the prospective cohort or the 146 babies from the retrospective cohort, none had elevated TSH levels.

#### **Conclusion:**

Iodine deficiency was prevalent in women with unexplained infertility. OSCM HSG causes marked iodine excess and the iodine excess can be predicted by a radiological assessment of delayed pelvic X-ray post HSG.

Subclinical hypothyroidism frequently and transient hyperthyroidism rarely occurs following OSCM HSG and necessitates thyroid monitoring for 4-6 months. Both conditions increase pregnancy complications and are associated with adverse fetal/ neonatal outcomes. However, in New Zealand, newborn hypothyroidism was not increased following OSCM HSG.

### FP4.3

## FACTORS AFFECTING BONE MINERAL DENSITY IN CHILDREN AND ADOLESCENTS WITH SECONDARY OSTEOPOROSIS

Min Jeong Jang

Catholic University College of Medicine, Department of Pediatrics

### Background:

The purpose of the present study was to investigate clinical factors associated bone mineral density (BMD) among children and adolescents with osteoporosis secondary to treatment for underlying clinical conditions.

### Methods:

The present study included children and adolescents aging between 10 and 18 with underlying hemato-oncologic, rheumatologic and gastrointestinal diseases and investigated their lumbar spine bone mineral density (LSBMD) measured by DXA (Dual-energy x-ray absorptiometry). Clinical and biochemical data were compared between groups with low bone mass defined by LSBMD Z-scores (standard deviation scores).

### Results:

A total of 117 children and adolescents, 92(78.6 %) children had underlying hemato-oncologic, 13(11.1 %) children had rheumatologic, and 12(10.3 %) had gastrointestinal diseases with median age of 11.0 years at diagnosis. Age at initial DXA assessment was 15.0 years. At initial DXA, mean LSBMD Z-scores were  $-0.72 \pm 1.31$  while, 19 (16.22 %) and 49 (41.9%) children had Z-scores less than -2.0 and -1.0, respectively. When subcategorized in regard with LSBMD Z-scores, height Z-scores were lower in children with LSBMD Z-scores less than -2.0 while no significant difference in height Z-scores was observed at underlying diagnosis. Bone metabolic markers including serum calcium, phosphorus, bone-specific alkaline phosphatase, parathyroid hormone, and calcidiol levels were not significantly different between children in regard with LSBMD Z-score of -2.0. Height Z-scores at underlying diagnosis ( $p=0.182$ ) and initial DXA assessment ( $p=0.286$ ) were positively correlated whereas accumulated steroid dose over the treatment period ( $p=0.248$ ) were negatively correlated with initial LSBMD Z-scores. After adjusting for height at underlying diagnosis and accumulated steroid dose, height Z-scores at initial DXA assessment were a significant risk factor associated with likelihood of being LSBMD Z-scores less than -2.0 or vertebral fracture (OR=0.492).

### Conclusion:

Considerable numbers of children after treatment of underlying chronic conditions are prone to secondary osteoporosis and the height deficit could indicate decreased bone mineral status. Close auxological monitoring at any time during the follow-up period is recommended to prevent further skeletal complications.

#### FP4.4

### **FUNCTIONAL CHARACTERIZATION OF PAX8 MUTATIONS CAUSING CONGENITAL HYPOTHYROIDISM**

Khishigjargal Batjargal

Department of Pediatrics, Mongolian National University of Medical Sciences

Paired box transcription factor 8 (PAX8) is essential for thyroid organogenesis and development. Heterozygous PAX8 pathogenic variants usually cause congenital hypothyroidism (CH) due to thyroid hypoplasia. However, PAX8 pathogenic variants have been identified in patients with gland in situ (GIS). Purpose: The aim of this study was to analyze in vitro the functional consequences of four PAX8 variants (p.D94N, p.E90del, p.V58I, and p.L186Hfs\*22) previously identified by us in CH patients with GIS. Methods: The transcriptional activation of PAX8 variants on the thyroglobulin (TG) promoter activation was assessed by the luciferase reporter assay and to evaluate the effect of variants on the interaction between PAX8 and its partner, NKX2-1 [encoding thyroid transcription factor 1 (TTF1)]. The protein expression levels were detected by Western Blotting and subcellular localization was detected by confocal microscopy. Results The levels of transcriptional activity on the TG promoter of p.E90del and p.L186Hfs\*22 were significantly reduced, while p.D94N and p.V58I had a normal activation. A dominant negative effect on wild-type (WT) PAX8 was detected in p.E90del and p.L186Hfs\*22. The presumed pathogenic variants of p.E90del and p.L186Hfs\*22 were rescued by the transcription factor of NKX2-1. Western blotting showed that the protein expression level of each PAX8 variant was comparable with that of WT. Moreover, most PAX8 variants were localized in the nucleus. Discussion: In this study, p.E90del and p.L186Hfs\*22 were thought to be pathogenic by in vitro analysis, but p.D94N and p.V58I were not. Similar to our study, Camats N et al. reported that CH patients with GIS had PAX8 variants (p.S59R, p.Y66del, p.S70G, p.R133W, and p.R133Q), which were proved to cause loss of function. It is well recognized that pathogenic variants of PAX8 show broad phenotypic variability from TD to GIS, even in familial cases. The precise reason for phenotypic variability caused by PAX8 defect has not been determined, PAX8 may be compensated by other transcriptional factors involved in thyroid development similar to the synergy with NKX2-1 and PAX8 observed at this TG promoter. This must be studied further. Conclusion: Two variants of PAX8 (p. E90del and p.L186Hfs\*22) might be pathogenic causes of CH with GIS. This study further expands clinical phenotypes due to PAX8 pathogenic variants.

## FP4.5

### RELATIONSHIP BETWEEN IODINE STATUS AND THYROID FUNCTION IN PRESCHOOL CHILDREN: FROM THE ENVIRONMENTAL AND DEVELOPMENT OF CHILDREN (EDC) STUDY

Yun Jeong Lee, Young Ah Lee, Youn-Hee Lim, Bung-Nyun Kim, Johanna Inhyang Kim, Yun-Chul Hong, Sun Wook Cho, Young Joo Park, Choong Ho Shin  
Seoul National University, Children's Hospital

#### Background:

We investigated iodine status and its association with thyroid function among preschool children residing in iodine-sufficient area.

#### Methods:

From the Environment and Development of Children study, 477 children were evaluated for thyroid function and urine iodine concentration (UIC) at age 6 during 2015-2017. After excluding children born with multiple birth and with congenital hypothyroidism or Hashimoto thyroiditis, 439 (231 boys) were included. Subclinical hypothyroidism (SCH) was defined as thyroid stimulating hormone (TSH) levels between 4.9-10  $\mu$  IU/mL with normal free T4 levels. Iodine status was evaluated by UIC and children were categorized into 4 groups: iodine deficient (UIC<100  $\mu$  g/L), adequate (UIC, 100-299  $\mu$  g/L), mild excessive (UIC, 300-999  $\mu$  g/L), severe excessive (UIC $\geq$ 1000  $\mu$  g/L).

#### Results:

Goiter was palpated in 64 (14.6%) with female predominance (26.0% vs. 4.3%,  $P<0.001$ ). Serum level of free T4 and T3 was  $1.2\pm 0.1$  ng/dL and  $148.1\pm 18.5$  ng/dL, respectively. The median TSH level was 2.3 (0.53-8.59)  $\mu$  IU/mL and the prevalence of SCH was 4.3% without sex-difference. The median UIC level was 606.2 (19.9-16409.7)  $\mu$ g/L, higher in boys (684 vs. 545  $\mu$ g/L,  $P=0.021$ ) than in girls. Iodine was deficient in 19 (4.3%), adequate in 96 (21.9%), mild excessive in 170 (38.7%), and severe excessive in 145 (35.1%). After excluding 19 iodine deficient children, the relationship between iodine status and thyroid function was evaluated by multiple regression analysis after adjusting for age, sex, birth weight, gestational age, body mass index Z-score, and family history. As iodine status increased from adequate, mild excessive to severe excessive group, T3 levels decreased, and TSH levels increased with marginal significance ( $P$  for trend $<0.1$  for T3 and TSH). When stratified by sex, similar association was found in only girls ( $P$  for trend=0.043 for T3, and 0.062 for TSH) but not in boys, and mild excessive group showed lower free T4 levels ( $\beta = -0.05$ ,  $P=0.013$ ) and severe excessive group had lower T3 levels ( $\beta = -7.04$ ,  $P=0.035$ ) than iodine adequate group in only girls, but not in boys.

#### Conclusion:

Iodine was deficient in 4.3%, adequate in 21.9%, and excessive in 73.8% among preschool children residing in South Korea. As iodine status increased from adequate to excessive group, TSH levels increased with decreasing free T4 and T3 levels in girls.

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## **CLINICAL CHARACTERISTICS OF CONGENITAL HYPOPITUITARISM IN CHILDREN: A SINGLE CENTER EXPERIENCE IN SRI LANKA**

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### **Background**

Congenital hypopituitarism can present as isolated pituitary hormone deficiency or as multiple pituitary hormone deficiency. Genetic defects of pituitary cell differentiation and proliferation leads to congenital hypopituitarism. Presentation of hypopituitarism is variable.

### **Methods**

A descriptive analysis of 52 patients with congenital hypopituitarism followed at Lady Ridgeway Hospital from 2013 to 2021 was undertaken. Patient characteristics and characteristics of magnetic resonance imaging, frequency and temporal association of development of hormone deficiencies were evaluated.

### **Results**

30(57.7%) males and 22(42.3%) females had congenital hypopituitarism with a median presenting age of 5.86 years (2 weeks to 12.5 years). 38.5% had low birth weight and 53.8 % had post neonatal risk factors (34.6% neonatal jaundice: 28.8% neonatal hypoglycaemia :51.5% of males had micropenis during infancy). 31(59.6%) presented with short stature and 17.3% with hypoglycaemia. 27(51.91%) had multiple pituitary hormone deficiency(MPHD). Children who had post-natal risk factors showed more risk of developing MPH (OR 2.036, 95% CI 1.94-3.786). 90.4% with GHD,46.2% with ACTH deficiency and 40.4% with TSH deficiency had the mean age of presentation 6.54 years, 6.11 years and 5.56 years respectively. 57% of children >13 years showed hypogonadism. hypoplastic anterior pituitary (40.4%), ectopic posterior pituitary (30.8%), pituitary stalk abnormalities (13.5%) and absent septum pellucidum (11.5%) were seen in 32 children who had MRI abnormalities. Imaging abnormalities were more commonly associated with MPH (OR 1.768, 95% CI 1.087-2.874). young maternal age was seen in 30% with Septo-optic dysplasia (10/52)

### **Conclusion**

Isolated pituitary hormone deficiency may evolve in to MPH with time and presence of post-natal risk factors is associated with the higher risk of MPH. Regular periodic hormonal evaluation is needed to diagnose developing additional pituitary hormonal deficiency.

Key words

Hypopituitarism, MPH, magnetic resonance imaging.

## PP 2

### DSD & Adrenal

#### TO REMOVE OR NOT REMOVE THE GONADS?

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A 15-year-old teen was referred for obesity and primary amenorrhoea. Client was born full-term vaginally with birth weight 2.720kg. Perinatal course was uneventful. Client had right hernia repair at 16 months. Operation revealed sliding hernia with right ovary and round ligament involving wall of hernia sac. Fallopian tube was not involved. Client had left hernia repair at 4 years. Operation found left indirect inguinal hernia of sliding type, with ovary on wall of hernia sac. There was no family history of puberty disorder or fertility issue.

Clinical examination showed body weight 70.8kg, body height 159cm, BMI 28kg/m<sup>2</sup> and blood pressure 134/77mmHg. Client had no Cushingoid features, no hirsutism, and no acanthosis nigricans. Client had stage V breast, no pubic and axillary hair. Female external genitalia were seen – urethral and vaginal openings seen, no palpable gonads, no clitoromegaly, bilateral hernia repair scar.

Preliminary investigations showed LH 21.0 IU/L (2.4-12.6), FSH 4.6 IU/L (3.5-12.5), oestradiol 122 pmol/L (98-571), testosterone 17.1 nmol/L (<1.7), androstenedione 6.6 nmol/L (1.1-6.5), 17-hydroxyprogesterone 4.0 nmol/L (0.6-4.0). USG did not identify uterus, and soft tissue mass at both adnexa might represent ovaries. MRI did not identify uterus, and oval enhancing soft tissue in bilateral adnexa, associated with small adjacent cysts, suggestive of bilateral cryptorchidism. Karyotype was 46,XY. No pathogenic variant in coding region +/- 10bp of exon/intron boundary of AR gene was detected. No pathogenic variant in coding region of DSD panel was detected.

Pros and cons of retaining or removing gonads were explained to client and family. Information was all along disclosed to both and there was no psychological issue. Joint care with paediatric urologist and gynaecologist initially suggested EUA, cystoscopy, vaginoscopy and laparoscopic bilateral orchidectomy. They opted for retaining gonads. Surveillance with AFP and hCG were normal. When client reached 18 years, all agreed for surgery.

EUA revealed female external genitalia with separate urethral and vaginal openings. Cystoscopy demonstrated female type urethra. Vaginoscopy showed blind-end vagina of 5.5cm, no cervix identified. Bilateral intra-abdominal testes were identified at pelvic brim, several small cysts over left epididymis and no uterus. Histology of both gonads showed similar histological features of intra-testicular well-circumscribed non-capsulated nodule of Leydig cell lesion. Immunochemical staining of Leydig cell lesion were positive for inhibin, calretinin, Melan A and weakly positive for SF1. Seminiferous tubules contained Sertoli cells only. No germ cells were highlighted by immunostaining OCT3/4 and PLAP. Oestrogen replacement was started after surgery.

### **ASSESSMENT OF SERUM CERULOPLASMIN FOR EARLY DIAGNOSIS OF WILSON'S DISEASE IN CHINESE CHILDREN**

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#### **Objectives:**

Serum ceruloplasmin is one of the major diagnostic parameters for Wilson's disease (WD). This study aims to define diagnostic criteria of serum ceruloplasmin for screening and early diagnosis of WD in children.

#### **Methods:**

Serum ceruloplasmin were measured in 317 WD patients, 21 heterozygotes, 372 healthy control children and 154 non-WD patients. Receiver operating characteristic (ROC) curve was used to determine the diagnostic accuracy of serum ceruloplasmin for WD in children.

#### **Results:**

Among healthy controls, serum ceruloplasmin was low before the age < 6 months, and then remain 29-34 mg/dL. 8.1% of healthy children had serum ceruloplasmin <20 mg/dL. Serum ceruloplasmin concentration in WD patients was significantly lower than that in non-WD children. Only 1.9% of WD patients had serum ceruloplasmin >20 mg/dL. Serum ceruloplasmin showed gender difference, higher in healthy boys than girls and also higher in asymptomatic WD boys than girls ( $p<0.01$ ,  $p<0.05$ ). Serum ceruloplasmin had genotype difference. WD patients with R778L homozygotes exhibited lower level of serum ceruloplasmin than WD patients without R778L ( $p<0.05$ ). The ROC curve revealed that serum ceruloplasmin, at a cutoff value of 16.8 mg/dL, had the highest AUC value (0.990) with a sensitivity of 95.9% and a specificity of 93.6%.

#### **Conclusions:**

Serum ceruloplasmin is a reliable biochemical parameter for early diagnosis of WD in children older than 6 months. Gender and genotype difference of serum ceruloplasmin should be considered at diagnosis of WD. The cutoff value of serum ceruloplasmin <16.8 mg/dL may provide the highest accuracy for diagnosis of WD in children.

Key words: Ceruloplasmin, Wilson's disease, children, diagnosis

Synopsis: The cutoff value of serum ceruloplasmin <16.8 mg/dL is an optimal criteria for diagnosis of WD in children older than 6 months.

## CHARACTERISTICS OF PAEDIATRIC PATIENTS AGED 18 YEARS AND YOUNGER WITH TYPE 1 DIABETES MELLITUS AT DIAGNOSIS IN BRUNEI DARUSSALAM

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### Background:

Type 1 Diabetes Mellitus (T1DM) is the most common type of diabetes affecting children and adolescents worldwide<sup>1</sup>. Multiple epidemiological studies have shown that incidence of T1DM is on the rise globally, however there are currently no published data on the incidence of paediatric T1DM in Brunei Darussalam.

### Aim:

The aim of this study is to characterise the prodrome, presentation, family history, and biochemical status at diagnosis of type 1 diabetes mellitus (T1DM) in children aged 18 years and younger. In addition, we also looked at the insulin regimen commenced and the incidence of T1DM in children aged 18 years and younger in Brunei Darussalam.

### Method:

A population-based retrospective medical case notes review on paediatric patients aged 18 years and younger diagnosed with T1DM was done from 2013 to 2018 for the country of Brunei Darussalam.

### Results:

A total of 31 children with mean age of 10.2 years old were diagnosed with T1DM, of which 66.7% presented in diabetic ketoacidosis (DKA), majority (71.4%) in severe DKA. However, none of the children had cerebral oedema. The mean HbA1c was 13.57 % at diagnosis with a mean serum glucose at diagnosis of 37 mmol/L (SD= +/-14.86) which was not statistically different between the DKA and non-DKA group. Majority of the children presented with classical osmotic symptoms associated with T1DM including polyuria (93.1%), polydipsia (92.9%), nocturia (90.0%) and weight loss (72.4%). None of the children had a first-degree relative with T1DM; however 19.4% had a first-degree relative with T2DM. 21 of the children (67.7%) were put on multiple daily injections of subcutaneous insulin whilst the remaining 10 patients (32.3%) were on twice daily injections with no patients being prescribed insulin pump therapy. The incidence of T1DM in children aged 18 years and younger is 4.9 per 100,000 for the year 2018.

### Conclusions:

Majority of the patients in our study presented in severe DKA, which highlights the importance of early identification of children with T1DM. Ideally they should be identified before the development of DKA as this acute condition is associated with high morbidity and mortality. Comparable to other studies, most of the children also presented with the classical osmotic symptoms associated with T1DM such as polyuria, polydipsia and nocturia<sup>2-3</sup>. Of significance, majority who presented with DKA did have an intercurrent illness ( $p=0.021$ ) at the time of diagnosis, which is important to note, as these symptoms of T1DM may be misinterpreted leading to delayed diagnosis and acute life-threatening complications. Therefore, healthcare providers should have a high index of suspicion of T1DM and DKA when managing any child presenting with such symptoms.

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## LONG TERM FOLLOW UP OF VITAMIN D DEPENDENT RICKETS TYPE I A CAUSED BY NOVEL MUTATION IN CYP27B1 IN A PAKISTANI BOY

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**Introduction:** Vitamin D dependent rickets type I A is an autosomal recessive disease caused by homozygous mutation in CYP27B1 gene. CYP27B1 gene encodes enzyme known as 1-alpha-hydroxylase (1 $\alpha$ -hydroxylase) which is responsible for converting vitamin D to its active form, 1,25-dihydroxyvitamin D<sub>3</sub>(calcitriol). This disorder can present in infancy with delayed motor milestones (walking), signs of rickets, poor dentition, short stature, muscle weakness, or metabolic fits

**Case Report:** The Proband is 2.5-year-old boy 4<sup>th</sup> issue born to consanguineous parents. He had history of multiple admissions due to seizures, recurrent chest infection and spontaneous fracture. Clinically he had signs of florid rickets, short stature, poor dentition and anemia. His biochemical profile revealed serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25(OH) vitamin D, and 1,25(OH)<sub>2</sub> vitamin D values were 6.3 mg/dL, 4.0 mg/dL, 1561 IU/L, 88.3 pg/mL, 45.6 ng/mL, and 10 pg/mL, respectively. Skeletal survey showed decreased bone density, periosteal reaction, cupping and fraying of the distal ulna and radius and bowing of both fibula. His arterial blood gases and urinary phosphorus was normal. The molecular genetic study revealed that the patient had homozygous mutation of variant c.171dup(p.Leu58Alafs\*275 in CYP27B1 gene and a variant of uncertain significance SLC34A1 c.1699G>A (p.Gly567Arg) heterozygous. Patient is treated with conventional therapy of calcitriol and oral phosphorus with improvement in his clinical findings and biochemical parameters. His elder sister died at of 2 years with similar complains where as no diagnosis made. Mother had significant history of abortion.

**Discussion:** This sequence change creates a premature translational stop signal (p.Leu58Alafs\*275) in the CYP27B1 gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in CYP27B1 are known to be pathogenic. The CYP27B1 gene is constituted of 9 exons spanning 5 kb. Till date, more than 70 mutations have been reported in the CYP27B1 gene, including missense or nonsense mutations, deletions, splicing mutations, and duplications. The clinical symptoms and biochemical findings improve within months of sufficient treatment with calcitriol, but the necessary dose varies which can be explained by molecular studies of the specific mutations. Newer agents burosumab are available in high income countries whereas resource limited countries have only option of convention therapy

Keywords: 25-hydroxyvitamin D, the CYP27B1 gene, vitamin D-dependent rickets type 1, calcitriol

## HYPOPITUITARISM FOLLOWING BRAIN TUMORS IN CHILDREN- SRI LANKAN EXPERIENCE

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**Introduction:** Neuroendocrine disturbance in pituitary hormone secretion is common following brain tumors and cranial irradiation. Hypothalamo – pituitary function may severely have compromised at presentation and their presentation can be non-specific.

**Method:** A retrospective and prospective ongoing analysis of 42 children who developed hypopituitarism following brain tumors and had been following up at endocrinology unit of Lady Ridgeway hospital for children from 2013- 2021, was carried out. The presence of pituitary hormonal deficiencies at presentation and later in the follow up, was ascertained.

**Results:** The cohort included 25males (59.5%) and 17 females (40.5%) with a mean age of presentation 7.56 years and mean follow up duration 3.89years (range 3 months to 10 years). craniopharyngioma was the commonest ,57.1%(24) while medulloblastoma was the second commonest (13, 31%). 25(59.5%) children had received brain radiotherapy following surgery. 32(76.2%) developed MPHD.57.1% had hormone deficiency at presentation or during the immediate post-operative period and 87.5% of them had craniopharyngioma. The commonest hormone deficiency was ACTH deficiency (69%) and next common deficiencies were TSH deficiency (27. 64.3%), GHD (23, 54.8%), DI (21,50%). The median time lapse to develop hormone deficiencies after initial presentation was 0.63years, 0.53 years, 2.69 years and 0.24 years respectively., 66.7 % (28) had other morbidities; hydrocephalus (20,47.6%), obesity (13, 31%), visual defects (8, 19%) and neurological weakness (7, 16.7%)

**Conclusion:** Brain tumors are associated with significant endocrine morbidity. Majority of craniopharyngioma has compromised pituitary function at presentation and needs hormonal evaluation before intervention.

Key words: Hypopituitarism, brain tumors, radiotherapy, MPHD

## COMBINED GONADOTROPIN-RELEASING HORMONE ANALOGUE OR AROMATASE INHIBITORS WITH GROWTH HORMONE MAY IMPROVE HEIGHT POTENTIAL IN GROWTH HORMONE DEFICIENT CHILDREN

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### Abstract

Growth hormone (GH) deficient children on GH therapy yet to attain sufficient height at the start of puberty may result in short final height (FH), especially if late diagnosis (1). Combined gonadotropin-releasing hormone analog (GnRHa) or aromatase inhibitors (AI) to recombinant GH (rGH) to optimize FH is being more commonly practiced now, though the evidence remains controversial.

This study aims to compare the predicted adult height (PAH) outcome of pubertal idiopathic GHD (iGHD) children on rGH but with poor height potential, before and after added GnRHa or AI. Comparison of GnRHa versus AI as well as the duration of treatment was also assessed.

### Methods

A retrospective review of children diagnosed with iGHD between 2013-2020 who were treated with rGH and combined with either GnRHa or AI was conducted. PAH was assessed before and after commencing combination treatment using growth parameters and bone age (BA) assessment. All BA were read by a single observer, using the Tanner and Whitehouse 3 method (TW3) (2). PAH was calculated using the TW3 method based on the growth parameters and BA before starting GnRHa/AI and after (latest growth parameters and BA).

### Results

A total of 21 children were included. The mean duration of combination treatment was  $16 \pm 8$  months. There was a significant improvement between PAH before ( $161.53 \pm 8.59$  cm) and after combination therapy with GnRHa or AI ( $165.16 \pm 9.54$  cm), with an increased height gain of  $3.63 \pm 2.84$  cm,  $0.57 \pm 0.45$  SDS,  $p < 0.001$ . AI had PAH gain more than GnRHa. Those with longer combined therapy ( $\geq 20$  months) had greater PAH gain of  $6.17 \pm 1.21$  cm,  $0.96 \pm 0.46$  SDS,  $p = 0.004$ . Four children with combination therapy had FH closer to their familial target height as compared to 2 children who received GH alone.

### Discussion

This study had demonstrated that the addition of GnRHa or AI to rGH significantly increased the PAH of iGHD children who entered puberty at a suboptimal height, to near their height potential or MPH, consistent with other studies (3) (4) (5). AI group had a slightly better PAH increment. Further analysis of the study done demonstrated a positive correlation on the duration of added GnRHa or AI with predicted height increment. This is consistent with the literature which suggested a longer duration of GnRHa leading to better height gain (5) (6). Even though the use of AI in short stature children was still rather new with limited studies, there were encouraging results with good effect and safety profile for a combination of rGH and AI (6) (7) (8). The ability of the adolescent boys to continue to virilize while slowing down epiphyseal fusion offers a better alternative and potentially better FH as compared to the pubertal suppression with GnRHa.

### Conclusion

This study shows the combination of GnRHa or AI to rGH may improve the FH potential in iGHD pubertal children. Limitation of the study is retrospective in nature, lack of control group and small, heterogenous group of the subjects. Most patients had not reached FH, thus more conclusions can only be made later with longer follow-up.

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## RETROSPECTIVE STUDY ON THE CLINICAL OUTCOME OF CHILDREN WITH OSTEOGENESIS IMPERFECTA TREATED WITH BISPHOSPHONATES IN HOSPITAL TUNKU AZIZAH

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### Abstract:

Osteogenesis imperfecta (OI), also known as "Brittle Bone Disease", is a group of genetic disorders with collagen bone defect and bone fragility, commonly classified to Type 1-IV based on clinical presentation and severity (1). Previously management consisted mainly of rehabilitation and corrective surgery, however more promising data have been obtained by using bisphosphonates, a potent antiresorptive agents.

Here in Hospital Tunku Azizah, a tertiary centre, Pamidronate had been used since year 2012. Patient were given 1-3 monthly infusion aiming for dose of 6-9mg/kg/year. Zoledronate was introduced in year 2019 with 3-6 monthly infusion aiming at dose of 0.1mg/kg/year.

The objective of this study is to assess the clinical outcome of the children with OI treated with intravenous bisphosphonates in terms of bone mineral density (BMD), fracture frequency, mobility (Bleck's Score), and adverse effect.

### Method

This is a retrospective cohort study based on patient's medical records from year 2012 to 2020 for children with OI treated with bisphosphonates with either Pamidronate or Zoledronate in Hospital Tunku Azizah, Kuala Lumpur (KL). Statistical analysis was done with SPSS version 22. Paired sample T-test and non-parametric (Wilcoxon test) were used to compare the treatment outcome. Non-parametric (Kruskal Wallis) test was used to compare the correlation between the parameters

### Result

Data were collected for 27 patients with clinical OI Type I (18.5%, n=5), III (63%, n=17), and IV (18.5%, n=5) on bisphosphonates treatment from 0.5- 8 years. Most were male (66.7%, n=18) and from Malay ethnicity (92.6%, n=25). Most of them (65.2%, n=15) were diagnosed soon after birth but only started treatment at the median age of 4.2 (0.5-14.4) year-old. A quarter of them had family history of OI, however only 11% had genetic confirmation.

Only 11 patients had BMD recorded before and after the bisphosphonates with median duration of treatment 3.88±2.26 years. Paired T-test showed there was significant improvement in BMD of lumbar spine from Z score of -3.64±2.49 to -1.71±1.69, p=0.009. There was also significant reduction of fracture rate (n=27, p=0.009) as well as improvement in mobility Bleck's score (n=25, p=0.041). Type IV OI was noted to have better improvement of mobility Bleck's Score compared to Type I and III, p=0.021. No correlation was noted on BMD or fracture rate changes to the types of OI or duration of bisphosphonates treatment. No serious adverse effects were documented post bisphosphonates infusion.

### Discussion:

Our study showed significant improvement in lumbar spine BMD of patients with bisphosphonates treatment, corresponding to findings of most studies (2). There were significant reduction of fracture rate with bisphosphonates treatment, as well as improvement in mobility based on Bleck's score, though similar findings were not consistently found in other studies (3) (4). More genetic test should be considered in the future as it may help to predict the severity of illness (5).

### Conclusion:

Bisphosphonates remained the mainstay medical treatment for OI patients and our study showed it was safe with improvement in bone mineral accretion, fracture rates, and mobility score. However, the evidence was limited by the small and heterogeneous sample size.

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**COMPLIANCE TO GROWTH HORMONE TREATMENT IN CHILDREN AND ADOLESCENTS WITH GROWTH HORMONE DEFICIENCY AND TURNER SYNDROME: A PROSPECTIVE STUDY**

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**Abstract**

Adherence to recombinant growth hormone (rGH) in children is necessary to ensure good treatment outcome. Reported non-compliance to rGH in children varied from 5-82% with little data involving Asian population. The objectives of this study are to evaluate the rate of compliance in children and adolescents to rGH, effect of non-compliance on growth and factors affecting non-adherence.

**Methods**

This is a prospective cohort study over 1-year aiming at all patients aged 4-18 years treated with rGH in our centre in Putrajaya Hospital, a tertiary centre. Compliance was assessed from the number of returned medications and electronic record within device. Poor compliance was defined as missing injection  $\geq 1$  per week or compliance rate  $< 86\%$  of the prescribed doses.

**Result**

Thirty-four patients were recruited including 20 (59%) patients with GH deficiency and 14 (41%) with Turner syndrome (TS). Poor compliance was noted in 35% of patients. Poor compliance in GHD patients was significantly associated with an older age (mean  $12.55 \pm 3.33$  vs  $9.28 \pm 3.20$  years,  $p=0.038$ ) and longer duration of treatment (mean  $5.41 \pm 3.0$  vs  $2.93 \pm 2.18$  years,  $p=0.046$ ). Frequent reasons for missing doses were forgetfulness and inadequate medications. Participants who missed  $\geq 1$  injection per week had significantly reduced height velocity (HV) and HV standard deviation score (SDS) compared to those with good compliance ( $p<0.05$ ).

**Discussion**

Compliance to treatment is important to ensure efficacy and best outcome of treatment (1) (2). This was supported by the finding of this study, which showed significantly poorer HV and HV SDS in subjects with GHD with poor compliance. Poor compliance was higher among GHD patients as compared to TS; however, this was not statistically significant as the number of TS participants was small.

Two main factors were found to be significantly associated with poor compliance in this study, i.e., the duration of treatment and the age of the patients. There was significantly higher rate of poor compliance in the older age group and those with longer duration of treatment. These were consistent with the findings in other studies which reported poor adherence with longer duration of GH therapy (2) (3) and among adolescents (4).

The strength of this study was the prospective nature enabling accuracy in clinical data, measurements of growth velocity and assessment of compliance.

The limitation of this study was the small sample size, which could have resulted in the lack of significant associations for variables analysed especially among patients with TS. Since this was not a blinded randomised study, the compliance and height velocity rate could have been artificially raised during the study.

**Conclusion**

The findings of this study had reaffirmed the importance of compliance to daily rGH injection to ensure a good treatment outcome. Education and creating awareness should be emphasized early from the time of initiating rGH followed by regular monitoring. Measures to improve compliance must include addressing the underlying reasons. Larger, multi-centre double blinded randomized studies in the future are needed to provide more evidence on cause and effect of poor drug compliances.

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## **IMPROVING ADHERENCE IN PATIENTS RECEIVING RECOMBINANT HUMAN GROWTH HORMONE TREATMENT FOR GROWTH HORMONE DEFICIENCY: A 6-MONTH VIRTUAL PILOT STUDY IN KOREA TO INVESTIGATE THE DEVELOPMENT OF A BEHAVIORAL CHANGE TRAINING MODULE FOR A NURSE-LED PATIENT-SUPPORT PROGRAM AIMED AT CAREGIVERS**

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### **Introduction:**

The implications of growth hormone treatment may go beyond reduced growth outcomes, with the potential for associated treatment to impact on social, physical, and psychosocial aspects of patients' daily living.<sup>1</sup> Therefore, the importance of support for patients and their caregivers to reduce these burdensome aspects is paramount. Indeed, a historic survey of caregivers of children receiving recombinant human growth hormone (r-hGH) therapy reported that 83% would appreciate psychological support to overcome their children's anxiety concerning treatment administration.<sup>2</sup> Notwithstanding, good adherence to treatment with r-hGH is essential for children with growth disorders to achieve optimal growth and other outcomes. However, motivation to adhere to treatment with r-hGH can decrease over time. A patient support program (PSP) is being developed in Korea with dedicated nurse-led, targeted behavioral change and psychosocial support for caregivers to facilitate disease management and address the issues related to motivational factors affecting adherence in patients receiving treatment with r-hGH for growth disorders.

### **Objective:**

To describe the development and future implementation of a behavioral change training module for PSP nurses in Korea during a 6-month virtual pilot study of caregivers to pediatric patients with growth disorders (TuiTek® Korea).

### **Methods:**

An approach known as the behavior change wheel<sup>3</sup> was used to guide the development of the PSP and maintain the support program using future intervention strategies to further improve adherence to r-hGH. First, the key factors influencing adherence to r-hGH therapy were mapped to the Capability, Opportunity, and Motivation (COM-B) model of behavior.<sup>4,5</sup> After which, Disease and Treatment Coherence, Emotional Burden, Treatment-related Anxiety, Teenage Years, and Transition to Adult/Self-care were identified as the six most influential factors that determined a patient's adherence to treatment with r-hGH. Subsequently, a series of interventional call guides were developed using a range of behavior change techniques for use by a specially trained PSP nurse after obtaining informed consent to support caregivers to make positive changes in perceptions, beliefs, and behaviors regarding r-hGH therapy. These guides follow a standardized structure and include evidence-based coaching techniques, derived from the field of health psychology and known to promote behavioral change, allowing personalized support for caregivers. Associated resource packs have also been developed (e.g. Growth Hormone Deficiency - The Facts, Seeking Support, Managing Stress) to give caregivers the skills needed to manage r-hGH therapy and support their child during their treatment journey.

### **Results:**

Following virtual training sessions with patients/caregivers on the use of the relevant injection device – either easypod™ (in conjunction with easypod™ connect and the easypod™ augmented reality [AR] mobile app) or the Aluetta™ pen device – one dedicated PSP nurse will identify patients at-risk of poor adherence based on their caregivers' understanding of the training content using a personalization questionnaire (delivered via mobile app technology). They will also identify priority topics for discussion in subsequent follow-up video calls, which they will deliver using interventional call guides focused on Disease and Treatment Coherence, Emotional Burden, Treatment-related Anxiety, and Self-administration. These calls will be made every 2 weeks to caregivers of patients identified at-risk of poor adherence.

**Conclusions:**

We hypothesize that this behavioral change training module will enable PSP nurses in Korea to provide individualized support for caregivers, helping them to improve motivational factors and consequently maintain their child's adherence to r-hGH therapy and, in turn, optimizing growth and other clinical outcomes. This approach will support emerging digital health interventions in this region.

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## **FREQUENCY OF MICROVASCULAR COMPLICATIONS AMONG CHILDREN WITH TYPE 1 DIABETES MELLITUS: A CROSS-SECTIONAL OBSERVATIONAL STUDY FROM A DEVELOPING COUNTRY**

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### **Background:**

There is dearth of data on frequency of vascular complications among children and adolescents with type 1 diabetes (T1D). Further, most of the studies are from the developed world and the results are variable due to heterogeneity of the studied population.

### **Objective:**

To study the frequency of microvascular complications among children and adolescents with T1D and to identify the risk factors associated with these complications.

### **Methods:**

A cross-sectional study done at tertiary care centre in northern India from Jan 2019- June 2020 on 188 subjects (5 to 18 years) with T1D for at least 5 years or 2 years (if above 11 years of age). The fundus examination, nerve conduction studies, spot urine albumin/creatinine ratio and fasting lipid profile were performed to screen for retinopathy, neuropathy, nephropathy, and dyslipidaemia, respectively.

### **Results:**

Mean age of the subjects was 13.54 years and 48.4% were males. The mean HbA1c (over last 1 year) was 7.78%. Twenty-two percent subjects had at least one complication with retinopathy found in 0.6%; nephropathy in 13.3%; neuropathy in 14.9%; hypertension in 3.7% and dyslipidemia in 37.6%. Children with complications had significantly higher frequency of hypertension ( $p=0.045$ ) and duration of diabetes ( $p=0.021$ ), and lower frequency of sugar testing ( $p=0.019$ ) and family history of T1D ( $p=0.015$ ). Further, nephropathy was associated with long duration of diabetes ( $p=0.012$ ) and hypertension ( $p=0.045$ ).

### **Conclusions:**

Microvascular complications associated with T1D can present in childhood especially, among those with longer duration of disease and lower frequency of glucose testing.

**ADHERENCE TO GROWTH HORMONE TREATMENT IN ASIA-PACIFIC REGION: REAL-WORLD ANALYSIS OF 24 MONTHS OF USE FROM OVER 2000 PATIENTS USING A CONNECTED DEVICE**

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**Introduction:**

Adherence to growth hormone therapy is important for optimal growth outcomes.<sup>1,2</sup> The easypod™ connected injection device electronically records and transmits dose data from patients receiving recombinant human growth hormone (r-hGH) for growth failure. This enables assessment of real-time objective adherence.

**Objective:** Analysis of adherence to r-hGH treatment, associated growth outcomes and injection comfort settings in Asia-Pacific (APAC) patients using data extracted from the easypod™ connect ecosystem.

**Methods:** Adherence, growth data and injection comfort settings from 2382 patients aged <18 years of age from the APAC region (Australia, Hong Kong, South Korea, Taiwan, Thailand) transmitting data between January 2007–June 2021 were analyzed. Start of treatment was categorized based on nominal cut off for pubertal age (12 years for boys; 10 years for girls). Adherence was categorized, based on mg of r-hGH injected versus mg of r-hGH prescribed, as high (≥86%), intermediate (≥56%–85%), or low (<56%). Linear interpolation between height measurements was applied to calculate monthly catch-up growth (ΔHSDS) for the subgroup of patients with HSDS <-2 and ≤7 years at start, for which we assume an optimal catch-up growth, and all other patients. Percentage of users not transmitting or transmitting data (0–≥4 times per quarter [Q]) over one year, between Q1 2019 and Q1 2021 were analyzed.

**Results:** Median adherence since start of r-hGH treatment was maintained above 90% over time up to 5 years on treatment for those patients with data available: Year (Y) 0 (n=2382), Y1 (n=915), Y2 (n=375), Y3 (n=183), Y4 (n=83), Y5 (n=18). There were 587 active users over last 12 months as of 31 May 2021 (407 Taiwan; 136 South Korea; 40 other countries). Analysis of this population showed mean age at start of treatment was 10.5 years and 11.2 years for girls and boys, respectively. The average prescribed dose was within the range of worldwide data available, and time between r-hGH dose changes was a median of 91.0 days, which is shorter compared with Worldwide and European data (median 161 and 174 days, respectively). In active users in 2021 (n=312), 74%, 23%, and 3% of patients had high, intermediate, and low adherence, respectively. Adherence was generally similar between Taiwan and South Korea (median adherence over last 12 months: 91.9% Taiwan; 98.8% South Korea). Growth data were available for 807 patients with 3576 measurements. The majority of patients with height data available were older than 8 years of age. Mean ΔHSDS between 0–24 months was +0.99 for the subgroup of patients (n=62) with HSDS <-2 and ≤7 years at start and +0.52 for all other patients (n=745). Median duration of use was 0.7 years (n=2159), and the mean number of transmissions per quarter for active users in both 2019 and 2021 was 2.4. The majority of patients active in 2021 used 6 mm injection depth setting and medium injection speed.

**Conclusions:** High adherence to r-hGH treatment was observed in APAC patients, with positive growth outcomes, indicating the importance of connected device solutions for r-hGH treatment in patients with growth disorders in this region.

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## AN X-LINKED KALLMANN SYNDROME WITH A CONTIGUOUS MICRODELETION AT XP22.31

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### Introduction

Kallmann Syndrome (KS) is a genetic condition characterised by hypogonadotropic hypogonadism (HH) and anosmia. Mutation of the *ANOS1* gene located at Xp22.31 is responsible for X-linked KS. We encountered a child with HH, anosmia and other additional features including bimanual synkinesis.

### Case Presentation

AHZ was a 13-year-old boy, born term weighing 4 kg via Caesarean section for two previous scars. His mother has type 2 diabetes mellitus on insulin. He was short and had bilateral lower extremities ichthyosis since infancy. During preschool years, he started complaining of being unable to smell and had mirror movement of his fingers, the latter more noticeable upon performing one-handed activities thus became cumbersome. He was reviewed by the paediatric surgeon at 3 years old for right cryptorchidism but was subsequently lost to follow-up. His early developmental milestones were appropriate. However, he had poor academic performance upon attending mainstream school. His appetite increased significantly in the last 6 years with noticeable rapid weight gain.

He has an elder sister with Crouzon Syndrome. Family pedigree drawn confirmed similarly affected maternal uncles and granduncle with anosmia, bimanual synkinesis, microphallus and ichthyosis. None of them has any offspring.

On examination, he was short and obese. His weight was 61.4 kg (+1.65 SDS), height 139.5 cm (-1.95), and BMI 31.55 kgm<sup>-2</sup> (+3.05 SDS). He was not dysmorphic. He had acanthosis nigricans grade 1 and was normotensive. He had bimanual synkinesis, and ichthyosis at the anterior aspect of his legs. He was pre-pubertal, had small left testicular volume (1 ml) and right undescended testis with stretched penile length of 1.3 cm (<10<sup>th</sup> percentile).

The baseline LH & FSH were low at <0.1 and 0.3 IU/L respectively. Short HCG stimulation test showed poor Leydig cell function. Testosterone remained low pre and post HCG stimulation at <0.087 nmol/L. Other pituitary hormones and karyotype were normal (46, XY). Metabolic screening revealed dyslipidaemia and mildly elevated transaminases. Diabetes screening was unremarkable. Electrocardiogram showed sinus bradycardia of 56 bpm.

His bone age was 11 years 2 months at chronological age 12 years 8 months. MRI pelvis revealed testicular volumes of 1.6 ml and 0.3 ml for right and left testis respectively, with right cryptorchidism. MRI brain showed bilateral olfactory bulbs hypoplasia with normal hypothalamus and pituitary. Ophthalmological and hearing assessments, renal ultrasound, and echocardiography were unremarkable. Psychological assessment showed extremely low intellectual functioning.

Whole exome sequencing revealed a 4 Mb microdeletion at Xp22.31. In addition to the *ANOS1* gene, he showed contiguous gene deletion of the nearby genes including the *STS* gene, thus confirming X-linked KS with additional clinical features of obesity, learning difficulties and ichthyosis. Genetic counselling and testing of other at-risk family members are ongoing. To the best of our knowledge, this is the first reported case of KS due to a microdeletion in Malaysia.

He is currently managed by a multidisciplinary team and planned for pubertal induction later.

**Conclusion**

Early recognition and assessment of patients with HH and anosmia are vital, as early diagnosis and multidisciplinary intervention for KS may improve their quality of life.

## TOURAINÉ-SOLENTE-GOLE SYNDROME (PACHYDERMOPERIOSTOSIS).. A RARE MIMICKER OF ACROMEGALY

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### Abstract Introduction:

Pachydermoperiostosis is a rare genetic disorder having autosomal dominant and sometimes autosomal recessive mode of inheritance. It is characterized by pachydermia, anhydrosis, clubbing and periostosis. The diagnosis is extremely challenging even for experienced clinicians because of its rarity and marked clinical similarity with acromegaly. Two genes have been identified to cause this rare condition HPGD and SLCO2A1. It has 3 forms complete, incomplete and fruste. It usually presents at time of puberty and progresses for 5- 20 years before stabilization.

### Case

We present a case of 16 year old male child resident of Swabi Pakistan presented to our endocrinology clinic with progressive broadening of hand and feet, coarsening of features, excessive sweating and joint pain for past one year. All his complains had great psychological impact on him and his mobility was limited due to joint pain . His shoe size was increased from 8 to 13 in one year and his current photographs revealed prominent difference as compare to past. On examination he had acromegaloid features with wide nose, obvious cheek bone, thick lips and forehead buldge. He had deep furrows on forehead and scalp giving appearance of cutis verticis gyrata, digital clubbing and generalized hyperhidrosis . His height was 167cm(  $-1.2$  SDS ) and weight of 54 kgs (  $-1.1$  SDS ) with tanner staging P4 G4 A4 and bilateral testicular volume of 20ml. His knee and ankle joints were grossly swollen F. His blood investigations showed IGF1: 168 ng/dl (220-978), TSH: 1.29 ulu/ml (0.3-4.2) , T4 : 12.05 (5.1-14.1 ug/dl), LH: 5.4 IU/L ( 1.7-8.6) , FSH 5.9 IU/L (1.5-12.4) , uric acid 4.5 mg/dl, serum insulin: 5.4 ulu/ml (2-25), HbA1C :5.1 % , normal fasting lipid profile and oral glucose tolerance test with 75 gm glucose showed normal growth hormone suppression, MRI pituitary protocol was normal with normal stalk and optic chiasma. Skeletal survey showed mild calvarial thickening and enlarged frontal and maxillary sinus. Diffuse periosteal new bone formation and cortical thickening noted in longitudinal bones of upper and lower limb. Radiological findings were suggestive of pachydermoperiostosis. Based on the clinical and radiological features in the absence of GH hypersecretion, a diagnosis of pachydermoperiostosis was made. . Option of botulism toxin was discussed He was kept on NSAIDs, colchicine ,corticosteroids & bisphosphonates with improvement of his symptoms. His genetic analysis from INVITAE showed homozygous SLCO2A1 gene of c.1264-1265del(p.Thr422Profs\*10) variant.

### Report:

### Discussion:

Pachydermoperiostosis is a rare cause of pseudoacromegaly which can be onerous to diagnose. The precise incidence is unknown. It was first described by Friedreich in 1868 . Adolescent males are predominantly affected with male-to-female ratio of approximately 7:1. The pathogenesis is not fully understood recently it has been suggested that locally acting PGE2 has a role. High levels of PGE2 and decreased levels of PGE-M, a metabolite of PGE are found in these patients. Treatment is mainly supportive and psychological impact of this disease is high. Mortality is not reported but morbidity is very high and patients may be left with chronic debilitating complications, which include severe kyphosis, restricted movements, and neurologic manifestations.

### Keywords:

Touraine-Solente-Gole syndrome. Periostosis. Pachydermia. Hypertrophic osteoarthropathy.

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## PREVALENCE AND RISK FACTORS OF DIABETIC NEPHROPATHY AMONG ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN MALAYSIA

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### Introduction:

Type 1 Diabetes Mellitus (T1DM) is a common chronic disease among children and adolescents. Poor control of DM is associated with multiple complications, with diabetic nephropathy (DN) as one of the most frequent long-term complications. Microalbuminuria is a known early marker of DN. The 2nd annual report of the Malaysian Diabetes in Children and Adolescents Registry (DiCARE) reported prevalence of microalbuminuria was 7.3% and nephropathy was 3.2%, adding up to 10.5% of DN1. However, no further details on the risk factors which lead to the DN was studied.

### Objective:

This study aims to determine the prevalence of DN among adolescents with T1DM and to identify the risk factors associated with DN.

### Methodology:

This is a cross-sectional study using data of the patients' medical records carried out in the paediatric DM clinics of University Malaya Medical Centre (UMMC) and Universiti Teknologi MARA (UiTM). Data collected include the demographic data, age at T1DM onset, duration of T1DM, insulin regime and other clinical data which includes the anthropometry data; weight (kg), height (cm), BMI (kgm<sup>-2</sup>), blood pressure (mmHg), HbA1C, lipid profile and urine for urine albumin/creatinine ratio (ACR). Cumulative result of two out of three samples for early morning urine ACR more than 2.5 – 23 mg/mmol in males and more than 3.5 – 25 mg/mmol in females is diagnostic for DN.

### Result:

Eighty-four adolescents with T1DM were recruited; mean age 14.7 +/- 2.3 years with mean age at T1DM diagnosis 8.3 ± 2.9 years, and mean duration of diabetes of 6.4 ± 3.1 years. A total of 56% were females (n = 47). The prevalence of DN in our study was 15.5%. There is a trend showing that the mean HbA1C of the patients with DN was higher (11.8% ± 3.6) as compared to those without DN (9.8 ± 2.4). Primary analysis revealed eight risk factors with p-value of <0.25, which were further analyzed with Multiple Logistic Regression (MLR). The risk factors were gender (p = 0.098), current age of the patients (p = 0.006), ethnicity (Indian vs Non-Indian) (p = 0.098), duration of T1DM (p = 0.177), HbA1C (p = 0.076), Triglyceride level (p = 0.087), LDL level (p = 0.089) and HDL level (p = 0.001). Multiple logistic regression identified 3 risk factors strongly associated with DN including current age (OR 1.67, p = 0.014), HbA1C (OR 1.34, p = 0.027) and HDL, which were found to be protective with adjusted OR 0.097 (95% CI 0.015 – 0.647, p = 0.016) The area under the curve of ROC curve was 0.871, which showed that these 3 factors were able to accurately discriminate 87.1% the risk of DN of patients in this study.

### Conclusion:

The risk factors of DN in adolescents with T1DM include poor glycemic control, older age and lower HDL level. Understanding the risk factors of DN in these adolescents will help healthcare providers to

identify those at risk and formulate strategies and evidence to improve patient care among this vulnerable group.

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## NEONATAL HYPERTHYROIDISM RESULTING FROM THYROTROPIN RECEPTOR GENE MUTATION MET453THR

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### Background

There are two main types of neonatal hyperthyroidism which are autoimmune and non-autoimmune. The autoimmune form is associated with maternal Graves' disease where maternal thyroid stimulating antibodies cross the placenta. The non-autoimmune form results from mutations in the thyrotropin receptor (TSHR). A rare form of TSHR mutation Met453Thr has been reported in literature and has been associated with thyroid carcinoma. This case presentation will describe how this rare form of TSHR mutation was detected and the course of treatment.

### Case Presentation

A 10-day old male presented with persistent tachycardia (180-190bpm) and irritability. This baby was born prematurely at 33 weeks and 5 days by caesarean section with a birth weight of 2.17kg. The antenatal period was uneventful apart from one episode of foetal tachycardia (160-180bpm). There was no maternal or family history of thyroid disease. Postnatally, this baby was admitted to the neonatal intensive care unit for congenital pneumonia and required invasive ventilation for 1 day. The cord blood thyroid stimulating hormone (TSH) was 0.49 mIU/L ( $\leq 14.29$  mIU/L) and free T4 (fT4) was 14.6 pmol/L (10.25-16.32 pmol/L).

On day 10 of life, the TSH  $<0.01$  mIU/L (0.72-11 mIU/L) and fT4  $>100$  pmol/L (11.5-28.3 pmol/L). Treatment with methimazole (MMZ) 0.55mg/kg/day and propranolol 2mg/kg/day was initiated and clinically the tachycardia improved (120bpm) with good weight gain. The treatment was later changed to propylthiouracil (PTU) as the thyrotoxicosis was difficult to control.

Maternal thyroid function test (TFT), thyroglobulin antibody (TGA<sub>b</sub>) and thyroid peroxidase antibody (TPO) were all normal. However, maternal thyroid stimulating hormone receptor antibody (TSHR<sub>Ab</sub>) was slightly elevated at 1.3 IU/L ( $<1$  IU/L). The baby's TGA<sub>b</sub>, TPO and TSHR<sub>Ab</sub> were all normal initially. At 2 months of age, there was an elevation in the baby's TSHR<sub>Ab</sub> which was later found to be falsely positive.

It was noted that there was a quick rebound in the fT4 level when anti-thyroid medications were stopped, and a high dosage of PTU (3mg/kg/day) was required even after 3 months of age. Further investigations including TSHR mutation analysis showed Heterozygous p.Met453Thr activating mutation. Parental TSHR mutation analysis showed no mutation. Ultrasound of the baby's thyroid showed diffuse coarsening of the thyroid parenchyma and with increased vascularity.

After the gene mutation was found at 5 months of life, block and replacement therapy with MMZ and thyroxine was started. The growth of this child was normal with some mild development delay especially in language. A visible goitre was detected at the age of 3 years.

### Conclusion

A non-autoimmune neonatal hyperthyroidism due to a TSHR activating mutation can be difficult to diagnose where there is a history of maternal elevation of TSHR<sub>Ab</sub>. The main features are absence of autoantibodies, an unusual long and difficult to control course of illness with a quick relapse of fT4 as soon as antithyroid medications are stopped. Close monitoring of the thyroid is important and future thyroidectomy and iodine radiotherapy will be expected.

## **CARBOPLATIN INDUCED RENAL SALT WASTING SYNDROME IN PAEDIATRIC PATIENTS WITH INTRACRANIAL GERM CELL TUMOURS AND CONCOMITANT DIABETES INSIPIDUS**

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### **Introduction:**

Renal salt wasting syndrome (RSWS) is a rare but serious side effect of platinum-based chemotherapy. Concomitant central diabetes insipidus (DI) and RSWS following the administration of carboplatin has not been reported in the literature before.

### **Objective:**

To investigate the occurrence of carboplatin-induced RSWS in paediatric patients with intracranial germ cell tumour (GCT) and concomitant central DI.

### **Methods:**

Retrospective review of paediatric patients (age <19 years at diagnosis), with newly diagnosed intracranial GCT at the Hong Kong Children's Hospital from the opening of the hospital in July 2019 to January 2021. Using electronic patient records, we reviewed the laboratory results, clinical details, and medications of this cohort.

### **Results:**

Fourteen patients were identified to have newly diagnosed intracranial GCT during the study period. They were aged 7-18 years at diagnosis, with a median age of 13 years; 8 (57%) were male. All 14 (100%) had central DI, 11 (78.6%) had central adrenal insufficiency and 10 (71.4%) had central hypothyroidism. Among the 14 patients, 2 (14.3%) underwent tumour resection, 7 (50%) underwent tumour biopsy and 5 (35.7%) did not undergo any neurosurgical procedure before the first course of chemotherapy. Ten (71.4%) had germinomatous GCT and 4 (28.6%) had non-germinomatous GCT.

All patients were administered etoposide and carboplatin following the diagnosis of intracranial GCT. One patient had adipsic DI, with a baseline serum sodium level of 160mmol/L; all other patients had a normal baseline serum sodium level ranging from 135-145mmol/L (median 138mmol/L). All 14 patients were found to have hyponatraemia following the first cycle of carboplatin despite significant negative fluid balance. The nadir sodium level ranged from 122 to 133 mmol/L (median 128 mmol/L). Paired urine sodium levels were high for all patients (40 to >250mmol/L). Ten patients (71.4%) required oral sodium supplementation and 7 (50%) required intravenous supplementation. Two patients (14.2%) developed hypotension and three (21%) required fludrocortisone treatment.

Fourteen patients in this series received 36 subsequent cycles of carboplatin following the first cycle of chemotherapy. Hyponatraemia with serum sodium ranging 118-134mmol/L (median 132mmol/L) was noted following 16 (44.4%) of these cycles. Paired urinary sodium was high during these episodes (97 to >250mmol/L). All patients had normal long-term renal function and were able to be weaned off fludrocortisone and sodium supplements after completion of chemotherapy.

### **Conclusion:**

RSWS was common following the administration of carboplatin in this cohort of patients with intracranial GCT and DI. The combination of DI and RSWS and their respective effects on serum sodium, urine output and fluid balance make the diagnosis elusive and the management of these patients challenging. Clinicians prescribing carboplatin should be alert to the risk of RSWS, particularly in patients who are already vulnerable to electrolyte disturbances.

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Diabetes

### **CLINICAL PROFILE AND TREATMENT OUTCOMES OF DIABETIC KETOACIDOSIS IN THE PHILIPPINE GENERAL HOSPITAL: A TEN YEAR RETROSPECTIVE REVIEW**

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#### **Background:**

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM) characterized by metabolic acidosis, hyperglycemia and ketonemia. Despite the increasing incidence of type 1 and type 2 DM among pediatric patients in the Philippine General Hospital (PGH), data on DKA are limited. In order to improve DKA management and prevention, the clinical profile and treatment outcomes of DKA among pediatric patients in PGH were sought.

#### **Objective:**

To determine the clinical profile and treatment outcomes among pediatric patients admitted with DKA from January 2009 to December 2018

#### **Methodology:**

Retrospective review of medical records of patients aged 0-18 years old admitted for DKA from January 2009 to December 2018

#### **Results:**

Sixty-seven subjects, with a mean age of  $12.0 \pm 4.5$  years, were included. Thirty (44.77%) were newly diagnosed and 37 (55.23%) were established DM cases. Only three subjects had Type 2 DM. Newly diagnosed patients were younger, more undernourished and had longer duration of symptoms. Over half (51.4%) of known DM patients had a history of insulin omission and 11 (29.7%) had  $\geq 2$  previous DKA. The mean time to resolution of acidosis was  $28.3 \pm 16.1$  hours and the mean length of hospital stay was  $5.4 \pm 5.3$  days. Most common complications were hypokalemia (49.3%) and hypoglycaemia (35.8%). Acute renal failure occurred in nine (13.4%) patients. Overall mortality rate was 7.5%.

#### **Conclusion:**

DKA can occur in newly diagnosed and known DM patients, particularly adolescents with insulin omission and poorly-controlled blood glucose. Hypokalemia often occurs during treatment with intravenous insulin and requires monitoring. Acute kidney injury leading to renal failure is a significant morbidity and cause of mortality in pediatric DKA patients. Prompt diagnosis and proper management of DKA is important to improve outcomes.

## A PHASE 2 TRIAL OF LONG-ACTING PEGYLATED RECOMBINANT HUMAN GROWTH HORMONE IN CHILDREN BORN SMALL FOR GESTATIONAL AGE IN CHINA

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### Background and objective:

Pegylated human growth hormone (PEG-rhGH) has a longer half-life and requires less frequent dosing than rhGH. PEG-rhGH was effective and well tolerated in children with growth hormone deficiency in previous phase 1–3 trials. This study aimed to evaluate the efficacy and safety, and determine the optimal dose, of PEG-rhGH in short-stature children born small for gestational age (SGA).

### Methods:

Prepubertal children from 9 hospitals in China who were born with SGA and did not achieve catch-up growth were enrolled in this phase 2 study (NCT02375620). SGA was defined as birth weight or length below the 10th percentile for the gestation age in China. Eligible patients were randomized 1:1 to receive subcutaneous injections of PEG-rhGH at either 0.1 mg/kg/week (low-dose) or 0.2 mg/kg/week (high-dose) for 52 weeks or until unacceptable toxicity or investigator decision. The primary end point was change from baseline in height standard deviation score (HT-SDS) at week 52. Other growth parameters such as height, growth rate, bone maturity, and serum concentrations of blood insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3) were measured.

### Results:

A total of 96 subjects were randomized to either low-dose group (n=48) or high-dose group (n=48); 1 subject in the high-dose group was excluded from the analysis due to lack of posttreatment data. At week 52, HT-SDS significantly increased from baseline in both treatment groups. The mean change from baseline  $\pm$  standard deviation (SD) in the high-dose group and the low-dose group was  $0.923 \pm 0.352$  ( $P < 0.0001$ ) and  $0.511 \pm 0.336$  ( $P < 0.0001$ ), respectively. The increase in HT-SDS from baseline was significantly greater in children in the high-dose group than the low-dose group ( $P < 0.0001$ ). Height velocity was significantly higher in the high-dose group compared with the low-dose group ( $9.80 \pm 1.525$  cm/year vs  $8.25 \pm 1.477$  cm/year;  $P < 0.0001$ ). Greater improvements in height (mean change from baseline  $\pm$  SD,  $10.08 \pm 1.608$  cm vs  $8.40 \pm 1.501$  cm; inter-group  $P < 0.0001$ ) and IGF-1 SDS ( $1.867 \pm 1.747$  vs  $1.168 \pm 1.193$ ; inter-group  $P = 0.0189$ ) from baseline were observed in the high-dose group compared with the low-dose group. Improvements in bone maturity (high-dose vs low-dose, mean change from baseline  $\pm$  SD,  $0.94 \pm 0.36$  vs  $0.97 \pm 0.46$ ; inter-group  $P = 0.7309$ ) and IGF-1/IGFBP-3 molar ratio ( $0.046 \pm 0.044$  vs  $0.031 \pm 0.033$ ; inter-group  $P = 0.0521$ ) were observed in both groups at week 52 from baseline. Most treatment-emergent adverse events (TEAEs) were mild to moderate, 1 patient experienced a severe TEAE; 7.4% of patients experienced serious adverse events and 2.1% discontinued treatment due to TEAEs. The most common TEAEs were upper respiratory tract infection (60%), fever (14.7%), and cough (10.5%). Similar safety profiles were observed in both treatment groups.

### Conclusion:

PEG-rhGH at a dose of either 0.1 mg/kg/week or 0.2 mg/kg/week for 52 weeks was effective and well tolerated in children born with SGA. There was a significantly greater improvement in HT-SDS at 0.2 mg/kg/week. This study supports further investigation of PEG-rhGH at 0.2 mg/kg/week in children born SGA.

## GENETIC SPECTRUM OF 26 KOREAN PATIENTS WITH CONGENITAL HYPOTHYROIDISM BY TARGETED NEXT-GENERATION SEQUENCING

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### Introduction:

Congenital hypothyroidism (CH) is caused by underdeveloped thyroid gland or defect of thyroid hormone synthesis. The prevalence of CH in Korea is 1 per 4,225 people, and *DUOX2* mutations were previously known as the most prevalent mutation in Korean patients with CH. This study was performed to identify the correlation between etiology and genetic mutations in patients with CH in a single tertiary hospital.

### Methods:

This study enrolled 26 patients (12 males and 14 females) with CH (9 ectopic thyroid, 8 dysmorphogenesis, 6 hypoplastic thyroid, 3 athyrosis) between February 2020 and April 2021. All exons and exon-intron boundary sequences of the 23 causative genes were analyzed in 26 patients by targeted next-generation sequencing (NGS) panel.

### Results:

The median age of patients performed NGS was 10.4 years (range 3.3-22.6 years). Seventeen variants in 6 genes (*DUOX2*, *TPO*, *TSHR*, *DUOX2A*, *SLC16A2* and *SLC26A4*) were identified in 13 patients (4 males and 9 females). *DUOX2* mutations (23.5%), *TPO* mutations (23.5%) and *TSHR* mutations (23.5%) were most common detected variants in our patients. Among them, 5 patients (20%) carried biallelic mutations in *DUOX2A*, *DUOX2*, *TPO* and *TSHR*. Three compound heterozygotic mutations in *DUOX2A*, *DUOX2*, *TPO* and one homozygotic mutation in *DUOX2A* were all found in patients with dysmorphogenesis. One compound heterozygotic mutation in *TSHR* was found in patient with hypoplasia. Biallelic mutations in *DUOX2A* were most common (40%), which can be regarded as genetic diagnosis.

### Conclusions:

This study included 18 patients with thyroid gland dysgenesis and 8 patients with thyroid dysmorphogenesis. *DUOX2*, *TPO* and *TSHR* mutations were most common variants. The yield of genetic diagnosis using NGS panel was higher in patients with dysmorphogenesis (50%) than in patients with dysgenesis (5.6%), and *DUOX2A* mutations were the most common biallelic mutations.

## **A CASE OF CONGENITAL HYPOPITUITARISM WITH PITUITARY STALK INTERRUPTION SYNDROME AND NF1 MUTATION**

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Congenital hypopituitarism is defined as deficiencies of one or more pituitary hormones. It may occur due to developmental defects of the pituitary gland, genetic mutations, or perinatal and neonatal events. Clinical manifestations are results of isolated or combined pituitary hormone deficiencies and the onset time of each symptom can be variable. Pituitary stalk interruption syndrome (PSIS) is characterized by ectopic posterior pituitary gland, thin (<1mm) or absent pituitary stalk and anterior pituitary hypoplasia. Genetic causes were identified only in 5% of PSIS cases, and active research has been conducted to find genes related to PSIS.

A 19-month-old boy was admitted due to hypoglycemic seizure. He was diagnosed with central type hypothyroidism at 25 days and had been on levothyroxine. He also showed short stature and developmental delay. Initial serum glucose level was 14 mg/dL. Congenital ACTH deficiency was diagnosed during admission and hydrocortisone replacement was initiated. Brain MRI revealed ectopic posterior pituitary gland and small anterior pituitary gland, which confirmed PSIS. Growth hormone deficiency was diagnosed by growth hormone stimulation test at 24-month-old, and growth hormone replacement was started. Targeted gene panel was performed and it revealed the mutation of the gene NF1 (c.3104T>A, p.Met1035Lys). He had multiple café-au-lait spots, but there was no other abnormality in the brain MRI and ophthalmological examinations. Now he is 3 years and 4 months old and has been managed with levothyroxine, cortisol, and GH.

We report a case of congenital hypopituitarism with PSIS and NF1 mutation (c.3104T>A, p.Met1035Lys).

## **CLINICAL PREDICTORS OF METABOLICALLY UNHEALTHY OBESITY IN CHILDREN AND ADOLESCENTS**

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Ajou University Hospital

### **Background:**

Children and adolescents with obesity can now be classified according to the risk of metabolic and cardiovascular complications, as those with metabolically healthy obesity (MHO) and those with metabolically unhealthy obesity (MUO). We aimed to determine the prevalence of MUO and identify its clinical predictors in pediatric patients with obesity.

### **Methods:**

We evaluated the medical records of 233 boys and girls with overweight and obesity. The children were divided into MHO and MUO groups, and anthropometric and biochemical parameters were assessed. Insulin resistance was confirmed in both groups through an oral glucose tolerance test (OGTT), and binary logistic regression analysis was used to determine predictors of MUO in children with obesity.

### **Results:**

Of the 233 children, MUO was found in 73.4% (n=171) and MHO in 26.4% (n=62); those in the MHO group were younger than those in the MUO group. Blood pressure, triglyceride, total cholesterol, and uric acid levels were significantly higher in the MUO group than in the MHO group. Further, the MUO group exhibited a significantly higher co-occurrence of non-alcoholic fatty liver disease (42.1% vs 27.4%,  $P < 0.05$ ) and higher level of insulin resistance ( $P < 0.001$ ) than the MHO group. Serum levels of uric acid and homeostasis model assessment of insulin resistance index (HOMA-IR) were confirmed as clinical predictors of the MUO phenotype in children with obesity.

### **Conclusion:**

The prevalence of MUO in children with obesity was relatively high; further, serum levels of uric acid and HOMA-IR can be used as clinical predictors of MUO.

**CASE REPORT: HYPERPHOSPHATAEMIC HYPOCALCAEMIC SEIZURES IN AN AUTISTIC CHILD WITH DAILY CONSUMPTION OF COCA-COLA**

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**Introduction**

Excessive consumption of Cola, which has a higher phosphorus content (about 15–20 mg/dL) than other soft drinks, is an unusual cause of hypocalcaemia. Here, we illustrate a case of a boy with autism spectrum disorder and highly selective diet with daily cola presenting with hypocalcemic seizures.

**Case Presentation:**

A 5 year old boy presented to the children's emergency with generalized tonic clonic seizures. Investigations were significant for hypocalcaemia (ionized calcium 0.69 mmol/L [1.15-1.35]), hyperphosphataemia (2.38 mmol/L [1.28-1.98]), hypomagnesemia (0.67 mmol/L), severe vitamin D deficiency (25-OH vitamin D level of 5.1 ug/L [ $>30$ ]), and normal alkaline phosphatase and parathyroid hormone levels (7.9 pmol/L). His urine creatinine:calcium ratio of 0.09 was normal. ECG showed prolonged QT interval. His seizures were aborted with correction of the hypocalcemia. He did not have any evidence of tetany or rickets.

Further history revealed that he had autism spectrum disorder. He was pre-verbal and attended a special education school. He had a restrictive diet consisting of clear broth, nuggets or hot dogs and daily cola of 480 mL/day. This diet was low in calcium and vitamin D (amongst other nutritional deficiencies) and high in phosphorus (597 mg/dL), consistent with his biochemical derangements.

He was started on calcium and vitamin D supplementation with resolution of his hypocalcaemia and improvement in vitamin D levels. There were no further seizures. His diet remained highly challenging to manage and he has defaulted several appointments to see the multi-disciplinary feeding and nutrition clinic and endocrine clinic. His parent stopped his daily cola ingestion, and stopped all supplements on their own one month after discharge. With cessation of his daily cola intake, his calcium and phosphate levels remained normal even after one year post discharge, although his vitamin D levels were still low at 7.6 ug/L.

**Discussion:**

Excessive exogenous phosphate intake can lead to hyperphosphataemia, thereby inhibiting 1-alpha hydroxylase and causing a decrease in the formation of 1-alpha, 25-hydroxy vitamin D<sub>3</sub> resulting in hypocalcaemia (1-2). Consequently, hyperparathyroidism develops, although in our patient's case, it was inappropriately normal due to hypomagnesemia from his restrictive diet. Extremely low levels of magnesium can induce a paradoxical block of PTH secretion. The mechanism is traced to the activation of the Calcium sensing receptor (a G protein coupled receptor) which causes inhibition of PTH secretion. In addition, the inhibition of bone resorption along with precipitation of calcium-phosphate complexes in soft tissues can lead to reduced serum calcium (2).

Mazariegos-Ramos et al has previously described 5 children who had consumed large amounts of soft drinks presenting with hypocalcaemic tetany, whose clinical and biochemical abnormalities subsequently resolved after cessation of the soft drink (3). The same group proceeded to publish a case control study of 57 children, which demonstrated that an intake of at least 1.5L a week of soft drinks containing phosphoric acid is a risk factor for the development of hypocalcaemia (4).

The learning point from this case is that the assessment and management of a child with hypocalcemia should include a detailed dietary history, paying close attention to soft drinks intake with high phosphoric content and other dietary sources of phosphate, especially in this context of an autistic child with a restrictive diet.

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## THYROID DYSHORMONOGENESIS DUE TO DUOXA2 MUTATION MIMICKING TRANSIENT TYPE CONGENITAL HYPOTHYROIDISM

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**Context:** Dual oxidase maturation factor 2 (DUOXA2) is necessary for enzymatic activity of dual oxidase 2 (DUOX2) to generate hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) production during thyroid hormonogenesis. Genetic mutations of DUOXA2 cause congenital hypothyroidism.

**Case Description:** Two Korean boy and girl initially suspected to have transient CH after 30-day trial-off therapy were confirmed to have permanent CH with known DUOXA2 gene mutations. For a boy, first trial-off therapy attempted at 3.0 years was failed with elevated TSH more than 10 mIU/L despite normal radionuclide scan, but second trial at 4.5 years was succeeded with TSH less than 10 mIU/L and normal thyroid ultrasound scan. For a girl, trial-off therapy at 2 years was succeeded with TSH less than 10 mIU/L and normal thyroid radionuclide scan. However, they showed elevated TSH more than 10 mIU/L after 1.5 year and 2.0 year respectively. As a result, they resume taking thyroxine again. Next generation sequencing showed compound heterozygosity with DUOXA2 gene mutations at Y138X and Y246X in the boy, and homozygosity with DUOXA2 gene mutation at Y246X in the girl.

**Conclusion:** Regular follow-up is recommended even after termination of treatment in transient CH and genetic study might be helpful to assess the permanence of hypothyroidism in case of mildly elevated TSH after trial-off therapy.

**RATE OF WEIGHT GAIN AND ITS ASSOCIATION WITH HOMEOSTATIC MODEL ASSESSMENT-INSULIN RESISTANCE (HOMA-IR) AMONG OBESE CHILDREN ATTENDING PAEDIATRIC ENDOCRINE CLINIC, HOSPITAL UNIVERSITI SAINS MALAYSIA**

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Universiti Sains Malaysia

**Objective:**

We aimed to study the median time to gain weight from baseline and factors that were associated with rate of weight gain among obese children attending pediatric endocrine clinic Hospital USM.

**Methodology:**

We recruited 70 participants with the mean age of  $10.1 \pm 2.94$  years with exogenous or simple form of obesity from June 2019 until September 2020. We analyzed their demography (age, gender, ethnicity, family background), measured their anthropometry (weight, height, BMI) and monitored monthly weight increment and finally analyzed their HOMA-IR at baseline and after 6 months of follow up.

**Results:**

The mean time to gain 5 kg from baseline was 16 weeks (95% CI): (15.2, 16.7). Multivariate analysis showed only HOMA-IR after 6 months was a significant predictor affecting time to gain 5 kg; Adjusted HR: (95%CI) 1.617 (1.232, 2.123), ( $p=0.001$ ).

**Conclusion:**

The time to gain 5 kg from baseline weight was increased 1.6 times in the presence of insulin resistance at 6 months follow up in patients with obesity. More intensive education and closed follow-up are recommended for children with obesity.

**Keywords:**

HOMA-IR, prognostic factor, obesity, insulin resistance

## CLINICAL CHARACTERS AND PROGNOSIS OF A CASE WITH BIFOCAL GERM CELL TUMORS IN CHILDREN

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### Background:

In children and adolescents suffered from primary intracranial germ cell tumors, bifocal GCTs are rare and were reported a bad prognosis. In this study, we report a case and summarize the clinical characteristics and prognosis.

**Methods:** A boy suffered from bifocal GCTs (Basal ganglia and pineal region) was diagnosed in our hospital and accepted chemotherapy+radiotherapy, and was followed up.

### Results:

1. A 8 year and 2 month old boy came to our hospital because of enlargement of the penis for 5 months with pubic hair growth. Facial acne, beard, deepening of the voice, gynecomastia and enlarged penis(9cm\*3cm) were found. Bilaterally testicular volume :8mL. Tanner stage of pubic hair: stage 3. No headache, nausea or vomiting, and no abnormal signs of nervous system.

Laboratory data: Basal FSH and LH levels decreased, with the elevated serum testosterone levels: 9.35ng/ml. And the gonadotrophin-releasing hormone agonist(GnRHa) stimulation test showed GnRH independent precocious puberty. Serum  $\beta$ -human chorionic gonadotropin( $\beta$ -hCG) increased (22.3mIU/ml), along with elevated cerebrospinal fluid (CSF)  $\beta$ -hCG (21.31mIU/ml), but both serum and CSF levels of the AFP were normal. MRI scans revealed bifocal germ cell tumors located in the pineal gland and basal ganglia. No other extracranial metastases were found. When compared to other primary solitary intracranial GCTs cases( published before by our team), no differences of the serum and CSF  $\beta$ -hCG levels, serum testosterone levels and clinical manifestations were found.

3. The boy accepted regular chemotherapy and radiotherapy. After one course of chemotherapy, the serum levels of  $\beta$ -hCG, as well as the CSF  $\beta$ -hCG levels decreased significantly. Serum testosterone levels returned normal.

**Conclusion:** Peripheral precocious puberty is usually the first or one of the typical symptoms in boys with hCG-secreting GCTs. There are no differences in clinical manifestations between solitary and bifocal primary intracranial tumors. Patients with basal ganglia lesions do not necessarily have neurological symptoms. The combination of the detection serum hCG and CSF hCG levels may be significant for early diagnosis, the determination of the tumor locations.

**Miscellaneous****LONG TERM FOLLOW-UP OF A BOY WHO HAD SUPRASSELLA TUMOR RECURRENCE 4 YEARS AFTER THE FIRST DIAGNOSIS OF EXTRACRANIAL GCTS**

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**Background:**

In children with extracranial germ cell tumors(GCTs), brain metastases are rare and are classified as "poor prognosis". The longest interval to brain metastases was 36 months after diagnosis in children, however, it is still less understood about the brain metastases in children with extracranial GCTs .

**Methods:**

We report a boy who had suprasella tumor recurrence 4 years after the first diagnosis of extracranial GCTs (thymus) and summarized the clinical characters and prognosis of the case.

**Results:**

1. The patient was a 6 year and 6 month old boy and presented with penis enlargement and gynecomastia for 2 months. He had mild polydipsia and polyuria since he was 5 year old, but the diagnosis of central diabetes insipidus could not be confirmed. Physical examination showed gynecomastia, pigmentation of the areola, enlarged penis(6.5cm\*2.5cm), increased testicular volume (4mL) and pubic hair(Tanner stage 2).
2. Laboratory data showed elevated serum levels of testosterone(30.51nmol/L) and serum levels of Estradiol(201pmol/L), while basal LH and FSH levels remained very low. No response to GnRHa stimulation test. The levels of serum  $\beta$ -hCG were ranged from 56 mIU/ml to 193mIU/ml, while serum AFP levels were in normal range. No elevated levels of hCG were found in CSF (<1.2mIU/ml). Pituitary functions were found normal. MRI scans showed the tumor in the thymus(8mm\*8mm). Sellar MRI found no abnormalities, pituitary size was 9mm, posterior pituitary was normal also, however, a cisterna magna arachnoid cyst was found. No difference of the serum levels of hCG was found between this case and other children with extracranial tumors (published by our team).
3. The boy accepted surgery therapy and the diagnosis of teratoma combine with malignant germ cell tumor was confirmed by pathology. After surgery, chemotherapy and radiotherapy was performed routinely. The serum level of  $\beta$ -hCG decreased rapidly in the second day after surgery and could not be detected there after (The serum levels of hCG were followed up every 1 month in the after surgery, and then every 3 months in the next 2years, and then every 6 months).
4. Three years later, the boy presented multiple pituitary hormone deficiency(growth hormone deficiency, central hypothyroidism, central adrenal insufficiency). Sellar MRI showed empty sella and disappearance of posterior pituitary gland. But the serum and CSF levels of  $\beta$ -hCG remained negative. Hormone replacement therapy(HRT) has performed since then. Four years after the first diagnosis( 10 year and 9 month old), the boy again had penis enlargement and erection, and laboratory data showed elevated levels of serum  $\beta$ -hCG(181.4mIU/ml) and CSF  $\beta$ -hCG(14.1mIU/ml). MRI scans showed thickened pituitary stalk and suggested the suprasella region recurrence, but no other metastases were found(mediastinum, lungs, liver, pelvis, and spine were normal). Routine chemotherapy+ radiotherapy was performed again and serum and CSF  $\beta$ -hCG levels returned normal very fast. After the relapse, the boy has been follow-up for more than 7 years. No second recurrence occurred, but panhypopituitarism persistent and lifelong HRT needed.

**Conclusion:**

GnRH independent precocious puberty is usually the first or one of the important clues for the diagnosis in boys with hCG-secreting GCTs. The detection of serum levels of hCG combined with GSF hCG levels may be significant for early diagnosis, the determination of the tumor locations and evaluation of tumor recurrence. The interval of relapse in children with extracranial GCTs can be 4 years, so the long term followed up is needed, and the prognosis is satisfied in our case.

### ASSESSMENT OF CAROTID INTIMA MEDIA THICKNESS IN CHILDREN WITH AND WITHOUT TYPE 1 DIABETES MELLITUS: A CASE CONTROL STUDY

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**Background:** Children with Type 1 Diabetes mellitus (T1DM) are predisposed to endothelial dysfunction and subclinical vascular disease.

**Objective:** Compare the carotid intima media thickness (CIMT) in children with T1DM with age, sex and BMI matched healthy children and determine their risk factors.

**Methods:** Cross sectional study was conducted on children 8-18 years with T1DM on insulin therapy for > 1 y and free from acute complications and known comorbidities. Age, sex, and BMI matched healthy children were recruited as controls. All participants underwent detailed clinical and biochemical evaluation and were screened for diabetic complications. The assessment of CIMT was done in all subjects by radiologist, who was blinded to the study groups using ultrasound in linear probe (5-12 MHz).

**Results:** A total of 100 children were enrolled with 50 in each group. The mean age and duration of diabetes among the cases was  $6.96 \pm 3.2$  years and  $5.29 \pm 3.3$  years respectively. A significantly increased CIMT was observed in children with T1DM as compared to controls ( $0.49 \pm 0.06$  vs.  $0.43 \pm 0.06$  mm; p value <0.001). Amongst the cases, CIMT was reported higher in males and those with a family history of cardio-vascular risk factors. No significant correlation was found between CIMT and age, BMI, duration of diabetes, lipid profile, presence of micralbuminuria and HbA1c in children with T1DM.

**Conclusions:** Children with T1DM are susceptible to increased CIMT independent of their BMI, lipid profile, glycemic control and duration of diabetes. Non-invasive methods for monitoring vascular changes like CIMT are useful to facilitate early detection.

## HYPERINSULINISM INDUCED FASTING HYPOGLYCAEMIA IN A PATIENT WITH ACUTE LYMPHOBLASTIC LEUKAEMIA ON 6 MERCAPTOPYRINE

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### Introduction:

Advances in treatment of acute lymphoblastic leukaemia (ALL) have improved the survival rate and treatment associated toxicities over the years<sup>1</sup>. 6 mercaptopurine (6-MP) is the backbone of maintenance treatment in ALL. It is well known to cause myelosuppression in patients with low thiopurine methyltransferase (TPMT) activity. However, 6-MP induced fasting hypoglycaemia is a rare occurrence, first reported 20 years ago<sup>2</sup>. Higher thiopurine methyltransferase activity results in increased production of 6-MMP (6-methyl-mercaptopurine) in symptomatic hypoglycaemic patients<sup>3</sup>. Other studies reported hyperinsulinism is responsible, yet the exact mechanism is unknown<sup>2,4,5</sup>.

### Case report:

We report the first case of documented fasting hypoglycaemia in a patient under the MASPORE 2020, which is a protocol developed via collaboration between Malaysia and Singapore haemato-oncologists. A 10-year-old boy who was diagnosed with ALL in April 2020, was referred for recurrent symptomatic fasting hypoglycaemia. He was in the midst of maintenance phase of treatment. His height and weight were 144cm (90<sup>th</sup> centile) and 35kg (50<sup>th</sup> centile), respectively. He had symptoms suggestive of fasting hypoglycaemia a month after his 6-MP dose was increased. He complained of palpitations, nausea and lethargy in the mornings which resolved with meals.

The first documented hypoglycaemia occurred after an 8 hour fast for intrathecal methotrexate procedure. He was symptomatic with bedside glucose testing of 2.3 mmol/L, which was corrected after dextrose bolus and food intake. Procedure was rescheduled again with shorter fasting duration of 4 hours but hypoglycaemia recurred with capillary glucose of 2.4 mmol/L. Fasting test performed the next day revealed inappropriately high insulin and C-peptide levels (12.4 mU/L and 538 pmol/L, respectively) with venous glucose of 1.8 mmol/L. Incongruously, beta-hydroxybutyrate level was also elevated (1.6 mmol/L) in the setting of hyperinsulinaemia. Liver function test also showed conjugated hyperbilirubinaemia with raised transaminases. 6-MP was withheld and repeated fasting samples were taken to confirm hyperinsulinaemic hypoglycaemia. The serum insulin and C-peptide levels were greatly reduced to 1.8 mU/L and 208 pmol/L, with improvement of liver transaminases. He was able to fast up to 16 hours without hypoglycaemia nor ketosis 5 days after omitting 6-MP, suggestive of transient hyperinsulinism due to 6-MP. After 2 weeks, 6-MP was resumed at a reduced dose with split timing after normalisation of liver function test. No hypoglycaemia symptoms reported following the adjustment.

### Conclusions:

We have shown clearly hyperinsulinism is part of the pathogenesis of 6-MP induced hypoglycaemia. The hypoglycaemia was transient as resolution of symptoms was observed after withholding 6-MP. Reduction of 6-MP dose and splitting the timing can potentially help to prevent the occurrence of hypoglycaemia. The TPMT activity and metabolites were sent to further elucidate the pathogenesis but the results are pending.

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## **BETA CELL FUNCTION, INCRETIN HORMONES AND INCRETIN EFFECT IN OBESE CHILDREN AND ADOLESCENTS WITH PREDIABETES**

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### **Background:**

Defects of incretin hormones and incretin effect may be underlying mechanisms of abnormal glucose metabolism in youth.

### **Objective:**

To assess incretin hormone dynamics during an oral glucose tolerance test (OGTT) and incretin effect in obese children with prediabetes in comparison with those with normal glucose tolerance (NGT)

### **Methods:**

Overweight and obese children were enrolled and classified according to OGTT results as NGT and prediabetes. Insulin sensitivity, insulin secretion, incretin hormone concentrations during OGTT; and incretin effect derived from OGTT and intravenous glucose tolerance test were determined and compared between NGT and prediabetes groups. Results: Sixty-three patients (43 NGT and 20 prediabetes) were enrolled. Their median (interquartile range) age was 12.5 (11.1, 13.8) years. Peak glucagon-like peptide-1 (GLP-1) was demonstrated at 30 minutes during OGTT and was higher in the prediabetes group [49.2 (35.6, 63.6) vs 36.5 (27.6, 44.2) pmol/L,  $p = 0.009$ ]. However, incremental areas under the curves (iAUCs) of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) were not different between the two groups. There was no difference in incretin effect between NGT and prediabetes [NGT: 66.5% (60.2%, 77.5%) vs prediabetes: 70.0% (61.5%, 75.0%),  $p = 0.645$ ]. Incretin effect had positive correlations with iAUCs of both GLP-1 and GIP (GLP-1:  $r = 0.40$ ,  $p = 0.004$  and GIP:  $r = 0.37$ ,  $p = 0.009$ ).

### **Conclusions:**

Comparing between obese children with prediabetes and NGT, there were no differences in overall incretin hormone changes during OGTT and incretin effect. Incretin effect was positively correlated with iAUCs of GLP-1 and GIP.

### **SEVERE FIBROUS DYSPLASIA SECONDARY TO MCCUNE-ALBRIGHT SYNDROME**

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McCune-Albright Syndrome (MAS) is a rare genetic disorder caused by post zygotic somatic mutation in the GNAS1 gene causing hyperfunctioning of target organ. Patient with MAS usually presents with triad of symptoms of fibrous dysplasia, hyperfunctioning endocrinopathies and hyperpigmentation. We present a case of 9 years old girl who had closed right midshaft femur fracture after a trivial fall. Physical examination revealed, height 147cm (90<sup>th</sup> percentile), weight 34kg (50<sup>th</sup> percentile), Tanner stage of A2B3P2 and multiple pigmented patches with irregular borders at left lumbar region. Other systemic examinations were unremarkable. Biochemically revealed serum calcium 2.07 mmol/L, phosphate 1.37 mmol/L, alkaline phosphatase 899 U/L, iPTH 9.26 pmol/L, 25(OH) Vitamin D 21 nmol/L. Xray showed scattered patchy lucency of long bones and shepherd crook deformity in bilateral proximal femur which was suggestive of polyostotic fibrous dysplasia. Her bone densitometry showed osteoporotic bone with T score of -3.9 and -4.7 at L1-L4 and left hip respectively. Bone biopsy was consistent with fibrous dysplasia. With typical 'Coast of Maine' pigmentation, tall stature, fibrous dysplasia and early onset of puberty, she was diagnosed to have fibrous dysplasia secondary to MAS with concomitant vitamin D deficiency. She received vitamin D3 and calcium carbonate supplementation for 3 months and later was started on zoledronic acid.

## TRIGLYCERIDE GLUCOSE INDEX IS A SUPERIOR BIOMARKER FOR PREDICTING TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

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### Background:

The triglyceride-glucose (TyG) index has been associated with predicting type 2 diabetes mellitus (T2DM); however, its relationship with the homeostatic model assessment of insulin resistance (HOMA-IR) in T2DM has not been established.

### Objective:

Herein, we investigated the role of the TyG index for detecting T2DM in children and adolescents and compared it with the HOMA-IR index.

### Methods:

A cross-sectional study was performed using 176 overweight or obese children and adolescents, with a mean age of  $11.34 \pm 3.24$  years. The TyG index was calculated as  $\ln(\text{fasting triglyceride [TG] [mg/dL]} \times \text{fasting glucose [mg/dL]}/2)$ .

### Results:

Of the 176 subjects, 57 (32%) were diagnosed with T2DM. Significant differences were observed in the TyG index between T2DM and non-T2DM groups ( $p < 0.001$ ). The TyG index positively correlated with fasting glucose ( $r = 0.519$ ,  $p < 0.001$ ), HOMA-IR ( $r = 0.189$ ,  $p < 0.017$ ), HbA1c ( $r = 0.429$ ,  $p < 0.001$ ), total cholesterol ( $r = 0.257$ ,  $p = 0.001$ ), triglyceride (TG) ( $r = 0.759$ ,  $p < 0.001$ ), and low-density lipoprotein cholesterol (LDL-C) ( $r = 0.152$ ,  $p < 0.001$ ), and demonstrated a negative correlation with high-density lipoprotein cholesterol (HDL-C) ( $r = -0.107$ ,  $p < 0.001$ ) after controlling for sex, age, and body mass index (BMI) standard deviation score (SDS). In multiple regression analyses, 91.8% of the variance in the TyG index was justified by age, glucose, HOMA-IR, TG, LDL-C, and HDL-C ( $p < 0.001$ ). In the receiver operating characteristic analysis, the TyG index (area under the curve [AUC] 0.839) exhibited better performance than HOMA-IR (AUC 0.645) in identifying patients with T2DM ( $p < 0.001$ ).

### Conclusions:

The TyG index was significantly associated with insulin resistance in T2DM and could be superior to HOMA-IR in predicting T2DM in children and adolescents.

## CLINICAL FEATURES OF HYPERPROLACTINEMIA IN CHILDREN AND ADOLESCENTS

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### Background/Purpose:

Hyperprolactinemia is a rare endocrine disorder in childhood and there are limited etiological, clinical, and demographic data. The purpose of this study was to evaluate the clinical features and course of hyperprolactinemia in childhood and adolescents and to help diagnose and plan the management.

### Methods:

In this single-center retrospective study included 21 patients with hyperprolactinemia from Ajou University Division of Pediatric Endocrinology. Clinical symptoms, brain magnetic resonance imaging (MRI), serum prolactin (PRL) levels, associated diseases, medications, and post-treatment course were reviewed.

### Results:

Among 21 patients (male=10, female=11) with hyperprolactinemia, 5 females were diagnosed with prolactinomas (median age 16.1 years, range 15.2–17.0 years). 16 patients were diagnosed with idiopathic hyperprolactinemia (median age 10.9 years, range 6.3–16.2 years, 6 females, 10 males). The mean PRL level at diagnosis was higher in patients with prolactinoma ( $134.12 \pm 112.05$  ng/mL) than in patients with idiopathic hyperprolactinemia ( $27.48 \pm 9.13$  ng/mL) ( $p=0.008$ ). Children with hyperprolactinemia presented variable clinical symptoms. The clinical manifestations of hyperprolactinemia at diagnosis were headache (7/11, 63.6%), menstrual irregularities (5/11, 45.5%), galactorrhea (3/11, 27.3%), visual field defect (1/11, 9.1%), obesity (1/11, 9.1%) in girls. In boys, gynecomastia (8/10, 80%) and obesity (6/10, 60%) were present. Headache and menstrual irregularities were more common in patients diagnosed with prolactinoma than in patients with idiopathic hyperprolactinemia. Cabergoline as medical treatment ( $n=2$ ) decreased the tumor volume and normalized the PRL level.

### Conclusion:

In children and adolescents with irregular menstrual cycles and headache, hyperprolactinemia is suspected of prolactinoma and cabergoline was effective for the treatment of prolactinoma.

**THE RELATIONSHIP BETWEEN BODY MASS INDEX CHANGES AND BONE AGE PROGRESSION DURING GONADOTROPIN-RELEASING HORMONE AGONIST TREATMENT IN GIRLS WITH IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY**

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**Purpose:**

To analyze the relationship between body mass index change and bone age progression during gonadotropin-releasing hormone agonist(GnRHa) treatment in girls with idiopathic central precocious puberty

**Methods:**

65 girls with idiopathic central precocious puberty who are treated with GnRHa more than 2 years were retrospectively reviewed. Height, weight, Tanner stage, bone age were measured every 6 months from the start of treatment. The degree of obesity was evaluated using the body mass index (BMI) standard deviation score (SDS), and the relationship between the change in obesity and the progression of bone age was analyzed. Overweight was defined as a BMI greater than or equal to the 85th percentile. The chronological age at the start and end of treatment was  $7.00\pm 0.00$  years and  $10.63\pm 0.50$  years in the overweight group (16 patients), respectively, and  $6.86\pm 0.35$  years and  $10.71\pm 0.54$  years in the other group (49 patients), respectively.

**Results:**

There was no difference in bone age between the normal weight group and the overweight group at the start of treatment ( $9.85\pm 0.57$  years vs  $10.04\pm 0.73$  years,  $P=0.263$ ). Bone age was higher in the overweight group, but after 1 year of treatment, 2 years of treatment, and at the end of treatment, the overweight group had a higher bone age than the normal weight group ( $10.47\pm 0.56$  years vs  $10.87\pm 0.57$  years,  $P=0.02$ ;  $11.06\pm 0.47$  years vs  $11.46\pm 0.51$  years,  $P=0.004$ ;  $11.70\pm 0.46$  years vs  $12.01\pm 0.52$  years,  $P=0.03$ ). Bone age at the end of treatment was related to overweight at the start of treatment ( $r=0.265$ ,  $P=0.03$ ) and the increase in BMI SDS from normal to overweight during treatment ( $r=0.285$ ,  $P=0.02$ ). There were 11 children (17%) whose BMI SDS increased from normal weight to overweight during treatment, compared with the other patients, there was no difference in bone age during 2 years of treatment, but bone age at the end of treatment was higher ( $12.09\pm 0.60$  years vs  $11.71\pm 0.47$  years,  $P=0.02$ ), and the difference in bone age before and after treatment was also greater ( $2.31\pm 0.68$  years vs  $1.79\pm 0.52$  years,  $P=0.01$ ). Linear regression analysis demonstrated that the increase in BMI SDS from normal to overweight during treatment had a positive correlation with bone age at the end of treatment ( $\beta=0.31$ ,  $R^2=0.07$ ,  $P=0.03$ ).

**Conclusion:**

In girls with central precocious puberty, an increase in obesity from normal weight to overweight during GnRHa treatment does not affect bone age progression until 2 years from the start of treatment, but might be a risk factor for bone age progression at the end of treatment.

## A YOUNG INFANT WITH COMPLETE ANDROGEN INSENSITIVITY SYNDROME

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Complete androgen insensitivity syndrome (CAIS) is a rare X-linked recessive genetic disorder resulting from maternally inherited or de novo mutations involving the androgen receptor (AR) gene. The diagnosis of CAIS is based on the presence of female external genitalia in an individual with 46, XY karyotype having normally developed but undescended testes and target tissue unresponsiveness to androgen. Our case presented at the age of 2 months with asymmetric labia majora with bilateral labial mass. Pelvic ultrasound revealed absence of female internal genital organs and testes at labial folds. The child was found to have 46 XY karyotype.

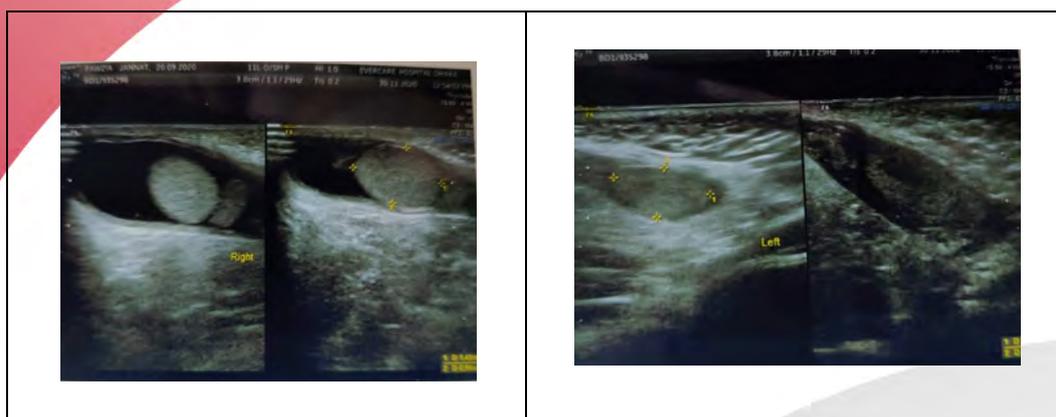
### Introduction

Complete androgen insensitivity syndrome (CAIS) is a classic type of androgen insensitivity syndrome (AIS) with an estimated prevalence of 1 in 20,000 to 64,000 newborn males.<sup>1</sup> Approximately 900 different mutations have been linked with AIS.<sup>2</sup> Seventy percent patients with CAIS result from maternally inherited mutations, while the remaining 30% are de novo mutations.<sup>3</sup> In humans, the vital period for genital virilization is between 8 and 14 weeks of gestation and depends on androgen secretion and functioning androgen receptors.<sup>4</sup> Clinical diagnosis of CAIS is established following the typical presentation of an inguinal hernia or labial swelling in a female infant or primary amenorrhea at puberty with a 46, XY karyotype.<sup>5</sup> Pelvic ultrasounds or MRIs could be helpful in confirming the absence of Mullerian structures, revealing the presence of a blind-ending vagina and identifying testes. Finally, the diagnosis is based on clinical presentation, laboratory tests and imaging in a female with a 46, XY karyotype and confirmed throughout AR gene analysis.<sup>6</sup>

We report a 2 months old female child who presented with bilateral labial mass. She was diagnosed as a case of CAIS after doing hormone assay, imaging study and karyotyping. This is the first reported youngest case with CAIS from Bangladesh.

### Case Summary:

Two months old child presented to outpatient clinic of Evercare Hospital Dhaka to address asymmetry of labia majora with palpable mass. She was first born child of 1<sup>st</sup> degree consanguineous Bangladeshi healthy parents. She was delivered pre-term by caesarean section at 34 weeks gestation with low birth weight (2.2 kg) due to premature labor with foetal distress. At presentation, she was on exclusive breast feeding weighing 4.42 kg and length 53 cm. She had normal external female genitalia with only one external opening. There was asymmetry in size of labia majora with right side slightly enlarged than that of left having bilateral palpable gonads. Ultrasound revealed, absence of uterus and presence of bilateral testes in the labial folds measuring 1.4 X 0.91 cm on right side and 1.3 X 0.7 cm on the left side (Fig 1). The results of hormonal studies at 2 and 4 months are shown in Table I which were within normal range. The patient's karyotype was that of a normal male, i.e., 46, XY. They were proposed the molecular study of the AR gene for the patient and mother for confirmation and genetic counseling.



**FIG I:** Ultrasound showing (a) right testis (1.4 X 0.91 cm) and (b) left testis (1.3 X 0.7 cm) in both labial folds.

**TABLE I:** Serum hormone concentrations at 2 and 4 months age

Hormone (units), ref. range	2 months age	4 months age
TSH ( $\mu$ IU/ml) (0.4-5.3)	4.1	
FT4 (ng/dl) (0.8-1.9)	1.3	
17 $\alpha$ -OHP (ng/ml) (0.49-4.1)	2.52	
LH (mIU/ml) (0.02 – 7)		4.1
FSH mIU/ml (<4) (0.16 – 4.1)		2.3
S. Testosterone (ng/ml) (0.6 – 4)		2.4
5 $\alpha$ -Dihydrotestosterone (pg/ml) (120 – 850)		124

## Discussion

Our reported case presented during early infancy with normal female external genitalia with bilateral palpable gonads at labial folds and only one external opening resembling blind ending vagina. Only 1 to 2% of the CAIS cases present in the neonatal period with the appearance of bilateral inguinal or labial swellings containing a testis in an apparently female infant.<sup>7</sup>

In our case, pelvic and local labial ultrasound revealed absence of uterus and bilateral testes respectively. In CAIS, Leydig cell secretion of testosterone is normal, which is normally converted into dehydrotestosterone (DHT) through 5-alpha reductase; but the effect of DHT is virtually nil due to the presence of non-functioning AR. Moreover, anti-mullerian hormone (AMH) secretion from Sertoli cells prevents the Müllerian system from developing into a uterus and other internal structures.<sup>8</sup>

In adolescent women with AIS, breast and female adiposity develop because estrogens are converted from androgens by the normal functioning of aromatase enzyme. However, pubic and axillary hair is absent or sparse.<sup>9</sup> Cases of CAIS are mostly raised as females. The reported case is raised as female and we explained in detail regarding the necessity of genetic test for genetic counselling, serial follow up and future risk of tumors of gonads; and possible medical and surgical treatment plan.

## Conclusion

Appropriate and timely diagnosis of a child with CAIS is crucial. A team approach involving endocrinologists, clinical geneticists, urologists, gynecologists, and psychologists is required.

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## PREVALENCE OF THE COELIAC DISEASE AND ITS CHARACTERISTICS AMONG PATIENTS WITH TYPE 1 DIABETES FOLLOWED UP AT THE LADY RIDGEWAY HOSPITAL FOR CHILDREN COLOMBO SRI LANKA

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### Introduction:

Type 1 diabetes and Coeliac disease share common HLA markers and the prevalence of coeliac disease in type 1 diabetes ranges from 1-11% in the globe<sup>1,2,3</sup> and has a geographical variation<sup>3</sup>. Most of the children with Coeliac disease remained asymptomatic<sup>1,3</sup>. The serological testing for antibodies and intestinal biopsy plays a major role in the diagnosis. The diagnosis is aided by serological tests that measure antigliadin (AGA), antireticulin (ARA), antiendomysial (AEA), and ant tissue transglutaminase (AtTG)<sup>4</sup>. The biopsy of small intestine helps in confirmation of the diagnosis in case of low antibody levels<sup>2</sup>. In Asia, similar to the global trend, prevalence of Diabetes is rising in the children. But there are no sufficient epidemiological data available in most countries<sup>3,5</sup>. In this disease, a gluten free diet prevents the hypoglycemic episodes and improves the glycemic control<sup>3</sup>. Screening for the coeliac disease in diabetes is a recommended practice, though it is not done in our country due to financial restrictions.

### Objectives

To describe the prevalence of positive coeliac screening in a cohort of patients with type 1 diabetes attending to the Pediatric endocrine clinic at Lady Ridgeway Hospital Colombo Srilanka.

### Methodology:

This is a descriptive cross-sectional study, where the study population was serologically confirmed type 1 diabetes patients. Our sample size was 56 patients, aged 1-16 years, comprised of 29 females with 27 male patients from multiple sociocultural backgrounds. The subjects were recruited randomly using random number calculator. The demographic data was collected via data collection sheet and blood was withdrawn for serum IgA level and tissue transglutaminase Ig A level.

### Results:

Out of the 56 children only two were found to be positive for coeliac screening. Thus, the calculated prevalence was 3.5%. Ig A transglutaminase antibody level of >800AU/ml and 64AU/ml (normal range <8) was seen in the two children. They did not have any gastrointestinal symptoms related to coeliac disease. Both of them underwent endoscopy and biopsy. The histology reports had evidence suggestive of coeliac disease and were commenced on a gluten free diet

### Conclusion:

Prevalence of Coeliac disease among children with type 1 Diabetes in Srilanka is relatively low compared to western population and some of the Asian countries. Further studies are needed recruiting larger population to decide whether routine screening for coeliac disease is beneficial in our children.

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## ETIOLOGIES, CLINICAL CHARACTERISTICS, AND OUTCOME OF TREATMENT OF CHILDREN AND ADOLESCENTS WITH YOUTH-ONSET DIABETES AT SIRIRAJ HOSPITAL – A SINGLE TERTIARY CARE CENTER EXPERIENCE

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### Background:

Youth-onset diabetes is a chronic and burdensome disease on patients and caretaker, type 1 diabetes (T1D) in particular. The incidence of both T1D and type 2 diabetes (T2D) has increased in many parts of the world, however, report on etiologies, glycemic control, and complications of youth-onset diabetes in Asian countries is limited. The objectives of this study were to 1) identify the etiologies of youth-onset diabetes, 2) evaluate clinical characteristic and outcome of treatment of patients with T1D and T2D, and 3) to determine factors associated with good glycemic control in T1D and T2D patients.

### Material and methods:

A prospective cross-sectional Pediatric Diabetes Registry Project was conducted since March 2016. Patients diagnosed with diabetes before 18 years of age were recruited. The initial registry was conducted during March 2016 to August 2018, and the follow-up phase was conducted during March 2019 to March 2020. Demographic, clinical characteristic, diabetes autoantibodies, treatment regimen, glycemic control, co-morbidities, and complications were collected. Factors associated with good glycemic control in T1D and T2D patients were assessed using logistic regression analysis.

### Results:

There were 300 patients recruited at the initial registry. Majority of patients were T1D (77%, n=231). T2D were found in 15.3% of the patients (n=46). The other specific types were monogenic diabetes (n=10, 3.3%), disease of the exocrine pancreas (n=4, 1.3%), drug-induced diabetes (n=2, 0.7%), and other genetic syndromes sometimes associated with diabetes (n=7, 2.3%). The mean age at diagnosis in T1D and T2D were  $7.7 \pm 3.4$  and  $12.3 \pm 2.5$  years, respectively. Around 62-65% of T1D patients had at least one pancreatic  $\beta$ -cell autoantibodies. In T1D patients, mean HbA<sub>1c</sub> was  $8.96 \pm 1.98\%$  [median (IQR) HbA<sub>1c</sub> was 8.60% (7.70%, 9.70%)]. Good glycemic control (HbA<sub>1c</sub> <7.5%) was found in 22.5% of patients. Less than half of patients (43.5 %) performed SMBG  $\geq 4$  times/day. Majority of T1D patients (64%) were on intensive insulin regimen (IIT). In univariate analysis, factors associated with good glycemic control were: SMBG  $\geq 4$  times/day (OR 3.66, 95%CI 1.70, 7.84, p=0.001); IIT (OR 4.84, 95%CI 1.79, 13.12, p=0.002); and paternal education of diploma level or higher (OR 2.59, 95%CI 1.19, 5.61, p=0.016). In multivariate analysis, older age (OR 1.16, 95% CI 1.01, 1.32, p=0.032) and SMBG  $\geq 4$  times/day (OR 4.63, 95%CI 1.78, 12.00, p=0.002) were associated with good glycemic control. In T2D patients, mean HbA<sub>1c</sub> was  $7.56 \pm 2.21\%$  [median (IQR) HbA<sub>1c</sub> was 6.50% (5.95%, 9.28%)]. Good glycemic control (HbA<sub>1c</sub> <7%) was found in 56.5%. Twenty-one patients (45.7%) required insulin treatment. In univariate analysis, older age (OR 0.70, 95%CI 0.53, 0.94, p=0.018) and longer duration of diabetes (OR 0.37, 95% CI 0.21, 0.68, p=0.001) were associated with suboptimal glycemic control. In the follow-up phase, there were 211 patients (n=176 in T1D, n=23 in T2D, and n=12 in other types).

Compared to 7.4% of T1D, as high as 28.3% of T2D were lost to follow-up. Prevalence of diabetic retinopathy (DR) and diabetic nephropathy (DN) were higher at the follow-up phase than at initial registry in T1D (DR 0% vs. 1.5%; DN 3.4% vs. 5.8%). Only DN rate was increased in T2D (9.1% vs. 17.4%).

**Conclusion:**

Majority of youth-onset diabetes were T1D. The most important factor associated with good glycemic control in T1D was SMBG  $\geq 4$  times/day. In T2D, older age and longer duration of diabetes negatively affected glycemic control and almost one third of patients were lost to follow-up.

Keywords: type 1 diabetes, type 2 diabetes, glycemic control, youth-onset, diabetic retinopathy, diabetic nephropathy

**PHEOCHROMOCYTOMA WITH NEGATIVE METANEPHRINE: A RARE CASE REPORT OF DOPAMINE SECRETING TUMOR**  
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**Introduction:**

Hereditary Pheochromocytoma can occur in multiple endocrine neoplasia Type 2, von Hippel-Lindau syndrome, neurofibromatosis(NF) type1 and familial paragangliomas. It's also been reported that the frequency of Pheochromocytoma occurring in pediatric NF patients is 4%, and mostly characterized by secretion of epinephrine and norepinephrine. Therefore, we report the first case of dopamine secreting pheochromocytoma in NF type 1 adolescent patient in Korea. We described the patient's clinical, biochemical, imaging and surgical treatment results.

**Case:**

A 13-year-old boy, known NF type 1 patient incidently found high blood pressure. He was identified a 2cm-sized left adrenal gland mass in the abdomen CT scan by hypertension work up. He was diagnosed with NF1 due to multiple café au lait spots at the age of 6, and there were no specific findings symptoms other than occasional complaints of headache. At the time of admission, There was no weight loss, fever, fatigue, headache and sweating, which are symptoms suggestive of catecholamine secretion. With BP 150/79 mmHg and HR 94 beats/min, the patient belonged to stage 2 hypertension. His body mass index(BMI) was 29.4kg/m<sup>2</sup>. Serum 17aOHP, 11-DOC, DHEA-S, cortisol and renin activity were within the normal range and with echocardiography and doppler kidney USG were unremarkable. Fractionated 24 hour urinary metanephrine excretion 0.47mg/day (normal : <=0.80mg/day) was not elevated. Of the urinary catecholamines, epinephrine 17.58 ug/day (normal : <=40ug/day) and norepinephrine 26.32ug/day (normal : <=80ug/day) were within normal range, but dopamine 572.24ug/day (normal : 60-400ug/day) was elevated. On Abdomen CT, a 1.2x1.4x1.7cm sized well defined homogeneous nodular lesion in the left adrenal gland were identified. In reading, it was highly suggestive of lipid-poor adenoma, but impossible to exclude the possibility of pheochromocytoma. The images of the I123 metaiodobenzylguanidine (MIBG) scan, a clear MIBG uptake was observed in the nodule of the left adrenal gland and in both of 24-hour and 48-hour, which considered as pheochromocytoma. Multidisciplinary conference was carried out and according to the result, it was hard to conduct a surgery using a laparoscopy immediately, because the tumor was small, the symptom was vague and only the dopamin value rose. For this reason, the progress was monitored at intervals of three months. After six months, an increase in adrenal mass size(2.0x1.9x2.0cm) was identified in the Abdomen CT and a focal significant uptake of the lesion in 18F-FDOPA PET/CT was identified. Therefore, laparoscopic left adrenalectomy was performed under suspicion of dopamine secreting pheochromo

## VITAMIN D PROFILE IN CHILDREN WITH EPILEPSY IN SAIFUL ANWAR HOSPITAL MALANG, INDONESIA

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### Background

Vitamin D is important for bone health, vitamin D deficiency may contribute to other disorders (e.g., autoimmune, infections, cancer, degenerative, diabetic, and vascular). Epilepsy is a common neurological disorder in children of all ages with a prevalence ranging from 4-8 per 1000 population. Children less than 10 years have a prevalence of 6 per 1000 children. The diagnosis of epilepsy is based on the history taking, physical examination and electroencephalography. Epilepsy treatment is a long-term treatment that requires good cooperation between doctors, patients and the patient's family to ensure good treatment compliance. Several previous studies have suggested that the use of antiepileptic drugs will increase bone catabolism thereby causing a decrease in vitamin D levels. One mechanism is the activation of pregnane X receptors which are induction mediators of cytochrome P450 which are involved in the metabolism of antiepileptic drugs.

### Aims

We examined the prevalence of vitamin D deficiency in children with epilepsy in Saiful Anwar Hospital Malang, Indonesia.

### Methods

This study uses an observational analytic and the sampling method is consecutive sampling. Sixty-one epilepsy patients who met the inclusion criteria were collected from the pediatric neurology outpatient clinic of RSUD. Dr. Saiful Anwar Malang in August 2020 - February 2021. The basic characteristics of the study subjects included gender, age, vitamin D status and the type of antiepileptic drug used. Blood samples were taken from peripheral veins and measured in serum vitamin D levels by the ELISA method. Vitamin D 25-OH levels were categorized as deficient (<20ng/ml), insufficient (20–29ng/ml), or normal (30-100ng/ml).

### Results

Vitamin D levels were obtained on sixty-one patients with epilepsy. The results showed that female characteristics compared to male were 1.26: 1 with a mean age of 4.69 years. 52% patient on monotherapy using valproic acid only, and 48% patient on polytherapy with valproic acid, fenobarbital, and fenitoin. Vitamin D deficiency was present in 70% children with epilepsy, 20% was insufficient, and 9,8% was normal.

### Conclusion

Vitamin D deficiency is common in patients with epilepsy on antiepileptic drugs. Monitoring of vitamin D should be considered as part of the routine management of patients with epilepsy.

Keywords: Vitamin D, antiepileptic drugs, Children with epilepsy

Themes: Vitamin D profile

## PP 46

Puberty

### **EFFECT OF GONADOTROPIN-RELEASING HORMONE AGONIST MONOTHERAPY OR COMBINATION WITH GROWTH HORMONE ON FINAL ADULT HEIGHT IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY**

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#### **Purpose:**

This study aimed to compare clinical parameters such as final adult height (FAH) in girls with central precocious puberty (CPP) treated with gonadotropin-releasing hormone agonists (GnRHa) with and without growth hormone (GH).

#### **Methods:**

This retrospective study reviewed data of 229 girls with CPP who had reached FAH in a long-term trial of GnRHa treatment. The subjects were divided into GnRHa treatment group (n=204), and the combined GnRHa+GH treatment group (n=25). Chronological age, bone age, height, height standard deviation score, predicted adult height (PAH) and FAH, tanner stage, hormone levels were assessed during the treatment period.

#### **Results:**

At the start of treatment, PAH was 156.5±6.4cm in GnRHa treatment and 150.6±5.0cm in GnRHa+GH combination treatment (P<0.001). At the end of treatment, PAH was 162.1±5.3cm in GnRHa group and 160.4±4.9cm in the combined GnRH+GH treatment group, which increased compared to the start of treatment. The annual growth velocity was 5.3±0.7cm in the GnRHa group and 6.3±0.9cm in the GnRHa+GH combination group (P<0.001). The FAH in the GnRHa group and GnRHa+GH combination group was 160.9± 4.8cm and 159.8±3.7cm, respectively, without significant difference. However, the height gain (FAH- initial PAH) was significantly higher in GnRHa + GH combination group than GnRHa group (8.5±6.0cm vs 4.5±5.2cm, P=0.002).

#### **Conclusion:**

In our study, the combination treatment with GnRH and GH may improves the growth prognosis in girls with CPP.

Keywords: Precocious puberty, Gonadotropin-releasing hormone, Growth hormone

**DIFFERENCES IN LONGITUDINAL GROWTH PATTERNS OF CHILDREN AND ADOLESCENTS WITH TRANSFUSION-DEPENDENT HEMOGLOBIN E/ $\beta$ -THALASSEMIA DISEASE AND THOSE ACHIEVING HEMATOPOIETIC STEM-CELL TRANSPLANTATION**

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**Background:**

Short stature is one of the most common endocrinopathies among children with transfusion-dependent (TD) thalassemia. Hematopoietic stem cell transplantation (HSCT) is the only effective curative treatment for TD thalassemia. The objectives of this study were 1) to evaluate longitudinal growth pattern of children and adolescents with TD Hb E/ $\beta$ -thalassemia, the most common TD thalassemia among Southeast Asian population and those who underwent successful HSCT 2) to compare the prevalence of short stature between both groups and 3) to identify factors related to height among these patients.

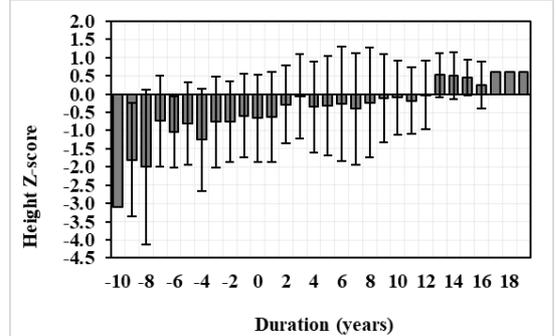
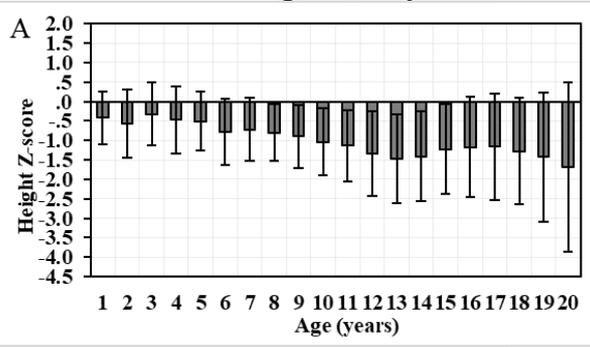
**Methods:**

We reviewed medical records of 39 patients with TD Hb E/ $\beta$ -thalassemia who received regular transfusion every 2-5 weeks and 39 post-HSCT subjects (ex-thalassemic subjects). Longitudinal data including weight and height Z-scores, hemoglobin (Hb) and serum ferritin(SF) levels at each age range for TD group and at each year before and after HSCT for post-HSCT group were recorded.

**Results:**

The percentage of children and adolescents with short stature in post-HSCT group was significantly less than TD group (2.6% vs. 28.2%, P=0.002). One TD patients and one post-HSCT subject who received growth hormone therapy were excluded from the longitudinal analysis.

(Remarks..There are two figures in my abstract. Please see the attached abstract in Word file.)



**Longitudinal height Z-scores of TD patients post-HSCT subjects**

**Longitudinal height Z-scores of (At 0 year = Time at HSCT)**

Regarding longitudinal height of TD patients, mean height Z-score decreased over time and was at the lowest at the age of 13 years during growing period. Despite iron chelation therapy, mean SF levels at any age were still above 1000 ng/mL.

For post-HSCT group, the significant improvement of mean height Z-score was observed at 3 years after HSCT. After one year post-HSCT, mean Hb levels remained  $> 10$  g/dL. While, mean SF levels gradually decreased after HSCT and became  $< 300$  ng/mL at 8 years post-HSCT.

Factors significantly related to longitudinal height Z-scores among TD patients were only age and deferoxamine therapy but not average Hb, SF levels or LIC (liver iron concentration) measured by MRI. We did not find any relationship between longitudinal height Z-scores vs. age at HSCT, duration of follow-up after HSCT, Hb and SF levels or deferoxamine among post-HSCT subjects.

### **Conclusion**

The present study clearly demonstrates the differences in the longitudinal growth patterns of children and adolescents with TD Hb E/ $\beta$ -thalassemia and those who underwent successful HSCT. Moreover, the study clearly shows that HSCT not only cured TD Hb E/ $\beta$ -thalassemia but also significantly improved the height outcomes of those patients.

**MIXED GONADAL DYSGENESIS IN A CHILD WITH 45X/46 X, ISODICENTRIC Y CHROMOSOME (P.11.31)**

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**Background**

Mixed gonadal dysgenesis (MGD) is a term used to describe individuals who have chromosomal mosaicism as well as dysgenetic gonads and variable internal and external reproductive anatomy. Mixed gonadal dysgenesis is difficult to managed in gender assignment and high reported malignancy risk.

**Objective**

To demonstrate management of mixed gonadal dysgenesis (MGD) with isodicentric Y chromosome.

**Case**

Our patient is a 1-year-old “boy” consulted to Pediatric Endocrine clinic for evaluation of ambiguous genitalia. The patient was referred due to hypospadias with scrotum bifidum, small penis of 2.5 cm in length, right testicle was not palpable in scrotal nor inguinal area, and the left testis was palpable, in the scrotum, volume of 1 ml. Karyotype examinations showed 45,X/46,X,Idic(Y)(p11.31) and the genitography showed urogenital sinus with fusion in mid urethrae with vagina. The testosterone level was high on hCG test. Laparoscopic examination showed bifid uterus, streak gonad on the left side, and fallopian tube on the right side. Cystoscopy result did not showed vagina and fistulae appearance. Histopathology showed dysgenetic testicle with seminiferous tissue but no spermatogenesis found. This patient was managed by pediatric endocrinologist, urologist, pediatric surgeon and psychiatrist. This patient was assignment as female and was planned to undergo gonadectomy and genitalia reconstruction.

**Conclusion**

One of the challenges in patients with ambiguous genitalia is gender assignment. Management of these patients needs multidisciplinary team.

**Keywords**

Mixed gonadal dysgenesis, isodicentric Y chromosome, management.

## **CONGENITAL HYPERINSULINISM AND GLOBAL DEVELOPMENTAL DELAY IN A 10 MONTHS OLD BOY: A CASE REPORT**

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### **Introduction**

Hyperinsulinaemic hypoglycemia (HH) is an important cause of recurrent and severe hypoglycemia during infancy and childhood. In children, congenital hyperinsulinism (CHI) is the most common cause of HH and it typically presents in early infancy.

### **Case Presentation**

We presented a case of congenital hyperinsulinism and global developmental delay in A 10 months old boy The diagnosis was established by a history of lethargy and seizure 3 days before admission. The random blood glucose result on the day of admission was low. Laboratory results confirm hyperinsulinaemic hypoglycemia with the pH 7,38, keton 0,3 mmol/L, lactate 1,7, insulin 132,5 mcU/ml and growth hormone 10,4ng/mL. From radiological work-ups in MRI of the pancreas showed normal size, there is no visible pathological signal. He was treated with Intravenous glucose infusion, intravenous hydrocortisone therapy, subcutan Octreotide, oral nifedipine and cornrice diet. The patient also received physiotherapy for treatment of global developmental delay.

### **Discussion**

The American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) have both accepted that plasma glucose values drop down to 30 mg/dL (1.67 mmol/L) in the first 2 hours of life and subsequently rise to a value of at least 45 mg/dL (2.5 mmol/L) before stabilizing around 12–24 hours. Hyperinsulinaemic hypoglycemia (HH), refers to a clinically, genetically and morphologically heterogeneous group of disorders associated with dysregulated insulin secretion. It is the most common cause of persistent hypoketotic hypoglycemia in neonates and infants and is associated with a significant risk of permanent brain damage. The goal of emergency treatment is to achieve normoglycemia immediately, keep plasma glucose levels at a safe range (>3.5 mmol/L/65 mg/dL) while the etiological investigations for differential diagnosis and long-term treatment planning are in progress.

### **Conclusion**

A prompt diagnosis and immediate management of HH is essential to avoid complications. A thorough clinical examination and utility of laboratory examination from the critical sample can be used to diagnosed the etiology of HH.

Keyword: Hypoglycemia, hyperinsulinaemic, global developmental delay

## THE RELATIONSHIP BETWEEN BODY MASS INDEX AND THERAPEUTIC EFFECT IN CHILDREN WITH IDIOPATHIC GROWTH HORMONE DEFICIENCY

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### Purpose:

The aim of this study is to investigate the influence of body mass index (BMI) on therapeutic effect in prepubertal children with idiopathic growth hormone deficiency (IGHD).

### Methods:

We conducted a retrospective study by chart review in a single center. A total of 138 patients (male n=90, female n=48) with idiopathic growth hormone deficiency who were treated growth hormone for at least 2 years from January 2010 to May 2019 were analyzed.

### Results:

Among the 138 patients, 128 were normal weight (BMI<85th percentile) and 10 were overweight (95th>BMI≥85th percentile) and obese (BMI≥95th percentile). At the start of growth hormone treatment, birth weight (P=0.020), Weight SDS (P <0.001), BMI (P =0.003), and BMI SDS (P <0.001) were higher in the overweight and obese patient groups than in the normal group. During 2 years of growth hormone treatment, height SDS in normal weight patients increased from  $-2.64 \pm 0.49$  to  $-1.22 \pm 0.60$ , and height SDS in overweight and obese patients increased from  $-2.58 \pm 0.40$  to  $-0.96 \pm 0.78$  in patients. The height gain for 2 years in overweight and obese group was higher than in normal weight group (P =0.024). In multiple regression analysis, BMI SDS was positively association with growth velocity (P =0.001) and the gain in height SDS (P <0.001).

### Conclusion:

BMI SDS was positively related with growth velocity and the gain in height SDS during 2 years of growth hormone treatment in IGHD patients. Growth hormone treatment had a better therapeutic effect in obese and overweight IGHD patients.

Keywords: Body mass index, Growth hormone, Growth hormone deficiency

## A CASE OF A MALE INFANT WITH MICROPENIS IN KLEEFSTRA SYNDROME

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### Introduction:

Kleefstra syndrome is characterized by intellectual disability, childhood hypotonia, and characteristic facial features. The diagnosis of Kleefstra syndrome is made in a proband who has a heterozygous deletion or intragenic EHMT1 pathogenic variant at chromosome 9q34.3. We report a case of infant with Kleefstra syndrome who has micropenis.

### Case:

A boy was born at 38weeks 5days of gestational age via normal vaginal delivery. Routine antenatal care during pregnancy was normal. Genital examination showed micropenis with stretched penile length measured at 1.9 cm (-2.5SD for age is 2.5cm; mean is 3.5cm), palpable testicles bilaterally, and no hypospadias. Karyotype showed normal male (46, XY). Chromosomal microarray revealed deletion at 9q34.3. Serum adrenocorticotrophic hormone(ACTH), cortisol level and 17 alpha-OHP level were also in normal range. At the age of 3 months old, LH 0.14mIU/mL (normal: 0.02-7.0), FSH 2.59mIU/mL (normal: 0.16-4.1), testosterone <0.03ng/ml (normal: 0.6-4.0), dehydrotestosterone 7ng/dl (normal :12-85). hCG stimulation test showed increased testosterone level from <0.03ng/ml to 2.3ng/ml. Intramuscular testosterone enanthate injection of 25mg given to the patient once every 3 weeks for 3 months. He had good response to testosterone injections with an improvement of stretched penile length from 1.2cm to 3cm (-2.5SD for age is 2.3cm; mean is 4.3cm) after 4 doses.

### Conclusion:

We report a case of an infant male diagnosed with Kleefstra syndrome due to deletion at chromosome 9q34.3 with micropenis. The patient showed a good response after testosterone treatment during infancy. Continuous monitoring is needed about pubertal progression and fertility.

**THE ROLE OF FETUIN-A-TO-ADIPONECTIN RATIO IN OBESE CHILDREN AND ADOLESCENTS WITH DIABETES MELLITUS**

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The Fetuin-A and adiponectin are markers inflammatory cytokines associated with insulin resistance in childhood obesity. The aim of this study is to examine their levels in diabetic children in relation with obesity and investigate their role as future indicators of metabolic complications. Fifty-four children/adolescents with type 1 or 2 diabetes mellitus (DM) and 44 controls aged 7-18 years were included and divided into obese/overweight/normoweight subgroups with respect to body mass index standard deviation score (BMI SDS). Baseline clinical and laboratory characteristics including plasma fetuin-A and adiponectin were compared in association of BMI and type of DM. Regression analyses were performed to identify risk factors for increased fetuin-A-to-adiponectin ratio (FAR). Out of 98 children, 53 (54.1 %) children were obese while 18 (18.4 %) children were obese and diabetic. Fetuin-A was significantly higher whereas adiponectin was lower in obese controls compared to non-obese controls. FAR was significantly higher in obese compared to non-obese diabetic children and in type 2 compared to type 1 diabetic children. Fetuin-A, adiponectin and FAR of diabetic children were significantly correlated with BMI and multiple indices indicating insulin secretion and resistance. After adjusting for type and duration of DM, glycated hemoglobin, and indices for insulin secretion and resistance, BMI remained significantly as unique risk factor associated with increased FAR (OR=78.979). Receiver operating characteristic curve of FAR and BMI SDS greater than 1.64 identified optimal cut-off points and area under the curves (sensitivity, specificity) for diabetic children was 226.52 and 0.80 (0.59, 0.82). Plasma fetuin-A, adiponectin and FAR are significantly increased in obese children and adolescents and could be useful indices assessing insulin resistance and  $\beta$ -cell function in those who are diabetic. BMI may be an independent risk factor for increased FAR.

## TREATMENT OF MATURITY ONSET DIABETES OF THE YOUNG (MODY) ACCORDING TO MODY TYPE BASED ON TARGETED PANEL SEQUENCING

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### Purpose:

Gene related to MODY is hardly found in Asian people. Moreover, studies about treatment according to MODY types are lacking. Therefore, we present the treatment and progress according to each MODY type based on targeted panel sequencing.

### Methods:

Using targeted panel sequencing, we were able to make molecular genetic diagnoses for 16 patients with suspected monogenic diabetes. We classified patients as MODY type, and investigated about their age, sex, treatment and the change in HbA1c level.

### Results:

MODY genes were identified in HNF4A, GCK, HNF1A, HNF1B and CEL. Five patients were diagnosed as GCK-MODY, and HbA1c level at diagnosis ranged from 6.4 to 15.3%. Two patients are doing well without medication. Their HbA1c level changed from 6.7 to 6.2%, and 6.7 to 6.9%. One obese patient taking metformin has changed HbA1c level from 6.4 to 6.8%. One patient showed significant reduction on insulin injection (0.25IU/kg/day) and HbA1c level (12.9 to 5.3%). One patient, confirmed as both GCK variant and 17q12 deletion (HNF1B deletion), had insufficient reduction in HbA1c level (15.3 to 7.9%) even though on insulin (0.3IU/kg/d) treatment. Another patient with HNF1B-MODY is using insulin (1.28IU/kg/d) and HbA1c has reduced from 13.6 to 6%. There were four patients with HNF1A/HNF4A-MODY, in which sulfonylurea is known to be effective. One HNF4A-MODY patient is still using insulin (1.24IU/kg/d) due to abdominal pain after taking oral sulfonylurea. Her HbA1c level has reduced from 9 to 6.3%. Among three patients diagnosed as HNF1A-MODY, one patient successfully changed from insulin (0.33IU/kg/d) to oral sulfonylurea. HbA1c level reduced from 9 to 7.4%. One patient is on the course of increasing the amount of sulfonylurea because HbA1c increased from 5.8 to 8.3% after stopping insulin. One patient is taking both sulfonylurea and insulin (2.1IU/kg/d) due to poor glycemic control (HbA1c 9.6 to 9.7%) with sulfonylurea alone. Among six patients with CEL-MODY, three patients needed insulin injection (1.5-2.4IU/kg/d). Their HbA1c level has declined from 14.7 to 8%, 12 to 8.7%, and 13.2 to 8.6%. Two patients with obesity had reduction in HbA1c with metformin only. (15.9 to 5.8% and 10.5 to 7.9%). One patient is in good glycemic control without any medication. (HbA1c level 14.3 to 5.8%)

### Conclusions:

Response to the treatment was in some part similar to the previous report, but varied for each individual. There is need for a larger scale study about the appropriate treatment and progress according to MODY type confirmed by sequencing.

## THE RELATIONSHIP BETWEEN IODINE STATUS AND THYROID FUNCTION IN CONGENITAL HYPOTHYROIDISM WITH EUTOPIC THYROID GLAND

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### Background:

We investigated the relationship between iodine status and thyroid function in children with congenital hypothyroidism (CH) with eutopic gland. We also evaluated whether the presence of iodine organification defect (IOD) or pathogenic genetic variants affects the association between iodine status and thyroid function.

### Methods:

A total of 31 children (14 boys) with CH participated in the study, who repeatedly underwent thyroid function test and urine iodine concentration (UIC) without levothyroxine (LT4) medication after 3 years of age (1-5 times per patient). After confirming eutopic gland, IOD was demonstrated by the positive perchlorate discharge test with a discharge rate >10%. Genetic analysis was performed using targeted gene sequencing including 23 genes.

### Results:

We identified likely pathogenic or pathogenic variants in 14 cases (45.2%): 1 case with triallelic (digenic) variants (DUOX2 and TSHR), 4 cases with biallelic variants (3 DUOX2 and 1 TSHR), and 9 cases with monoallelic variants (7 DUOX2, 1 DUOXA2, and 1 TSHR). Among 26 cases treated with LT4 from neonatal period, thyroid function after LT4 discontinuation was euthyroid (n=7), subclinically hypothyroid (n=15), and overtly hypothyroid requiring LT4 (n=3). The other 5 cases without LT4 treatment remained subclinical hypothyroid. After excluding 2 cases with TSHR, 29 cases (with 72 samples) were included to analyze the relationship between iodine status and log-transformed TSH (log-TSH) using generalized estimating equation models. The positive IOD (n=17) was not associated with presence of DUOX2/DUOXA2 variants (n=12). Iodine status of urine samples was categorized into adequate (UIC<300 µg/L, n=25), mild excessive (UIC=300-599 µg/L, n=14), and severe excessive (UIC≥600 µg/L, n=33) groups. When stratified by the presence of IOD, log-TSH significantly increased in severe excessive group ( $\beta=0.52$ ,  $P=0.014$  vs. iodine adequate group) among negative IOD group, but rather decreased in mild excessive group ( $\beta=-0.84$ ,  $P<0.001$  vs. iodine adequate group) among positive IOD group. Meanwhile, when stratified by the presence of DUOX2/DUOXA2 variants, no significant association was found between iodine status and log-TSH levels.

### Conclusion:

DUOX2 mutation was most common in CH patients with eutopic gland. The relationship of iodine status with thyroid function differed by presence of IOD.

PP 56

Puberty

## **EARLY REEVALUATION OF GONADOTROPIN LEVELS IN GIRLS WITH SUSPECTED PRECOCIOUS PUBERTY**

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### **Objective:**

Gonadotropin-releasing hormone (GnRH) stimulation test, the gold standard for diagnosis, is performed after confirming various clinical symptoms and laboratory findings in the child for suspected precocious puberty. However, in early puberty, the LH level may be low in the GnRH stimulation test, and sensitivity is relatively low. Therefore, the purpose of this study was to evaluate the results by retesting girls who showed a low LH of less than 5 in the test

### **Methods:**

This retrospective study reviewed 780 children who visited the hospital from 2003 to 2020 and had the GnRH stimulation test performed twice within 6 months. This study compared clinical and laboratory test results by dividing the 2nd GnRH stimulation test into a positive group (n = 186) and a negative group (n = 594).

### **Results:**

After the 1st GnRH stimulation test was negative, the 2nd test performed within 6 months was divided into negative and positive groups and compared. weight SDS ( $1.15 \pm 0.92$  vs.  $0.97 \pm 0.79$ ,  $p = 0.013$ ), and BMI SDS ( $0.83 \pm 1.07$  vs.  $0.59 \pm 0.94$ ,  $p = 0.002$ ) were significantly higher in the negative group. 1st test basal LH ( $0.25 \pm 0.4$  IU/L vs.  $0.39 \pm 0.52$  IU/L,  $p < 0.001$ ), 1st test peak LH ( $2.91 \pm 1.06$  IU/L vs.  $4.00 \pm 0.73$  IU/L,  $p < 0.001$ ), and bone age ( $9.83 \pm 0.80$  years vs.  $9.99 \pm 0.72$  years,  $p = 0.011$ ) were significant higher in the positive group. In binary logistic regression analysis, the 1st test peak LH level is a very significant predictor in deciding to retry the GnRH stimulation test. Based on the ROC curve, cut off value of 1st test LH peak is 3.15 IU/L with sensitivity 87.6% and specificity 58.1%.

### **Conclusion:**

When the 1st GnRH stimulation test is negative, we have to consider several factors in deciding to retest. The 1st test peak LH should be considered as one of the very important factors that determine whether to perform the 2nd test and increase the likelihood of a positive test.

## LATE ONSET NEONATAL HYPOCALCAEMIA IN TWENTY-DAYS-OLD BABY: A CASE REPORT

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### Introduction

Neonatal hypocalcaemia is a common metabolic problem in newborn period and infancy. Neonatal hypocalcaemia has an impact on the cardiac system in the form of impaired heart pump contractility and affects the repolarization of heart muscle fibers, it also affects the central nervous system and neuromuscular function. Central nervous system manifestations such as jitteriness, general hyper reactivity, and jumpiness, are classically reported in hypocalcaemic neonates.

### Case Presentation

We report a case of late onset neonatal hypocalcaemia in twenty-days-old baby. He was born on 38-39 week of gestational age by caesarean section, without asphyxia nor neonatal infection. The patient had refractory general seizure with duration of 1-2 minute each seizure, there was no history of fever, diarrhea and vomiting prior to seizure. Laboratory result showed refractory hypocalcaemia (5.2 - 5.4 mg/dL) and vitamin D deficiency (11.23 ng/mL). He has increased alkaline phosphatase level, normal parathyroid hormone, magnesium and phosphate level. This patient was given oral vitamin D therapy and there was an improvement in calcium level.

### Discussion

Neonatal hypocalcaemia can be a potentially life-threatening condition, but often asymptomatic. Hypocalcaemia is defined as total calcium serum <8mg/dL or ionized calcium <4,4 mg/dL for term infants or preterm infants weighing >1500 gram at birth and total calcium serum <7mg/dL or ionized calcium <4 mg/dL for very low birth weight infants weighing <1500 gram. Early onset hypocalcaemia is generally asymptomatic therefore, screening for hypocalcaemia at 24<sup>th</sup> dan 48<sup>th</sup> hour after birth is required for infants with high risk of developing hypocalcaemia. Late onset hypocalcaemia which is generally symptomatic, develop after the first 72 hours and towards the end of the first week of life. Excessive phosphate intake, hypomagnesemia, hypoparathyroidism, and vitamin D deficiency are the most common cause of late onset hypocalcaemia. Elementary calcium of 10 to 20 mg/kg (1-2 mL/kg/dose 10% calcium gluconate) is given as a slow intravenous infusion in the acute treatment of hypocalcaemia in patients with symptoms of tetany or hypocalcaemic convulsion.

### Conclusion

Since most infants with hypocalcaemia are usually asymptomatic, serum total or ionized calcium levels must be monitored in preterm infants with a gestational age <32 weeks, small for gestational age infants, infants from diabetic mothers and infants with severe prenatal asphyxia with Apgar score <4 in the first minute. The treatment of hypocalcaemia should be initiated immediately in infants with reduced calcium levels while searching for the etiology.

Keywords: neonatal hypocalcaemia, vitamin D deficiency, parathyroid hormone

PP 59

Growth

## **EFFICACY OF GROWTH HORMONE TREATMENT IN GROWTH HORMONE DEFICIENCY CHILDREN WITH LEUKEMIA**

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### **Background:**

Survivors of childhood leukemia are at risk of growth impairment due to intensive cytotoxic agents and total body irradiation. The purpose of the study is to investigate children with growth hormone deficiency (GHD) diagnosed after leukemia treatment and examine the auxological change after growth hormone (GH) replacement.

### **Method:**

A total of 27 children diagnosed with GHD after leukemia treatment were analyzed. Clinical and biochemical data were collected retrospectively at diagnosis of leukemia, GHD and 1 year after GH replacement. Standard deviation scores (SDS) were calculated based on the age- and gender-adjusted population mean.

### **Results:**

Among a total of 1848 patients with diagnosed with leukemia, 27 (1.46 %) children finally diagnosed as GHD after leukemia treatment and 21 (77.8 %) children were treated with GH. Age at GHD diagnosis was 4.25 (1.25, 10.25) years while bone age delay 1.50 (0.5, 1.67) years. Height SDS between at leukemia diagnosis and at GHD diagnosis was significantly different (-0.63 vs. -2.58,  $P < 0.001$ ). Height SDS of 21 children at GHD diagnosis was -2.71 and increased up to -2.43 after 1 year of GH treatment. Eight out of 21 children had bone ages less than 12 years for boys and 10 years for girls and their height SDS was increased from -2.58 to -1.98 ( $P = 0.046$ ) with increment of height SDS being 0.53 (0.69, 0.69). In regression analyses, the peak GH concentration after GH stimulation test was associated with post-therapeutic height SDS ( $B = 0.243$ ,  $P = 0.048$ ).

### **Conclusion:**

For those with GHD diagnosed after childhood leukemia treatment, GH treatment could be beneficial and safe in improving the height status and the peak GH concentration could be a potential factor in predicting the therapeutic effect. Close auxological monitoring is recommended for any childhood cancer survivors who experienced post-treatment height decline.

## PP 60

Diabetes

### ADOPTIVE TRANSFER OF HO-1 HIGH EXPRESSION IMDC DELAYS THE ONSET OF T1DM IN NOD MICE

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#### Background:

The destruction and apoptosis of pancreatic  $\beta$ -cells mediated by T lymphocytes is the main mechanism for the development of type 1 diabetes mellitus. Dendritic cells, as antigen presenting cells, can induce immune tolerance in the immature state. Immature dendritic cells (imDC) induced in vitro have been found to play a crucial part in the inhibition of graft rejection. Immature dendritic cells were induced to overexpression Heme oxygenase-1(HO-1), showing a better protective effect in mouse heart transplantation model. However, it is still unclear whether high expression of HO-1 in imDC also has a protective effect on autoimmune diabetes.

#### Objective:

To investigate whether imDC with high expression of HO-1 could delay the occurrence of type 1 diabetes mellitus in NOD mice.

#### Methods:

Murine bone marrow-derived dendritic cells were induced with rGM-CSF and rIL-4 in vitro. Suspended cells stimulated by LPS were used as mature dendritic cells (mDC). Adherent cells were used as imDC induced with CoPP (HO-1 inducer) or SnPP (negative control). Detected the expression level of costimulatory molecules on DC surface and intracellular HO-1.

NOD mice (6 weeks old) were divided into four groups: control group and three treatment groups treated with imDC, CoPP-induced imDC or SnPP-induced imDC. Saline or  $2 \times 10^6$  cells with different treatment were injected into mice at 8 and 10 weeks old. Blood glucose was monitored once a week from 8 weeks of age until the onset of diabetes or the end of the study (20 weeks of age). At the end of study, the incidence of diabetes, the degree of islet inflammation, the area of insulin-secreting pancreatic  $\beta$  cells and serum insulin level in each group were compared.

#### Results:

Compared with imDC, the mean fluorescence intensity (MFI) of co-stimulatory molecules CD80 and CD40 on the surface of cells with CoPP treatment was reduced ( $P < 0.05$ ), the expression level of HO-1 protein in cells with CoPP treatment was significantly increased ( $P < 0.05$ ).

In vivo, compared with the control group, the incidence of T1DM in the CoPP group was significantly reduced (30.8% VS control group: 61.5%,  $P < 0.05$ ), the insulinitis score was also decreased ( $P < 0.05$ ). The differences in serum insulin level, body weight and the remaining islet  $\beta$  cell area among all groups were not significant.

#### Conclusion:

CoPP-induced imDC with high expression of HO-1 have a stronger ability to inhibit immune response and reduce the incidence of diabetes in NOD mice, which may become a new treatment strategy for type 1 diabetes mellitus.

Keyword: Type 1 diabetes mellitus; dendritic cell; immature dendritic cell; heme oxygenase-1; immunoregulation; non-obese diabetic mice

## PP 61

Obesity & Metabolic Syndrome

### PREVALENCE OF METABOLIC SYNDROME AND ITS ASSOCIATED RISK FACTOR IN PAEDIATRIC OBESITY

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#### **Objective:**

We aimed to study the prevalence of metabolic syndrome and factors that were associated with metabolic syndrome among obese children.

#### **Method:**

We recruited 175 subjects, aged 7-18 years old, referred for obesity. We studied their demography (age, gender, ethnicity, family background), performed clinical/auxological examinations (weight, height, BMI, WC, blood pressure), and analyzed their biochemical risks associated with metabolic syndrome (FBS, FLP, Fasting Insulin, LFT). Metabolic Syndrome was identified according to the criteria proposed by International Diabetes Federation (IDF) 2007 for paediatric obesity. Multiple logistic regression models were used to examine the associations between risk variables and MS.

#### **Results:**

The prevalence of metabolic syndrome among children with obesity was 56%, with a mean age of  $11.3 \pm 2.73$  years. Multiple logistic regression analysis showed age (adjusted OR, 95%CI); 1.27 (1.15, 1.45), and non-sedentary lifestyle 0.280 (0.12, 0.68) were the significant prognostic factors associated with metabolic syndrome among obese children.

#### **Conclusion:**

The prevalence of metabolic syndrome among obese children referred to our centers was 56%. Many factors were associated with metabolic syndrome; however, only two significant predictors for metabolic syndrome were the older age group and non-sedentary lifestyle.

## **VARIOUS GENOTYPE AND PHENOTYPE OF PATIENTS WITH ADRENAL HYPOPLASIA CONGENITA: EXPERIENCE IN A TERTIRAY MEDICAL CENTER IN THAILAND**

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### **Introduction**

X-linked adrenal hypoplasia congenita (AHC) is caused by mutations of the *DAX1* (*NROB1*) gene. Classic presentations include primary adrenal insufficiency (PAI) in infancy and hypogonadotropic hypogonadism (HH) in later life. However, underlying genetic disorders and clinical manifestations could vary between patients. Rarely, AHC can arise from the deletion of *DAX1* and multiple adjacent genes at Xp21, e.g., glycerol kinase (*GK*) and Duchenne muscular dystrophy (*DMD*), namely a contiguous gene syndrome. Herein, we demonstrate various genotypes and phenotypes of AHC patients with or without contiguous gene syndrome identified in a tertiary care center.

### **Methods**

We retrospectively reviewed clinical presentations and biochemical data of all AHC patients diagnosed between 2000-2020. Mutations of the *DAX1* gene were identified by direct sequencing. Multiplex ligation-dependent probe amplification (MLPA) for the *DMD* gene was performed in patients suspected contiguous gene syndrome to find evidence of Xp21 deletion. MLPA of the *DAX1* gene was not done because the test was unavailable.

### **Results**

Four patients were diagnosed with AHC. The diagnosis was made within three months after birth in two patients and beyond the infancy period in the other two patients. They all presented with symptoms of adrenal crisis, including poor feeding, failure to thrive, vomiting, diarrhea, and lethargy. Salt-wasting (hyponatremia, hyperkalemia, metabolic acidosis) and skin hyperpigmentation were common among them. A standard-dose ACTH stimulation test exhibited inadequate cortisol response and low steroidogenic precursors, indicating AHC in all patients. At 10 months old, one patient (index 3, Table 1) developed acne, rapid growth, and penile enlargement without testicular enlargement and was diagnosed with gonadotropin-independent precocious puberty (GIPP). GIPP subsided after hydrocortisone dose increment. The exact mechanism of GIPP in AHC remains unclear. Some postulated hypotheses include high ACTH stimulated testicular steroidogenesis<sup>1</sup>, autonomous Leydig cell hyperplasia in testes of AHC patients<sup>2</sup>, and overexpression of steroidogenesis factors due to the loss of transcriptional repression by *DAX1*<sup>3</sup>. We evaluated pubertal development in one patient who was older than 14 years. HH was diagnosed due to delayed puberty and low gonadotropins and testosterone after 100 µg GnRHa stimulation. Serum triglyceride (TG) and total creatine kinase (CK) levels were obtained in all patients to delineate contiguous gene syndrome involving glycerol kinase deficiencies and Duchenne muscular dystrophy, respectively. Two out of four patients showed elevated TG and total CK levels, indicating contiguous gene deletion. MLPA for the *DMD* gene was performed in one patient and found all exons deletion, confirming the diagnosis of contiguous gene syndrome. In two patients with normal TG and total CK levels, we identified two homozygous inactivating mutations of the *DAX1* gene (c.363delG, p.Gly122Valfs8142 and c.512G>A, p.Trp171X) by direct sequencing.

### **Conclusions**

Our study demonstrates various genotypes and phenotypes of AHC patients. Primary AI in males with low steroidogenic precursors is a diagnostic clue of AHC. Either HH or GIPP could be found in these patients. AHC can be part of contiguous gene syndrome, and serum TG and total CK levels could help establishing the diagnosis.

**Table 1.** Summary genotypes and phenotypes of the patients with AHC

Parameters	Index 1	Index 2	Index 3	Index 4
Sex	M	M	M	M
Age at diagnosis	1 y 7 m	1 m	8 d	4 y 4 m
Current age	12 y 10 m	4 y 11 m	18 y 6 m	5 y 7 m
Primary AI	Yes	Yes	Yes	Yes
Salt wasting	Yes	Yes	Yes	Yes
Hyperpigmentation	No	Yes	Yes	Yes
Hypogonadotropic hypogonadism	N/A	N/A	Yes	N/A
Other features	GDD, DMD, LV systolic dysfunction	DMD	GIPP	GDD
ACTH stimulation test				
- Baseline cortisol (ug/dL)	1.33	0.39	8.38	0.8
- Peak cortisol (ug/dL)	1.33	0.35	10.9	0.94
- Baseline 17OHP (ng/dL)	0.3	306.5	475	40.9
- Peak 17OHP (ng/dL)	<0.1	427.2	7160	48.4
Serum TG (mg/dL)	729	484	75	66
Total CK (U/L)	2168	5755	186	99
Type of mutation	Contiguous gene syndrome (MLPA – all exons of <i>DMD</i> deletion)	Suspected contiguous gene syndrome	<i>DAX1</i> gene mutation (p.Gly122Valfs*142)	<i>DAX1</i> gene mutation (p.W171X)

M, male; N/A, not available; AI, adrenal insufficiency; GDD, global delay development; DMD, Duchenne muscular dystrophy; GIPP, gonadotropin-independent precocious puberty; MR, mental retardation; 17OHP, 17-hydroxyprogesterone; TG, triglyceride; total CK, creatine kinase (normal range 0-195)

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## TWO CASES OF WT1 GENE MUTATIONS—→THE TIMING OF GONADECTOMY

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### Introduction:

Wilms tumour suppressor gene (WT1), located at autosome 11p13, is a regulator for early renal and gonadal development. Frasier and Denys-Drash syndrome are two inherited disorders caused by specific mutations in the WT1 gene. Since WT1 transcription factor regulates SRY expression during the initial stages of sex determination process, its mutation leads to abnormal testicular differentiation and a high propensity of gonadal tumour development. Here we report two cases with WT1 mutations, including one with very early onset carcinoma in situ detected in bilateral testes.

### Case 1

Baby A presented at birth with a bifid pre-penile scrotum, scrotal hypospadias with chordee and bilateral fully descended testes. Karyotyping confirmed 46XY and short HCG stimulation test showed satisfactory testosterone response. Urine steroid profile was unrevealing and ultrasound of the pelvis showed no Mullerian features. Staged repair of the hypospadias was initiated. He developed proteinuria and hypertension at the age of two years and renal biopsy suggested membranous glomerulonephritis. Genetic workup revealed a heterozygous mutation at IVS 9 of the WT1 gene, WT1:c.1432+4C>T, compatible with **Type II Frasier syndrome**. Serial ultrasounds performed for testes was normal, but bilateral testicular biopsy performed during a peno-scrotal fistula repair when the patient was 4 years of age revealed abnormal looking testes and histopathology confirmed carcinoma in situ in both testes. After detailed discussion with parents, bilateral gonadectomy was performed and it revealed intra-tubular germ cell neoplasia. PLAP, Oct 3/4, c-Kit and Ki-67 markers was positive. The child is on cyclosporin A and ACEI for proteinuria with partial control. He will require medications for pubertal induction as he approaches adolescence.

### Case 2

Baby J was born with bilateral undescended testes at the inguinal region. He has a formed scrotum and no hypospadias and a phallus size of 2.5cm. Karyotyping showed 46XY and HCG stimulation test showed poor testosterone response. He developed proteinuria and hypertension at 1 year of age. Imaging studies revealed multiple hypo-dense hypo-enhancing mass lesions in both kidneys suggestive of nephroblastoma. Genetic studies revealed a WT1 mutation (heterozygous NM\_024426.3(WT1):c.1384c>T) and the diagnosis of **Denys-Drash syndrome** was made. Neoadjuvant chemotherapy was started according to the SIOP protocol and right nephrectomy was performed with the tumour removed en bloc. Tumour biopsy report revealed triphasic nephroblastoma whilst non-tumour histology revealed diffuse mesangial sclerosis. His kidney function further deteriorated and left nephrectomy was decided because of the risk of malignancy in the functionless kidney with malignant potential. Child was then put on chronic haemodialysis. Detailed discussion with the parents and the multidisciplinary teams were carried out concerning the surveillance for testicular malignancy. Parents decided on bilateral orchidectomy prior to kidney transplant and immunosuppressant therapy. Bilateral orchidectomy was performed. His testes were small and microscopic examination revealed immature Sertoli cells without evidence of malignancy. Immunohistochemical detection for PLAP, OCT3/4, c-Kit are negative.

### Discussion:

Reports from literature has suggested that the average age of diagnosis of gonadoblastoma in Frasier syndrome is 11.7 years in children presenting with abdominal pain or mass, and 13.6 years in children presenting with renal or other issues. (1) Here we report a case of very early onset of carcinoma in situ in association with Frasier syndrome.

The lifetime risk of germinal cell malignancy in WT1 mutations are high. Frasier syndrome is reported to be 60%, and Denys Drash syndrome with a well defined Y chromosome (known as the GBY region) is 40% (2). As there are no existing consensus guidelines for timing of gonadectomy in these individuals, each patient should be looked at individually, and parents should be given multidisciplinary input to facilitate an informed decision.

In the absence of frank malignant changes, the gonads should ideally be preserved as far as possible through to adolescence to allow for spontaneous pubertal development and to protect the autonomy of the individual. However, in the context of diminutive gonadal function, the risk of malignant changes, made higher in the invariable use of high doses of immunosuppressants for steroid resistant nephrotic syndrome and kidney transplantation, could mean early gonadectomy is chosen as it is deemed more beneficial for the individual overall.

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**VITAMIN D STATUS RELATED TO CALCIUM SERUM LEVELS IN PEDIATRIC PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA RECEIVING GLUCOCORTICOID HORMONE REPLACEMENT THERAPY IN SAIFUL ANWAR GENERAL HOSPITAL MALANG**

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**Background**

Congenital adrenal hyperplasia (CAH) requires long-term glucocorticoid therapy. Decreased blood calcium levels associated with vitamin D status can be a side effect of glucocorticoid therapy at a dose of 5 mg/day for more than 3 months. Vitamin D and calcium supplements can be given after 3 months. Impaired cortisol synthesis reduces negative feedback to the hypothalamus and pituitary, resulting in increased production of corticotropin-releasing hormone (CRH) by the hypothalamus and production of *adrenocorticotrophic hormone* (ACTH) by the pituitary. This process causes the adrenal glands to hyperplasia and virilization occurs due to androgen accumulation. Glucocorticoids stimulate osteoclastic bone resorption and reduce osteoblastic bone formation thereby altering bone homeostasis.

**Objective**

To differentiate calcium levels on vitamin D status in CAH patients with 3 months and 6 months of glucocorticoid administration.

**Methods**

Twenty pediatric patients with CAH were evaluated at the pediatric endocrinology outpatient clinic at Saiful Anwar General Hospital Malang in June 2021 who had received oral glucocorticoids 10-15 mg/m<sup>2</sup>/ day for 3-6 months. Serum calcium and vitamin D level were analyzed by electrolyte analyzer with selective ion electrode and hormone method.

**Results**

Respondents in this study were pediatric patients with congenital adrenal hyperplasia who were given glucocorticosteroid therapy where it was found that males were more dominant (55%), with a mean age of 2.65 years. Based on vitamin D status in patients who receiving glucocorticoids for 3 months, it was found that respondents had insufficiency (33%), sufficiency (22%) and deficiency (44%) with the mean calcium value in patients with vitamin D insufficiency and deficiency was 8.51 mmol/L ± 1.05 (normal limit). Meanwhile, the vitamin D status in patients who receiving glucocorticoids for 6 months was found deficiency (91%), and insufficiency (9%) with an average calcium value was 8.3 mmol/L ± 1.05 (normal limit).

**Conclusion**

Administration of oral glucocorticoids 10-15 mg/m<sup>2</sup>/ day for 3-6 month has side effects on vitamin D status in patients with CAH. Vitamin D status in patients receiving glucocorticoids for 3 months and 6 months had different outcomes where deficiency was found in most patients receiving glucocorticoids for more than 6 months and calcium levels did not have a significant relationship with decreased vitamin D levels in patients with CAH. Vitamin D supplementation should be started routinely when oral glucocorticoid treatment has been running for more than 3 months.

Keywords: Serum calcium, vitamin D level. CAH. Long-term oral glucocorticoids therapy. Duration of glucocorticoids dose.

## PP 65

DSD & Adrenal

### DISORDER OF SEX DEVELOPMENT: A 9-YEAR SINGLE CENTRE EXPERIENCE IN KUALA LUMPUR

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#### Introduction:

Disorder of sex development (DSD) represents atypical development of chromosomal, gonadal and anatomical sex [1,2]. It is a rare disorder with an estimated incidence of around 1 in 5000 live births [2]. This study aims to describe the clinical features, hormonal and genetic analysis of children presented with DSD in University Malaya Medical Centre (UMMC), Kuala Lumpur.

#### Methods:

Children who were diagnosed with DSD between 2013 and 2021 were included in the study. Their data were retrospectively reviewed and analysed. Children with the diagnosis of Turner syndrome and Congenital Adrenal Hyperplasia were excluded. The age of presentation was categorised into neonatal (<28 days of life), prepubertal (from 28 days of life to immediately preceding puberty) and puberty (after onset of sexual maturation or  $\geq 11$  years old).

#### Result:

A total of 33 children were identified. There were 28 (84.8%) children who were 46XY DSD and 1 (3.0%) 46XX DSD. Sex chromosome DSD was identified in 4 (12.1%) children with 3 had 45XO/46XY and 1 had 47XYY.

Majority (20/33, 60.6%) presented at neonatal period followed by prepubertal (8/33, 24.2%) and pubertal (5/33, 15.2%).

Almost all neonates presented with ambiguous genitalia, with external genitalia score (EGS)  $6.7 \pm 1.9$  except one phenotypically female neonate who had karyotype-phenotype discordance.

Three were assigned as female. They were diagnosed as complete androgen insensitive syndrome (CAIS), Fraser syndrome and severe undervirilised mixed gonadal dysgenesis. All three had genetic tests done.

Among 8 children who presented at prepubertal period, 5 (62.5%) were initially brought up as male, 2 (25%) were female and 1 remained indeterminated. Median age at presentation was 2.0 (0.6-3.4) years. Six (75%) were 46XY and 2 had sex chromosomal DSD (47XXY and 45XO/46XY). EGS was  $7.8 \pm 2.6$ . The reasons for referral were middle/proximal hypospadias (6/8, 75%), micropenis (4/8, 50%), and virilisation (2/8, 25%). Gender for 2 female children with 46XY were reassignment to male once the diagnosis of gonadal dysgenesis and 5-alpha-reductase (5 $\alpha$ R) deficiency were established.

Five adolescents presented at pubertal period, all were initially brought up as female. Mean age at presentation was  $16.2 \pm 4.1$  years with EGS  $5.9 \pm 3.4$ . All had karyotype reported as 46XY. Four (80%) experienced virilisations during puberty and primary amenorrhea. They were assigned as male once genetically confirmed 5 $\alpha$ R deficiency. One was diagnosed with 46XY gonadal dysgenesis. She presented with end stage renal failure and primary gonadal failure. She was phenotypically female and was kept as female gender.

The most common diagnosis we found was AIS with the highest incidence (48.5%) followed by gonadal dysgenesis, 5 $\alpha$ R deficiency and ovotesticular syndrome with 18.2%, 15.2% and 6.1% respectively. No gender dysphoria was noted.

**Conclusion:**

A wide spectrum of DSD can be seen in our clinical setting. They may present at any time during childhood years. Early referral and investigation should be initiated once suspect ambiguity. Early genetic confirmation will benefit patient and family member, and assist physician to prognosticate long term plans.

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## PP 66

### Puberty

#### **EVALUATION OF BRAIN IMAGING AND CLINICAL FINDINGS OF CHINESE GIRLS WITH CENTRAL PRECOCIOUS PUBERTY IN HONG KONG**

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#### **Background**

The prevalence and findings of brain imaging among girls with central precocious puberty differ in different populations. While magnetic resonance imaging of brain was recommended for girls with central precocious puberty onset before six years of age, such recommendation remained controversial in girls with onset between six and eight years of age.

#### **Objective**

To evaluate the need for brain imaging in girls with central precocious puberty onset between six and eight years of age.

#### **Methods**

This retrospective review evaluated data of 162 girls diagnosed with central precocious puberty between 1st January 2010 and 31st December 2020 in a local hospital in Hong Kong. Magnetic resonance brain imaging findings of 127 girls with central precocious puberty were reviewed. Clinical, biochemical and radiological findings of 113 girls with central precocious puberty onset between six and eight years of age were analysed.

#### **Results**

A majority (104 of 127 girls, 81.89%) of girls had normal imaging findings. Brain lesions were identified in 18.11% of girls (23 of 127). The prevalence of brain lesions was lower in girls with central precocious puberty onset between six and eight years of age (18 of 113 girls, 15.93%) compared to those before six years of age (5 of 14 girls, 35.71%). One girl (0.79% of 127 girls), with onset of puberty before six years of age, had hypothalamic hamartoma which had strong association with central precocious puberty. Other brain lesions identified included nine Rathke's cleft cysts, six pituitary adenomas, two Rathke's cleft cysts or pituitary microadenomas, three non-suprasellar arachnoid cysts, two pituitary hyperplasia, one pineal cyst, one calum septum pellucidum and one duplicated posterior lobe of pituitary gland. None of the girls had neurological signs or symptoms or necessitated neurosurgical interventions. There were no significant differences in clinical, biochemical and radiological findings between the two groups.

#### **Conclusions**

Our study casted doubt on the benefit of routine brain imaging in girls with central precocious puberty onset between six and eight years of age without neurological concerns. A larger study would be invaluable in validating the current findings and to provide a more definite recommendation on the indications of brain imaging in this age group.

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## RARE CASE OF FIBROUS DYSPLASIA IN 9 YEARS OLD GIRL : A CASE REPORT

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### Introduction

Fibrous dysplasia (FD) is a rare, benign tumor-like condition in which tissue of fibro-osseous origin replaces the normal bony structure. The first report of the disease can be traced back to 1936, with the polyostotic disease first being described by Lichtenstein. The incidence rate is uncertain, but it is estimated to comprise 5-7% of all benign bone lesions (Baghdadi and Arkader, 2020). It is characterized by abnormal bone metabolism resulting in the production of weak, immature bone mixed in disorganized fashion with fibrous stroma (Yusof *et al.*, 2020). There is no gender predilection, and the most common sites of involvement are the femur, tibia, craniofacial bones and ribs (Baghdadi and Arkader, 2020). FD can present with swelling, pain, deformity, or with pathological fractures (Tripathy *et al.*, 2020).

### Case Report

A 9 year old girl presented with pain in her right thigh and limping since 2 months before admission. There is no history of falls. She has normal growth and development like children at her age. There is no family history with similar complaints.

On examination, the patient was well and looks comfortable without pain when walking. From the status localis of the patient's thigh area, there was no swelling or redness.

On plain radiograph examination of the lower limb, it was found with a sclerotic lytic lesion and expansive with a chondroid matrix impression on the right femur 1/3 proximal and in the distal 1/3 there was no visible fracture line. This suggests a primary bone tumor in the dextra femur.

On further examination, MRI of the dextra femur shows hypointense lesion (T1,T2), multiple heterogeneous hypointense lesions including metadiaphysis of the femur (including head, condylus medialis femur) with unclear boundaries. Hyperintense (T2, FS) and hypointense (T1) lesions were seen with firm borders on the right pelvic wing. No periosteal reaction was seen and the joint space was not narrowed. This suggests the appearance of a fibrous dysplasia with a differential diagnosis of fibroxanthoma accompanied by a suspected bone cyst in the right pelvic wing.

The patient was subjected to examination under anesthesia and biopsy. The histopathological examination revealed the presence a fragment of fibro-osseous tissue consisting of woven bone trabecular tissue with the edges surrounded by osteoblast cells (osteoblastic rimming). Among them are visible fibrous stroma consisting of ovoid nucleated spindle cells. There were also bleeding areas and there were no Chinese letters. These features suggest fibrous dysplasia.

The patient also had a laboratory examination and the result was vitamin D insufficiency (14.21 ng/mL), while the Calcium value was 9,5 mg/L

Patients are planned to be given zoledronic acid IV with a dose of 0.05 mg / kgBW / day every 4 months and to be given vitamin D supplements routinely.

### Discussion

Fibrous dysplasia is a benign lesion with a prevalence between 5 and 7% among benign bone tumors. The symptoms can be asymptomatic with the abnormality identified incidentally on radiologic studies obtained for unrelated reasons. When present, symptoms are nonspecific and include pain, swelling, tenderness, and stress or overt pathologic fracture. The usual appearance of fibrous dysplasia on X-rays includes a lucent lesion in the diaphysis or metaphysis, with endosteal scalloping and with or without bone expansion and the absence of periosteal reaction. On T1-weighted MRIs, the lesion has low-to-intermediate signal intensity equal to that of muscle. T2-weighted images also show low signal intensity owing to the high content of collagen and bone. From histopathological appearance with abnormal fibroosseous tissue with irregular, under-mineralized woven bone, and varying degrees of cellularity. Medical treatment, including pain management, and bisphosphonate therapy has been

shown to be effective in some patients. Although some literature on zoledronic acid therapy in FD is limited, the clinical and radiological response of zoledronic acid treatment in FD of children is promising. Further randomized control trials with a larger sample size are required to establish this drug as a first-line medical treatment in FD.

### **Conclusion**

Fibrous dysplasia can manifest itself in a young age. Radiographic diagnosis along with histopathological diagnosis may be necessary to confirm diagnosis of the disease.

Keyword: Fibrous dysplasia, zoledronic acid, vitamin D

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## GENOTYPE-PHENOTYPE CORRELATION AND CLINICAL CHARACTERISTICS IN THAI CHILDREN WITH 21-HYDROXYLASE DEFICIENCY

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### Background:

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorder. 21-hydroxylase deficiency (21-OHD) caused by mutation in *CYP21A2* gene is the most common form of CAH. This disorder has a broad spectrum of clinical phenotypes that depends on the patients underlying genotypes ranging from severe (classical) to mild (non-classical). The genotype-phenotype correlation and clinical characteristics of 21-OHD CAH children have been studied by several countries including Asian but not well established in Thai population.

### Methods:

This is a descriptive retrospective study and cross sectionally reviewed over a period of 21 years. Inclusion criteria was all patients with 21-OHD CAH diagnosed under the age of 18 years old based on clinical and biochemical diagnosis by endocrinologists. Patients without molecular confirmation were excluded. The patients were recruited from Siriraj pediatric endocrinology center and classified as salt wasting (SW), simple virilizing (SV), non-classical (NC) and prenatal diagnosis phenotype. Genetic analysis was performed by allele-specific PCR to detect eight common mutations in the *CYP21A2* gene and direct sequencing in other two exons (exon 9, 10). Genotypes were categorized into 5 groups according to their predicted enzymatic activity base on previous in vitro studies, which are null, A, B, C, and D. In each group, the expected phenotype was compared to the clinical phenotype to assess the genotype-phenotype correlation.

### Results:

In this study, 68 CAH patients were included. The genotype-phenotype correlation was analyzed in 54 patients, excluding group D and prenatal diagnosis patients. The overall genotype-phenotype correlation was 88.9%. The correlation was highest in group A (100%), following by group B (88.9%), group null (83.3%) and group C (0%). Total of 6 patients had genotype-phenotype discordance. The I2G/I2G was the most frequent mutation (14.7%), following by I172N/I172N (11.7%) and I172/Del-Conv (11.7%). The I2G was the most frequent alleles (32.4%), following by I172N (26.5%), and Del-Conv (18.4%). The most common presentation in SW group was adrenal crisis (64%) and precocious puberty (51%) in SV group. All female patients in classical group had clitoromegaly. All patients in SW group had hyperpigmentation. None of male patients had testicular adrenal rest tumor (TART). Majority of female patients had clitoral reduction (74%).

### Conclusion:

We identify a good genotype-phenotype correlation in 21-OHD CAH. Group A showed the highest genotype-phenotype correlation. This information provides useful data for prediction disease severity and could be helpful in prenatal diagnosis and genetic counseling for 21-OHD patients.

*Keywords: Congenital adrenal hyperplasia, 21-hydroxylase deficiency, genotype-phenotype correlation, CYP21A2, CAH*

### **EFFICACY OF LONG-ACTING GROWTH HORMONE PREPARATION IN CHILDREN WITH GROWTH HORMONE DEFICIENCY**

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#### **Objectives:**

Convenience of growth hormone (GH) use can lead to good adherence and result in satisfactory treatment outcomes. The aim of this study is to compare the long-term efficacy of weekly GH with daily GH in children with GH deficiency (GHD).

#### **Methods:**

Clinical data of 966 GHD children (773 treated with daily GH and 193 treated with weekly GH) were obtained from the "LG Growth Study", which is an observational Korean multicenter registry for GH treatment. The included data at baseline and every 6 months follow-up were chronological age, height, weight, pubertal status, parental height, IGF-I, IGFBP-3, and bone age. Linear mixed model (LMM) was used to compare height SDS and height velocity between two group.

#### **Results:**

At baseline, chronological age, mid-parental height SDS, and frequency of pubertal boys in weekly GH group were older, shorter, and higher compared to those of daily GH group ( $7.46 \pm 2.89$  vs  $8.46 \pm 3.44$ ,  $p < 0.001$ ;  $-0.88 \pm 0.73$  vs  $-1.02 \pm 0.84$ ,  $p = 0.044$ ;  $16.9\%$  vs  $34.0\%$ ,  $p = 0.006$ , respectively). However, baseline height SDS, BMI SDS, bone age delay, and IGF-I SDS were similar between two groups. Height velocity during the first 6 months and height SDS at 6 months were higher in daily GH group ( $10.10 \pm 2.82$  vs  $9.40 \pm 2.86$ ,  $p = 0.003$  and  $-2.16 \pm 0.68$  vs  $-2.40 \pm 0.76$ ,  $p < 0.001$ , respectively). Height SDS at 24 months, and 48 months were similar between two groups ( $-1.60 \pm 0.79$  vs  $-1.75 \pm 0.82$ ,  $p = 0.089$  and  $-1.27 \pm 0.93$  vs  $-1.50 \pm 1.28$ ,  $p = 0.194$ , respectively). In LMM analysis, the overall height SDS and height velocity during 48 months follow-up were similar. The percentage of maintaining GH at 48 months was higher in weekly GH group ( $21.3\%$  vs  $33.6\%$ ,  $p = 0.004$ ).

#### **Conclusion:**

This study showed better adherence and comparable long-term efficacy of weekly GH in Korean GHD children.

**A NOVEL MUTATION OF THE INS GENE IN AN INFANT WITH NEONATAL DIABETES MELLITUS IDENTIFIED BY FUNCTIONAL STUDY**

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Neonatal diabetes mellitus (NDM) is a hyperglycemic status usually diagnosed before first 6 months of life. NDM is caused by mutation of genes such as KCNJ11, ABCC8, INS, GCK and more, resulting in pancreatic malformation, or defect of insulin synthesis and secretion. INS gene mutation is the second most common cause of permanent NDM which is autosomal dominantly inherited, but the majority are de novo mutations. The mutation causes misfolding of proinsulin and accumulation in the endoplasmic reticulum, leading to endoplasmic reticulum stress and apoptosis of the beta cells. We report a case of NDM in a 2-month-old girl from Kazakhstan with a novel heterozygous mutation of the INS gene.

A 2-month-old girl presented with mild fever, polydipsia, polyuria, and lethargy for 1 week. The serum blood glucose was 702 mg/dL, pH 7.01, and serum and urine ketones were positive. She was diagnosed with NDM and diabetic ketoacidosis (DKA), and intravenous hydration and insulin infusion therapy were started. After resolution of DKA, she applied continuous glucose monitoring system and insulin pump. Next-generation sequencing revealed a novel heterozygous mutation in the INS gene. The newly discovered variant is c.64G>C (p.Ala22Pro). Further functional study was performed to identify its clinical implications. The insulin gene mutation (A22P) was made using a mutagenesis kit, and the mutation was confirmed through sanger sequencing. Human INS gene was transfected into the INS-1 (rat pancreas) cells, and protein and RNA expression level were confirmed. Western blot analysis and RT-PCR showed decreased expression of protein and RNA in A22P mutant compared to wild-type, respectively. Also, insulin levels were lower in the mutant than in the wild type by ELISA.

In conclusion, we found a novel mutation of INS gene in a 2-month-old girl diagnosed with NDM, and confirmed decreased insulin secretion from pancreatic beta cells based on various functional studies.

## THE ASSEMBLAGE OF SKIN FINDINGS IN THE TYPE 1 DM WITH INCORRECT INJECTION TECHNIQUE: A CASE REPORT

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### Objective:

Correct insulin administration technique, insulin type and dose play a pivotal role in attaining glycemic control. An error in any of the steps may lead to poor glycaemic control, which affects the patient in the short and long term. We are presenting here unusual skin findings in children with wrong injection technique.

### Case presentation:

Herein, we report a case of 10-year-old male child already diagnosed with type 1 Diabetes Mellitus, presented with poor glycemic control. On examination, we found skin rashes encircling most of his abdominal area circularly. Rashes were round to oval, well-circumscribed, hyperpigmented to hypopigmented to depigmented macules to papules surrounded by a hyperpigmented halo, 0.5 to 1 cm in diameter, painless varying in color from white to pinkish-red to light brown to brownish-black. On observing the administration technique of insulin, we found it was administration incorrectly as intradermal instead of subcutaneous.

### Conclusions:

Proper Diabetes education and insulin administration technique remain the cornerstone in the management of type 1 DM. We should ensure appropriate insulin administration on every visit.

Keywords: Type 1 DM, Insulin administration, injection technique

### Background

Type 1 Diabetes mellitus is a disorder of reduced production or absence of endogenous insulin and dependence on exogenous insulin to manage and prevent its complications. Type 1 diabetes accounts for about 5% to 10% of all patients with diabetes. It is the most diagnosed diabetes of youth (under 20 years of age) and contributes to  $\geq 85\%$  of all diabetes cases in this age group worldwide [1]. The incidence and prevalence of Type 1 diabetes (T1D) is suspected to be high in India, but due to the absence of a nation-wide registry, one cannot be sure of exact numbers. The Diabetes Atlas 2017 estimates that 128,500 children and adolescents with diabetes in India [2]. Administration of Insulin is the cornerstone in the management of type 1 DM. Correct insulin technique and the right insulin type and dose play a pivotal role in attaining glycemic control. An error in any of the steps may lead to glycemic variability, leading to hyperglycemia or Diabetic ketoacidosis, or hypoglycemic episodes affecting the patient in the short and long term [3]. Hence counseling on the part of physicians plays a significant role in managing diabetes mellitus type 1. We are presenting a case of type 1 diabetes mellitus who was being administered insulin intradermally instead of the subcutaneous route, leading to poor glycemic control and unusual skin rashes at the injection site. After proper education with the correct injection technique, his glycaemic control improved with rashes disappearance.

### Case Report

A 10-year-old male patient already diagnosed with type 1 Diabetes Mellitus presented to our hospital with poor glycemic control. The patient developed symptoms of polyuria with nocturia associated with polydipsia six months back. Initially, the mother thought polyuria might be secondary to polydipsia. Later, his mother got suspicious after noticing that ants were getting attracted to urine, and General Practitioner consulted the patient for the same. He was diagnosed with Diabetes Mellitus Type 1 and was started on premixed insulin (70/30) subcutaneously twice a day. At the presentation to our hospital

mother's main concern was poor glycemic control. His Initial complaints of polyuria and polydipsia were not a concern as it was relatively less, and there were no symptoms and signs suggestive of diabetic ketoacidosis. There was no family history of Diabetes Mellitus. He was vitally stable, and systemic examination revealed no abnormality. His blood sugar monitoring was done infrequently, mostly once every day or alternate day, due to fear of needle prick. His blood sugar readings were in the hyperglycemic range. On further examination, we found skin rashes encircling most of his abdominal area circularly. Rashes were round to oval, well-circumscribed, hyperpigmented to hypopigmented to depigmented macules to papules surrounded by a hyperpigmented halo, 0.5 to 1 cm in diameter, painless varying in color from white to pinkish-red to light brown to brownish-black (**Figure-1**). There were also few erosions and crusted plaques. New lesions were pinkish-red, while older lesions were either brown or white.

On further probing, we got to know that the insulin given was correct in type as prescribed with the appropriate dosage, and the storage condition was also adequate, but the administration technique was faulty. On observing the administration technique, the insulin was being given parallel to the skin over the abdominal surface, raising a bleb of about 0.5 to 1 cm, making the procedure faulty. It was delivered intradermally instead of subcutaneously. The glycemic status range of the patient at presentation was as follows: FBS-185 to 200 mg/dl and PPBS – 220 to 270 mg/dl with urine glucose 2+ on the dipstick without ketonuria. There was normal ABG with an HbA1C value of 7.6 %. The disease's pathophysiology and natural history were explained to the child and his parents, including the importance of regular glucose monitoring with proper record maintaining. The patient was started on a Basal bolus regime (injection glargine and injection aspart via prefilled pen with 4mm long needle). The proper subcutaneous injection techniques over the abdomen and thighs and upper arms in a rotatory pattern were demonstrated. Parents were made to administer insulin under supervision to gain confidence and do not repeat the faulty technique. Dietary counseling was done, and a diet chart was provided based on patient preference and accessibility of foods. They have explained the benefits of better glycemic control and were counseled regarding immediate management of hypoglycemia, and were provided with sick day guidelines. They were also equipped with a doctor's contact number in case of emergency. Over the follow-up visits over the next two to three months, his skin rashes started to disappear, and the patient attained better glycemic control. The patient and his parents attained confidence in managing the disease.

## **Discussion**

The most common complication of insulin injection was Lipohypertrophy, as reported by a worldwide injection technique questionnaire study. Insulin injection over the lipohypertrophied site leads to poor insulin absorption leading to variability in glycemic control [4].

Health care personnel plays a crucial role in that there should not just be the verbal transfer of information; they must employ the principle of "Therapeutic Education," which must be patient-centered and varies from patient to patient. Patients and parents must actively participate in management. It also takes into account the whole array of social, psychological, and biological factors. It focuses on motivational factors, bringing changes in the disease and management aspect better and, therefore, bringing changes in behavior helping patients in the short and long term [5].

In our case report, the mother was actively participating in the management. Due to faulty insulin technique, the patient developed unusual skin rashes with poor glycemic control. Patients and parents were given proper diabetic education and were taught to administer insulin subcutaneously, and correctness of administration was ensured during the hospital stay and on every visit. This highlights the importance of proper education and repeated demonstration if required, as understanding may vary from person to person. One should ensure appropriate insulin types, doses, and techniques at every visit as it may jeopardize patient health. Formal diabetes education will also help parent and patient in gaining confidence and better management of disease

There are very few related case reports. Sawatkar et al. reported hyperpigmented rashes encircling the abdomen attributed to blunt trauma due to repeated use of needles [6]. Sahasrabudhe et al. reported lipohypertrophy with scars that were attributed to intradermal injection of insulin [7].

In our case report, the patient presented with skin rashes, which were different from the above 2 case reports. It varied from hyperpigmented to hypopigmented macules to papules due to intradermal insulin injection. Skin biopsy would have been helpful to find out the exact etiopathology of these skin rashes, which could not be done in our case.

## **Conclusion**

Proper Diabetes education and counselling remain the cornerstone in the management of type 1 DM. Physicians and paediatricians taking care must also ensure appropriate insulin administration on every

visit. If required, they must demonstrate adequate insulin administration techniques. Such small steps may help the patient and family in long-term management.

**Learning points:**

- This is unusual skin manifestation of intradermally injected insulin
- it highlights the importance of Diabetic education and demonstration of proper injection technique

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**Conflicts of interest:** None declared

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**Figure-1:** , Hyperpigmented to hypopigmented macules to papules surrounded by a hyperpigmented, following intradermal insulin injection



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Diabetes

## **DIABETIC KETOACIDOSIS DURING COVID-19 PANDEMIC IN CHILDREN WITH T1DM AT DR. HASAN SADIKIN GENERAL HOSPITAL: A CASE SERIES**

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### **Introduction**

Diabetic ketoacidosis (DKA) is a potentially life-threatening condition due to hyperglycaemia and acidosis, causing respiratory problems. The frequencies of DKA is approximately 15-70% in Europe and North America, and 1-10% in established type 1 diabetes patients. In this pandemic corona virus disease 2019 (COVID-19) situation, every fever or respiratory symptoms must be ruled out of COVID-19 and diabetes is one of the most severe comorbid as mortality aetiology due to COVID-19.

### **Case Series Presentation**

We present five children having diabetic ketoacidosis with different precipitators. The youngest is 5, the oldest is 16 years-old and three of them are boys. One of the patient has Dengue fever and one patient was previously diagnosed with T-Cell lymphoma and neuroblastoma. Three of them already diagnosed with T1DM and the rest are the new ones. Four patients were successfully treated and one patient deceased due to severe septic shock. None of them had COVID-19.

### **Conclusion**

During COVID-19 pandemic situation, every diabetic ketoacidosis symptoms should be ruled out of COVID-19. Initial fluid management and managements of other comorbidities are very important for the outcome of the DKA patients.

**Keywords: COVID-19, diabetic ketoacidosis, diabetes mellitus type I, children**

## CLINICAL FEATURES AND GENETIC ANALYSIS OF SBBYS SYNDROME CAUSED BY KAT6B GENE MUTATION

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### Objective

To perform accurate diagnosis and genetic analysis for a case of a child with special facial features, congenital hypothyroidism, amblyopia, etc. as the main clinical phenotypes and his family, so as to provide a basis for clinical diagnosis and treatment of the family and genetic counseling. Methods A detailed assessment of the clinical symptoms of the children and their families. The child, a female, was diagnosed with "hypothyroidism" due to "growth retardation" and received levothyroxine sodium replacement therapy. During the period, due to poor TSH control, the dose was adjusted several times. At the same time, the whole exome sequencing analysis of a family of three was improved, and the Sanger sequencing method was used for verification and genetic analysis. Results The child had clinical manifestations such as special facial appearance, hypothyroidism, amblyopia and scoliosis, but the intelligence test, patella and genital development were normal. The whole exome sequencing results showed that the child's KAT6B gene c.621+1G>A Heterozygous variants were identified as unreported pathogenic variants by searching the Human Gene Mutation Database database. None of the parents of the children carried the variants and was considered as de novo. According to the ACMG variant classification guidelines (PMID: 25741868, 31690835) was judged to be a type 1-pathogenic mutation.

### Conclusion

The KAT6B gene c.621+1G>A heterozygous variant is the cause of the disease in the child. This pathogenic variant has not been reported at home and abroad. The clinical phenotype of this child has special facial features and congenital thyroid function. Low, amblyopia and scoliosis, but no intellectual disability is the first report. KAT6B variants are related to SBBYS syndrome and genitopatellar syndrome (GPS). The two diseases have a certain overlap in clinical features, such as generalized developmental delay, mental retardation, male genital abnormalities, skeletal hypoplasia, and thyroid abnormalities. The only features in SBBYS syndrome are long thumbs, long big toes, special facial features (mask-like face, ptosis, and ptosis, etc.) and abnormal lacrimal passages. Through the analysis of the clinical phenotype of the child, it is considered that the child is diagnosed with SBBYS syndrome, but patients with SBBYS syndrome usually have a certain degree of intellectual disability, developmental delay, language impairment, behavioral and mental problems, etc., and the child has Webster Intelligence test is normal. The child has a mild clinical phenotype, and the analysis may be related to the location of the mutation being a splicing site, but its specific mechanism still needs to be further studied. This type of mutation provides a basis for clinical diagnosis and treatment of the family and genetic counseling.

## PERMANENT NEONATAL DIABETES MELLITUS (PNDM): A CASE REPORT

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### Introduction

Neonatal diabetes mellitus (NDM) is a monogenic type of diabetes that develops within 6 months of birth in an insulin-dependent manner. It's approximately one out of every 100.000-300.000 live births. Clinically, NDM subgroups include transient (TNDM) and permanent NDM (PNDM). Most infants with NDM require insulin to improve their metabolic abnormalities and facilitate weight gain. Sulfonylurea therapy is effective in the treatment of hyperglycemia in patients with neonatal DM who have a mutation in the KCNJ11 and ABCC8 genes.

### Case Presentation

We report a case of a neonatal diabetes mellitus in an three- months-old baby boy, presenting with seizure, hyperglycemia, and a sign of severe dehydration. Based on the patient's laboratory examination, his blood glucose level was 394 mg/dL, his ketone level was 0,1 mmol/L ; his Hb-A1c was 10.,8%, his C-Peptide was 1.66 ng/mL (normal limit), and his GAD 65 was positive. The patient has had a high blood glucose level has known since he was 2 weeks old. The patient was found with persistent hyperglycemia (>150—200 mg/dL) until he was 3 months old. The baby patient was born by caesarean section, with neonatal asphyxia. Patient was given intravenous insulin immediately after admission, and with the addition of oral sulfonylurea. After the treatment, his blood glucose is more controlled than before, with no sign of seizure, and normal growth and development at his age.

### Discussion

Neonatal diabetes mellitus (DM) is defined by the onset of persistent hyperglycemia within the first six months of life. Clinical manifestations at diagnosis include intrauterine growth retardation, hyperglycemia, glycosuria, osmotic polyuria, severe dehydration, and failure to thrive. In this patient, the clinical manifestation is was hyperglycemia and severe dehydration, but the patient was in appropriate for his gestational age (no IUGR) and has normal birth weight. The onset of hyperglycemia was within the patient's 2 weeks of life and is still being found until the age of 3 months, suggesting the criteria that has been found in this patient whereas appropriate for permanent neonatal diabetes mellitus (PNDM).

### Conclusion

Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of hyperglycemia within the first six months of life with a mean age at diagnosis of seven weeks (range: birth to 26 weeks). Long-term treatment for neonatal DM requires the involvement of a multidisciplinary team. Blood glucose monitoring is recommended due to the risk of both hyperglycemia and hypoglycemia in children with neonatal diabetes

Keywords: Permanent neonatal diabetes mellitus, hyperglycemia,

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Bone

## **BONE HEALTH IN TRANSFUSION-DEPENDENT THALASSEMIA IN HONG KONG – A RETROSPECTIVE COHORT STUDY**

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### **Objective**

Aim to delineate the prevalence and associated risk factors of low BMD, osteoporosis/bone fragility and fracture in transfusion-dependent thalassemia (TDT) in the Chinese population in Hong Kong.

### **Design**

A retrospective cohort design was employed.

### **Methods**

Patients of TDT who had serial Hologic dual-energy X-ray absorptiometry (DXA) from 2010 to 2016 and received regular transfusion for at least 5 years were recruited in Hong Kong. Clinical and biochemical data, from 5 years before the first DXA scan, were retrieved from the electronic record system of the Hospital Authority, till 30th June 2020. Low bone mineral density, osteoporosis/bone fragility are defined by the ISCD 2019 position guidelines (1).

### **Results and Conclusions**

Seventy-seven patients were included in the analysis. The fracture prevalence of TDT among the Chinese population in Hong Kong is 15.58%. Up to 55.84% of patients had low bone mineral density and 5.19% patients have osteoporosis/ bone fragility state. Fracture was documented in 12 individuals, of whom one had recurrent fractures at femur. Four had sustained fracture at a median of 6.32 years (range 1.20 – 7.25 years) prior to their first DXA scan. The cumulative incidence at 5 years and 9 years from the first DXA scan, with exception of the four having fracture prior to first DXA scan, were 4.11% (3/73) and 10.96% (8/73) respectively. The median age at first fracture was 31.73 years (range 24.06 – 44.18 years). In the subgroup of participants who were naïve of bisphosphate before the first DXA scan (n=63), point prevalence of low BMD, bone fragility/osteoporosis and fracture were 65.1%, 7.9% and 12.7 % respectively. In terms of spine BMD Z-score, 46.0%, 38.1% and 15.9% had Z-score of above -2.0, between -2.0 to -3.0 and below -3.0 respectively. In terms of total hip BMD Z-score, 57.1%, 38.1% and 4.8% had Z-score of above -2.0, between -2.0 to -3.0 and below -3.0 respectively. In regression analysis, a higher log(10) transformation of average ferritin levels over 5 years before the first DXA scan (OR 310.73, 95% CI 3.99–24183.89, p=0.010) was significantly associated with fracture occurrence regardless of bisphosphonate treatment. Mean average ferritin level over 5 years was 6695.5±2365.7 pmol/L in the fracture versus 4350.7±3103.2 pmol/L in the non-fracture group (p=0.016). Hip and Spine BMD Z-score did not have statistically significant association with fracture occurrence. Iron overloading plays an important role in adverse bone health in TDT. Dual X-ray densitometry is insufficient in predicting fracture risk.

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Growth

## **BRAIN MAGNETIC RESONANCE IMAGING ABNORMALITIES AND EFFECT ON GROWTH RESPONSE IN CHILDREN WITH GROWTH HORMONE DEFICIENCY**

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### **Purpose**

There have been some studies on the association between structural abnormalities of pituitary gland and its function, but no studies have yet been conducted on children with idiopathic growth hormone deficiency (GHD) patients in Korea. We investigated the relationship between clinical and laboratory findings of patients with and without pathologies in the pituitary gland in Korean children with idiopathic GHD.

### **Material/Methods**

We included a total of 479 patients from LG growth study between Feb, 2001 and Feb, 2020 and who were found to have isolated growth hormone deficiency, received growth hormone treatment, and whose pituitary magnetic resonance imaging (MRI) were available. The data of all patients with isolated growth hormone deficiency were reviewed retrospectively for clinical characteristics, including chronological age at treatment start, bone age, height, height SDS, body weight, weight SDS, body mass index, puberty stage, pre-treatment growth rate, and post-treatment one-year growth rate. Pituitary MR images were evaluated. Patients were divided into 3 groups: those with (1) pathological findings including pituitary gland; (2) pathological findings outside the pituitary gland; (3) without pathological findings with MRI.

### **Results**

Of the 479 patients, 297 were males and 185 were females, and 198 patients (83.5%) were prepubertal and 39 patients (16.5%) were pubertal. Their mean age was  $7.56 \pm 2.95$  years (2–16 years). Pituitary images of 354 (73.9%) patients were normal. Of the patients with detected pathologies (26.1%), 77 (61.6%) had pituitary hypoplasia, 15 (12.0%) had Rathke's cleft cyst, 6 (0.05%) had partial empty sella, 6 (0.05%) had arachnoid cyst, 3 (0.02%) had ectopic neurohypophysis and 3 (0.02%) had pineal cyst. There was no statistically significant difference in the height increase rate after treatment compared to before treatment between groups with or without pituitary pathology ( $p=.09$ ).

### **Conclusions**

MRI is recommended in GHD patients because it helps determine the pathogenesis of GHD, but there is no significant differences in predicting its treatment response.

**NON-TRAUMATIC FRACTURE OF THE FEMORAL NECK IN A 14-YEAR-OLD GIRL WITH ASYMPTOMATIC OSTEOPETROSIS: A CASE REPORT**

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Osteopetrosis is a rare genetic defects of osteoclast formation and function. It was first described by Albers-Schönberg in 1904 as “marble bone disease” due to the intense sclerotic of the skeleton. It is a rare condition with slightly over three hundreds cases have been reported in the literature. According to the modality of transmission and the clinical severity, marble bone disease can be classified into two main types: malignant (autosomal recessive) and benign (autosomal dominant) type. The incidence of osteopetrosis is approximately estimated at 1:200,000 for autosomal-recessive osteopetrosis and 1:20,000 for autosomal-dominant osteopetrosis. In the benign type, osteopetrosis can be distinguished in two types according to the radiological aspect of the bones. In type I, bones are uniformly denser than normal and the cranial vault shows relevant sclerosis and thickening. Autosomal dominant osteopetrosis type II is characterized is characterized by generalized osteosclerosis with thickening of the vertebral end plates (i.e., sandwich vertebrae) and bone within bone in the pelvis. In both types, nearly half of the patient are asymptomatic, and the diagnosis of marble bone disease is occasionally suggested due to radiological examination of the bones. In the symptomatic forms, affected patients can be suffered from recurrent pathological fractures, osteoarthritis, skeleton deformities, osteomyelitis, and cranial nerves palsy. We reported a case of an 14 year-old-girl referred to endocrinology consultation for bone quality problem. She had a past history of non-traumatic fracture of the right femoral neck while descending from her mother’s motorcycle 18 months ago. In pediatrics, non-traumatic fracture cases of the femoral neck is extremely rare, and most of the cases are due to stress fractures. After recovery from the surgery, she had no other complaints. Classic radiologic features of the pelvis showed typical “sandwich vertebrae” or or “rigger-jersey” appearance strongly suggested of osteopetrosis. We can also found the evidence healing fracture of the right femoral neck with the screw (fig 1). Other standard radiographs of the skull and long bones also showed the thickening of cortical bones (fig. 2, 3). Genetic testing was performed with the result of the CLCN7 mutations of the chloride transporter. The results of whole-exome sequencing revealed homozygous nonsense mutation c.2299C>T (p.Arg767Trp). Her father aged of 47 and her little brother aged of 6 have also been carried the same gene mutations; but both of them do not show typical features of osteopetrosis in radiological examination. Matar (2014) and Behera (2016) reported two cases of femoral fracture due to osteoporosis in children aged of 12 and 8 respectively. To the best of our knowledge, this is the third case report of a non-traumatic fracture of the femoral neck due to marble bone disease in an 14 year-old girl.



Fig.1. The "sandwich vertebrae" or "rugger-jersey" appearance of the vertebrae (white arrow). Evidence of healing fracture of the right femoral neck with a screw (black arrow).

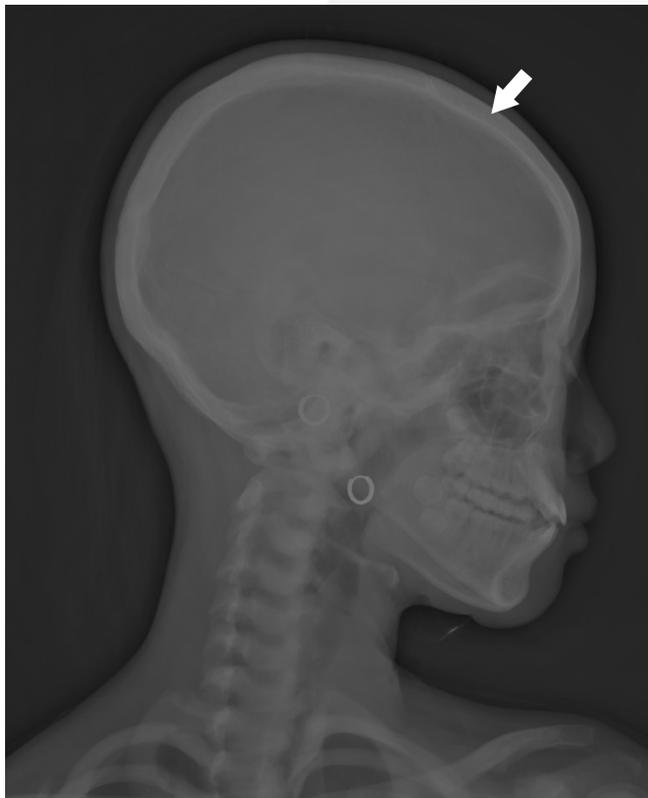


Fig 2 and fig 3. Thickening of the skull and cortical bone of the femur (white arrow)



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**PRIMARY HYPERTRIGLYCERIDEMIA IN CHILDREN: A CASE SERIES OF THE CLINICAL FINDINGS, GENETIC DIAGNOSES AND THE USE OF INTRAVENOUS INSULIN THERAPY**

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**Background:**

Hypertriglyceridemia (hTg) is defined as a fasting triglyceride (Tg) level above the age-sex adjusted 95<sup>th</sup> centile. HTg can be either primary or secondary. Primary hTg in children results from genetic variants governing triglyceride metabolism. Primary hTg is diagnosed based on the severity of Tg elevation, clinical features and family history and can be classified according to the Fredrickson classification. Clinical presentations are variable and affected individuals can be asymptomatic or present with severe manifestations such as acute pancreatitis or lipid encephalopathy. The reported incidence is 1:500,000- 1:1,000,000 but epidemiological data in the Asian population is limited. The mainstay of management in children with primary hTg is dietary manipulation with appropriate fat restriction with pharmacological therapy such as fibrates. However, in children who present with acute pancreatitis rapid reductions in serum Tg levels are necessary which cannot be achieved with dietary intervention. In such circumstances, alternative therapies, such as intravenous insulin infusion has been shown to be beneficial.

**Aim:**

This case series aims to report on the clinical findings, genetic diagnoses and the use of intravenous insulin infusion therapy in the management of primary hTg in a cohort of Malaysian children

**Methods:**

A retrospective review of the electronic medical records was conducted on children with primary hTg referred to a large tertiary University hospital. Data on clinical, biochemical, genetic and medical management for each proband was collected with a particular focus on the details of intravenous insulin infusion used

**Results:**

We report 4 cases of primary hTg in the Malaysian paediatric cohort. Of these, 3 (75%) were male and 3 (75%) had an initial presentation younger than 12 months of age. These 3 children also had confirmed genetic mutations of the lipoprotein lipase gene. The commonest clinical presentation was the incidental finding of lipaemic serum, but 1 child presented with pancreatitis. The serum Tg for all children was >10 mmol/L (range: 10.3-436 mmol/L). Though all children had some form of dietary intervention 3 required intravenous insulin infusion (0.005-0.01u/kg/hr) for up to 72 hours duration to rapidly reduce severely high serum Tg levels. There was a 30-76% reduction in serum Tg levels with a sustained reduction (<10mmol/L) in all cases. There were no episodes of hypoglycaemia in any of the 3 cases.

**Conclusion:**

This case series demonstrates that the use of low dose intravenous insulin infusion is an effective and safe therapeutic option in children and infants with primary hTg who have severely high levels of serum Tg (>10mmol/L) which requires rapid reduction to avoid progression to pancreatitis.

Keywords hypertriglyceridaemia, familial chylomicronaemia, children, insulin

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## **AN OBSERVATIONAL STUDY ON TRENDS IN DIABETIC KETOACIDOSIS OVER AN 11 YEAR PERIOD IN MALAYSIAN CHILDREN WITH TYPE 1 DIABETES**

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### **Background:**

Diabetic ketoacidosis (DKA) is a leading cause of death in newly diagnosed children with Type 1 diabetes (T1DM). Though osmotic symptoms commonly precede the initial diagnosis, a lack of recognition of these symptoms can lead to a delay in diagnosis or a misdiagnosis, and both can increase the risk of DKA at initial presentation. Analysis of the DiCARE registry data (2000-2009) showed that 64.7% of Malaysian children with T1DM present in DKA at initial diagnosis and that the frequency of DKA increased by 12.3% during that period.

### **Objective:**

The objective of this paper is to determine the incidence of DKA in Malaysian children with T1DM at initial diagnosis and to describe the trends in DKA over an 11 year period between 2010-2020 from a large single centre in Malaysia.

### **Methods:**

A retrospective observational study of newly diagnosed Malaysian T1DM patients aged less than 18 years of age presenting to the University Malaya Medical Centre (UMMC) between January 1<sup>st</sup> 2010 and December 31<sup>st</sup> 2020 was conducted. Data on demographics, clinical presentation, biochemical parameters from the electronic medical records was extracted and analysed.

### **Results:**

A total of 128 children with T1DM were identified during the study period. The DKA rate was 73% and 54% had severe DKA. Of those presenting in DKA, the mean age was 7.9±4.01 years and 27.1% were < 5 years of age at initial diagnosis. Females commonly presented in DKA (54.2%) as did those of the Malay ethnicity (43.8%). A large proportion (49%) of the DKA group were misdiagnosed and almost one-third (28%) had been seen by either 2 or more healthcare professionals prior to a diagnosis of T1DM. Intensive care unit admission was required in 62% of the DKA group. Trends analysis over the 10 years showed that the DKA rate fluctuated between 77-90% and peaked in 2015 (at 90%). Females were consistently the more common gender to present in DKA. The mean age at diagnosis in the DKA group fluctuated between 6.74-9.12 years as did the percentage of children aged <5 years presenting in DKA (0-43%), but no trends were detected. Severe DKA was consistently the most frequent presentation over the 10 years.

### **Conclusion:**

This study demonstrates that there are persistently high rates of DKA over the 11-year study period, in Malaysian children with T1DM, as compared to the preceding 10 years. Furthermore, the rates of severe DKA are persistently high as are the frequency of females presenting in DKA over the current study period. These findings highlight the need to raise awareness amongst healthcare providers and the general public about T1DM in children so that it may improve the current trends in paediatric DKA in Malaysian children.

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## **CUSHING'S SYNDROME IN A 7-MONTH OLD WITH AN ADRENOCORTICAL TUMOR**

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### **Introduction**

Cushing's syndrome, caused by prolonged exposure to high levels of cortisol, is a rare condition in infancy and is typically due to an adrenocortical tumor. In the Philippines, exact incidence is unknown and clinical presentation is not well documented.

### **Case Report**

A 7-month-old infant sought consult at Bicol Medical Center (Camarines Sur, Philippines) due to accelerated weight gain and poor linear growth. During the first 4 months of life, the patient exhibited normal growth rate of an average growing baby. By the 5th month, the patient exhibited rapid weight gain with notable facial, trunk & extremities swelling. Linear growth stopped & reddish macules resembling facial acne appeared. Initial consults advised diet modifications but as symptoms progressed, the patient sought specialty consult.

Physical exam showed obesity, hypertension, Cushingoid facies, and features of virilization. Biochemical examinations were done which showed elevated random serum cortisol. On imaging, the patient was noted to have bilateral noncalcified, enhancing suprarenal mass on the right, causing slight inferior displacement of the right kidney. Cranial imaging showed no pituitary tumor ruling out secondary Cushing's syndrome caused by a pituitary adenoma. Patient had no history of steroid use and exogenous cortisol sources were ruled out.

The patient was diagnosed with Cushing syndrome secondary to an adrenocortical tumor. Thereafter, the patient underwent right adrenalectomy and was given stress doses of steroids intraoperatively and postoperatively to mitigate adrenal suppression due to prolonged exposure to steroids from the tumor. Mortality rate is usually high for post-surgery adrenalectomy due to inadequate steroids and subsequent infections.

Histopathologic examination was performed and it showed that the tumor is an adrenal adenoma which was unequivocally benign based on the Wieneke Multiparameter criteria for adrenal tumors.

Post-surgery, the patient had hypertension which was managed medically. Three months postoperatively, hypertension was controlled, and her growth velocity began to increase. Cushingoid and features of virilization were slowly resolving. The patient was also observed to have a happier disposition as opposed to irritability exhibited pre-surgery.

Interestingly, the patient has a significant family history of cancer and although adrenal glands seldom become neoplastic, specimens will be sent overseas for the tp53 gene mutation estimated to occur in 80-90% of pediatric adrenocortical tumors. This allows for further prognosis, surveillance and genetic counselling for the family.

### **Conclusion**

Although rare, Cushing's syndrome should be considered in patients with excessive weight gain and poor linear growth. Adrenocortical tumors, on the other hand, should be considered as a differential diagnosis of Cushing's syndrome among the pediatric age group since this is one of the common endogenous causes. Early diagnosis, adequate perioperative management with glucocorticoid replacement, control of hypertension and complete excision of tumor with close follow up resulted in a better overall prognosis and survival of our patient.

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**A FEMALE WITH 46,XX GONADAL DYSGENESIS PRESENTING WITH HYPERGONADOTROPIC HYPOGONADISM AND NORMAL HEIGHT**

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**Introduction:**

Genes on the X chromosome (BMP15, FMR1) and autosomal chromosomes (FOXL2, RSPO1, WNT4) are known to influence ovarian development. 46,XX gonadal dysgenesis is a rare disease caused by chromosomal abnormalities, genetic mutations, and postnatal ovarian damage, leading to premature ovarian failure.

**Case Report:**

A 16-year-old female presented with primary amenorrhea and poor breast development. She was born at 40 weeks of gestation with a birth weight of 3.79 kg. She had no personal or family medical history. Her physical and intellectual development were normal. On physical examination, her height was 0.29 standard deviation score (SDS), weight 1.73 SDS, and body mass index 2.10 SDS. She revealed no feature of Turner syndrome or dysmorphism. On pubertal assessment, her breasts were Tanner stage 1 and her pubic hair was Tanner stage 3. Bone age measured 13 years. Hormonal studies revealed: serum follicle-stimulating hormone 104.9 IU/L, luteinizing hormone 26.4 IU/L, estradiol <4.0 pg/mL. Serum  $\beta$ -human chorionic gonadotropin, prolactin, testosterone, and thyroid hormones were within normal limits. Chromosome analysis revealed a 46,XX karyotype. A pelvic ultrasonography showed a streak uterus (fundus 21 mm, cervix 5 mm), with the absence of bilateral ovaries. Multidisciplinary management including hormonal replacement is necessary. Additionally, advanced diagnostic approaches using array-comparative genomic hybridization and next generation sequencing are prerequisites for genetic counseling.

**Conclusion:**

Further research on the genetic and non-genetic pathogenesis of 46,XX gonadal dysgenesis can contribute to better strategies for diagnosing and treating this rare disease.

## THE PREVALENCE OF ABNORMALITIES ON BRAIN MRI IN PATIENTS DIAGNOSED WITH CENTRAL PRECOCIOUS PUBERTY

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**Background:** The annual incidence of central precocious puberty (CPP) is increasing, and the brain resonance imaging (MRI) is recommended in cases suspicious of brain lesions. In 2018, the Korean Ministry of Health and Welfare has expanded the health insurance coverage for brain MRI for all patients with CPP. The study was designed to evaluate necessities of routine pituitary MRI in patients who are newly diagnosed with CPP.

**Methods:** This retrospective study reviewed data of newly diagnosed CPP patients who underwent routine pituitary MRI screening at Korea University Anam Hospital from March 2020 to July 2021. A total of 176 girls and 20 boys were enrolled in the study. Positive MRI findings were categorized as abnormal pituitary, non-pituitary incidental, or pathologic findings. We investigated the prevalence of MRI abnormalities and evaluated its association with clinical and laboratory factors.

**Results:** Positive MRI findings were observed in 73 patients (37.2%); pituitary abnormalities were observed in 64 patients (32.7%), and non-pituitary incidental findings were seen in 8 patients (4.1%). Pathologic finding was found in one patient (0.5%). Among pituitary abnormalities, Rathke's cleft cyst showed the highest incidence rate (15.8%). Only one girl patient had a pathologic brain lesion and was diagnosed with hypothalamic hamartoma. The number of abnormalities on MRI findings was higher in girls compared to boys (39.2% vs. 20.0%,  $P= 0.055$ ). No significant difference was found in prevalence of MRI abnormalities in different age groups in girls: girls aged 6-7.9 years and 8-8.9 years (34.0% vs. 34.9%,  $P= 0.511$ ). MRI findings of pituitary abnormalities did not show a significant correlation with peak LH or LH/FSH ratio.

**Conclusion:** The prevalence of abnormalities on pituitary MRI in CPP patients was relatively high, but true pathologic findings were rare. Considering substantial effects, routine screening of pituitary MRI in all CPP patients should be decided carefully.

Keywords: Precocious Puberty; Magnetic Resonance; Rathke's cleft cyst

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Diabetes

### GLYCEMIC CONTROL AND COMPLICATIONS OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS DURING THE COVID-19 OUTBREAK

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#### Background:

According to the rapid increase in obesity, incidence of type 2 diabetes mellitus (T2DM) has increased in children and adolescents worldwide. Incidence and severity of the pediatric obesity are on the rise especially during the coronavirus disease-19 (COVID-19) outbreak. This study was aimed to investigate the impact of the COVID-19 outbreak on the glycemic control and complications of T2DM in children and adolescents and its correlation with the obesity.

#### Method:

We retrospectively reviewed the medical records of 48 children and adolescents with type 2 DM visiting Korea University Hospital in both 2019 and 2020. We investigated changes in weight and body mass index (BMI) standard deviation scores (SDS), glycated hemoglobin (HbA1c), blood pressure (BP), liver and lipid profile from 2019 to 2020.

**Results:** The average age of 48 subjects in 2019 was 15.5 years old and 70.6% of patients were obese. From 2019 to 2020, HbA1c level has increased (median value  $6.5 \pm 2.72$  vs  $7.3 \pm 3.70$ ,  $P < 0.001$ ) and BP, total cholesterol, non-high density lipoprotein (HDL) cholesterol have also increased ( $P < 0.05$ ). Obesity was found to be independent predictor of increased HbA1c in multivariable analysis (95% confidence interval 1.071-50.384,  $P = 0.042$ ). In non-obese subjects, HbA1c level has not significantly increased during the COVID-19 outbreak. In obese subjects, HbA1c and BMI-SDS have increased during the COVID-19 outbreak (median value  $6.45 \pm 2.30$  vs  $7.20 \pm 3.05$ ,  $P < 0.001$ , median value  $2.88 \pm 0.75$  vs  $3.08 \pm 0.98$ ,  $P = 0.045$ , respectively). Diastolic BP, total cholesterol were also higher in 2020 compared to 2019 ( $P < 0.05$ ).

**Conclusion:** During the COVID-19 outbreak, glycemic control and complications of type 2 DM have deteriorated in children and adolescents. This tendency was prominent in obese patients. Obese type 2 DM patients should be more closely monitored in glycemic control and complications.

Keywords: obesity, type 2 diabetes mellitus, COVID-19, child

## HEIGHT OUTCOME IN CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY TREATED WITH GNRH AGONIST

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### Introduction:

Gonadotropin-releasing hormone agonist (GnRHa) is used mainly for pubertal suppression in central precocious puberty (CPP) where adult height is compromised.

### Method:

We analysed female children who completed GnRHa treatment between the year 2010 and 2020. Anthropometric measurement, calculated height SDS and pubertal Tanner staging were documented at initiation and termination of treatment. Final height (FHT) is documented at 2 years post GnRHa treatment and/or height velocity (HV) is below 2cm/yr. Adjusted mid-parental height (MPH) SDS (aMPHSDS) was defined as height SDS minus MPHSDS. Causes of precocious puberty were identified. Bone age (BA) was measured using Tanner-Whitehouse (TW3) method.

### Result:

A total of 33 children completed GnRHa treatment during this period. The most common causes of CPP were idiopathic (60.6%), followed by small for gestational age (12.1%) and pituitary microadenoma (9.1%). Thirteen children (39.4%) presented with advanced breast development (Tanner stage 3) and four (12.4%) presented with menarche. Although the mean BA pre-treatment was  $9.11 \pm 2.58$  years, 51.5% had 2 years advanced BA compared to their chronological age.

At the initiation of GnRHa treatment, the mean age was  $6.87 \pm 2.27$  years and the mean height was  $122.33 \pm 21.53$ cm ( $0.75 \pm 1.71$  SDS). Median height velocity was 5.26cm per-year during the first year of treatment [range 4.00-6.60cm] and slowed down to 3.97cm per-year during the second year of treatment [range 3.05-5.73cm]. Median duration on GnRHa treatment was 3.79 years [range 2.67-4.77 years]. Median height documented at last dose of GnRHa treatment was 142.60cm [137-148.55cm], -0.7 SDS [range -0.64 to 1.05 SDS]. At termination of GnRHa treatment, there were no significant difference seen in aMPHSDS comparing the group with advanced breast development and menarche ( $1.57 \pm 1.12$  SDS) to those presented earlier with breast Tanner stage 2 ( $1.20 \pm 1.31$  SDS)( $p=0.399$ ). Nine out of 33 (27%) had documented FHT. Their mean FHT was  $154.16 \pm 5.27$ cm ( $-0.45 \pm 1.01$  SDS), which showed no significant difference from their MPH  $156.22 \pm 7.04$ cm ( $-0.45 \pm 1.27$  SDS) ( $p=0.221$ ), as well as with the pre-treatment predicted height based on bone age of  $157.06 \pm 6.01$ cm ( $p=0.051$ ). The median age of menarche was 15 months [range 12-19 months] after completion of GnRHa treatment. Only 2 (6%) reported adverse effect towards GnRHa (1 breakthrough bleeding, 1 gluteal abscess).

### Conclusion:

The use of pubertal suppression preserves the final height outcome in children with CPP regardless of pubertal advancement at presentation. This audit showed that minimal significant adverse event was reported during the duration of treatment. Spontaneous progression to menarche after stopping GnRHa treatment was not delayed.

## COMPARATIVE ANALYSIS OF THE CLINICAL EFFECTIVENESS OF LASER LANCET FOR CAPILLARY BLOOD SAMPLING IN PEDIATRIC DIABETES PATIENTS

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### Objectives

Good glycemic control in diabetes is the key to preventing complications. In order to achieve targeted blood sugar, frequent checking is necessary. Diabetes patients currently use needle lancing device to monitor their blood sugar. However, fear of needles and pain hinders self-monitoring. Skin keratinization and scarring are also factors that lower compliance. Therefore, devices that are less painful and less traumatic are being developed. The purpose of this study was to compare the clinical effectiveness of laser lancing device without a needle to a conventional needle lancet for capillary blood sampling.

### Methods

A total of 27 diabetes patients aged 9-16 years who visited Korea University Ansan Hospital in July, 2021 were recruited. Of these participants, 8 patients were type 1 diabetes (29.6%) and 19 were type 2 diabetes patients (70.4%). Capillary blood was collected with a laser lancet and a conventional needle lancet on opposite fingers, the choice of which was randomly selected. After each puncture, blood glucose was measured and optical coherence tomography was taken. Close up photo of wounds were also taken right after the puncture and 24hrs after the puncture in order to evaluate the healing process. Pain score was measured with a scale from 0 to 10 where 0 was no pain and 10 was maximum pain possible. Overall satisfaction score was also measured with a scale from 0 to 10 where 0 was completely unsatisfactory and 10 was very satisfactory.

### Results

Average age of the participants were 13.8 years. Blood sugar measured showed no difference between laser lancet and needle lancet and the two groups showed positive correlation. Mean depth measured after laser lancet puncture was shallower than needle lancet ( $0.54 \pm 0.14$ mm, vs.  $0.87 \pm 0.03$ mm,  $p < 0.001$ ). Comparative analysis of pain showed that there was no difference between the two groups. When close up photos were compared, laser lancet group showed less redness and swelling compared to the needle lancet group indicating less trauma and faster healing. Overall satisfaction was higher in laser lancet group ( $7.90 \pm 1.77$ , vs.  $4.80 \pm 1.43$ ,  $p < 0.001$ )

### Conclusion

The laser lancing device produced accurate blood sugar and demonstrated faster healing than the conventional needle lancet. Pain felt during puncture was similar in both groups but overall satisfaction was higher with laser lancet.

Keywords diabetes mellitus, blood sugar, laser lancet,

**CASE REPORT OF FAMILIAL PRADER WILLI SYNDROME CAUSED BY RARE MICRODELETION OF SNRPN GENE AND ABNORMAL METHYLATION OF GRANDMA**

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**Purpose:**

The incidence of PWS is about 1/10000-1/30000, of which 1%-3% are imprinted gene mutations, and SNRPN gene mutations are rare. In this study, the first clinical manifestation of 1 case was hypotonia and the family identified the genetic etiology and genetic counseling.

**Methods:**

To evaluate the detailed clinical symptoms and family history of the children and their families, take 2ml of peripheral blood from the children and their parents, grandmother, and aunt for high-throughput sequencing and MLPA detection.

**Results:**

The clinical manifestations of the child were feeding difficulties, low muscle tone, and lagging growth and development at the time of consultation in January. The cousin had similar symptoms (without genetic testing), and the clinical phenotypes of his parents, grandmother, and aunt were completely normal. The MLPA test indicated that the child, his father, grandmother 15q11-13 region SNRPN gene exon 3, exon u5, intron u2 heterozygous deletion, and abnormal methylation detection. The initial report of high-throughput sequencing did not indicate an abnormality, and then based on the MLPA results, reanalysis indicated that the region was missing.

**Conclusion:**

SNRPN gene mutation is a rare genetic cause of PWS, and the risk of reproducing PWS is 50%. The second-generation sequencing may miss such causes. In clinical practice, pedigree analysis and paternal MLPA testing for chubby power syndrome caused by mutations in this gene are required to clarify the cause and genetic counseling.

## GENETIC AND CLINICAL PROFILE OF PRADER-WILLI SYNDROME

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### Background:

Prader-Willi Syndrome (PWS) is a multisystem complex genomic imprinting disorder due to lack of expression of the genes inherited from the paternal chromosome 15q11-q13 region. It is the most common syndromic cause of life-threatening obesity with an estimated prevalence of 1 in 10,000-20,000 births. We present the clinical data of the children diagnosed with PWS and currently being managed at our hospital.

### Methods:

A retrospective study of children with PWS was conducted for their genetic and clinical profile.

### Results:

A total of 26 children (1 year – 18 years) were included, of which 17 were boys and 9 were girls. The mean age of diagnosis was 28 months with 54% diagnosed within 1 year, 33% between the age of 1 to 5 years, and 12% after the age of 5 years.

The methylation defect (38%) was the most common genetic defect followed by deletion defect (33%). Hypotonia and delayed motor milestones were the most consistent finding present in 96% of the children. 50% of them were obese at the time of diagnosis.

Out of 26 children, 42% developed dyslipidaemia, 15% developed type 2 diabetes and 12% developed hypothyroidism. In view of increased day time sleepiness and snoring, 12 children underwent polysomnography and 9 of them showed some degree of obstructive sleep apnoea with 1 requiring C-pap. A total of 12 children (46%) were started on recombinant human growth hormone therapy either for extreme hypotonia or growth failure. Of 17 boys in this study, 94% had cryptorchidism (70% bilateral and 25% unilateral). A total of 7 children developed hypogonadism requiring hormone replacement therapy.

**Conclusion:** Early diagnosis of PWS is important for effective management and improvement in quality of life, to prevent complications and prolong life expectancy.

**DISTURBED EATING BEHAVIOURS IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES: A SINGLE CENTRE STUDY IN MALAYSIA**

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**Introduction:** Children and adolescents with Type 1 diabetes (T1DM) are at higher risk of developing disturbed eating behaviours (DEB) than their peers without diabetes. In addition, Malaysia has the second highest obesity rate among children in South East Asia aged 5-19 years [1] with the prevalence of overweight/obese as high as 29.8% [2]. The prevalence of DEB was observed in 21.2% of T1DM adolescents and young adult and 50.3% of those with type 2 diabetes in recent international studies. [3]

**Objective:** To explore the prevalence of DEB and evaluate its association with clinical and metabolic factors among children and adolescents with type 1 diabetes (T1DM), screened using the Diabetes Eating Problem Survey-Revised (DEPS-R) in Hospital Putrajaya, Malaysia.

**Methods:** A cross-sectional study on T1DM children and adolescent between 9-18 years old who attended the paediatric endocrine clinic Hospital Putrajaya, Malaysia between November 2019–August 2020. Clinical characteristic, average HbA1c and body compositions were evaluated. The Diabetes Eating Problem Survey-Revised (DEPS-R) questionnaire was administration. DEPS-R scores  $\geq 20$  was considered high, a level that warranted further assessment. [3,4] Percentage body fat (PBF) was measured using bioelectrical impedance analysis (Model Inbody 720). PBF  $\geq 85^{\text{th}}$  centile according to Hong Kong Chinese children reference was considered as excessive body fat.[5] Overweight and obesity were defined according to the WHO BMI standards.

**Results:** Total 52 T1DM were eligible for DEPS-R assessment and 43 answered (51.2% boys). The mean age was  $13.9 \pm 2.5$  years. Majority was in puberty (83.7%) with mean HbA1c  $10.2 \pm 2.1$  %. Mean weight SD was  $-0.6 \pm 1.3$  with girls heavier than boys ( $-0.2 \pm 1.3$  vs  $-0.9 \pm 1.2$ ,  $p = \text{NS}$ ). Eight (18.6%) were overweight/obese and 10 (23.3%) had excessive body fat. Prevalence of excessive body fat was higher in overweight/obese group compare to those with normal BMI (75% vs 11.5%,  $p = 0.01$ ). Nearly 1/3 (12/39, 30.8%) fulfilled the criteria for metabolic syndrome. Thirty-one (72.1%) scored DEPS-R  $\geq 20$  with mean score  $24.7 \pm 10.3$ . The prevalence of DEB increased with weight from 65% in normal BMI to 100% in overweight/obese group. Those scored DEPS-R  $\geq 20$  showed older age (14.2 vs 13.1 years old), longer diabetes duration (6.3 vs 5.4 years) and higher HbA1c (10.4% vs 9.4%). T1DM children with high DEPS-R score ( $\geq 20$ ) scored higher in DEPS-R factor 1 ( $p < 0.001$ ) and factor 2 ( $p < 0.001$ ). Chinese T1DM children had lower scores as compared to Indian and Malays in DEPS-R factor 1 ('Maladaptive Eating Habits',  $p = 0.017$ ) and they achieved better glycemic control (HbA1c 8.6% vs 11.1% vs 10.3%). Malays T1DM children scored highest in DEPS-R factor 3 ('Concept of Maintaining High Blood Glucose Values to Lose Weight',  $p = 0.038$ ). Gender, ethnicity, pubertal status, BMI and duration of DM did not show significant difference for DEPS-R factor 2 ('Preoccupations with Thinness or Weight'). Children with excessive body fat was associated with maladaptive eating habits ( $p = 0.001$ ) and scored significantly higher for overall DEPS-R ( $33.4 \pm 6.8$  vs  $22.06 \pm 9.8$ ,  $p = 0.001$ ).

**Conclusion:** High prevalence of DEB in children and adolescents T1DM was associated with poorer glycemia control and higher PBF. Diabetes-specific screening questions such as DEPS-R should be routinely used in outpatient T1DM clinic in a standardized manner. Early recognition of DEB is essential for successful treatment and effective prevention of long term cardiovascular complications.

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**CLINICAL, MOLECULAR AND CYTOGENETICS STUDIES ON 6 PATIENTS WITH WILLIAMS-BUEREN SYNDROME**

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**Objective:**

To investigate the clinical, molecular and cytogenetics features of Williams syndrome.

**Methods:**

Analyze the clinical characteristics of 6 cases of children with Williams syndrome, and conducting genome-wide CNV (cn) analysis method.

**Results:**

6 children with genetic testing fragment deletion size fluctuates 740Kb-2.36Mb, all contain ELN gene, 1 cases although ELN gene is missing, but normal cardiac structure;6 cases all have special features, there are 2 cases, respectively, 740 KB, 2.36 Mb in size and is not the same as the other 4 cases of nasal characteristics;5 cases missing pieces contain GTF2IRD1, 1 case of missing segment does not contain GTF2IRD1, 2 cases of missing size is 1.41 Mb, respectively 2.36 Mb children show the language expression ability, an overly friendly, talkative, like social, but mental impairment, 1 case of missing children with 740 KB of opposite personality, language development lag behind.

**Conclusion:**

Williams syndrome phenotype differences and lack of fragment size and related genes, but it is not the only factor that affect Williams syndrome phenotype characteristics of genetics mechanism needs to be studied further.

## **VALIDATION OF OPTIMAL SAMPLING DURATION OF CONTINUOUS GLUCOSE MONITORING IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES: REAL-WORLD DATA**

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### **Background**

Recently, continuous glucose monitoring (CGM) is increasingly used in type 1 diabetes (T1D) patients because it could complement disadvantages of self-monitoring of blood glucose and glycated hemoglobin (HbA1c) by measuring interstitial glucose continuously. CGM has also been shown to reduce hypoglycemia and improve glycemic control and glucose variability in children and adolescents with T1D. Several guidelines recommend sampling duration for the analysis of CGM should be at least 2 weeks, although these have not been evaluated in Korean pediatric patients with T1D.

### **Methods**

Twelve weeks of CGM data were collected before HbA1c measurement on 44 children and adolescents (aged 2-18 years) with T1D using the Dexcom G6 system and Medtronic Guardian Connect system. To ensure an adequate amount of data, participants with at least 70% of their expected CGM readings included in the analysis. CGM metrics including mean glucose, coefficient of variation (CV), glucose management indicator (GMI), percentage of time below the range (TBR), percentage of time in target range (TIR), percentage of the time above the range (TAR) were compared between a full 12-week and each sampling period using Spearman's correlation coefficient (R), absolute difference (AD) and relative difference (RD).

### **Results**

As the number of weeks for data collection increased, the correlation with the full 12 weeks data improved, reaching a plateau from around 3 weeks and thereafter. R values increased according to increasing sampling duration with excess over 0.90 for 3 weeks, particularly for mean glucose (0.913), CV (0.949), GMI (0.913), percentage of TAR >250mg/dL (0.934), percentage of TIR (0.909). AD showed a tendency to converge to 0 by increasing sampling period. RD showed lowest between 3 to 4 weeks of sampling duration.

### **Conclusion**

Among children and adolescents with T1D, 3 weeks of CGM data were reasonable to reflect a good estimation of glycemic metrics of the last 12 weeks.

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**TRENDS IN PREDIABETES AND NON-ALCOHOLIC FATTY LIVER DISEASE AMONG KOREAN YOUTH: BASED ON THE KOREA NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY BETWEEN 2009 AND 2018**

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**Objective:**

Prediabetes and non-alcoholic fatty liver disease (NAFLD), chronic diseases associated with cardiovascular diseases, are highly prevalent globally. However, investigations on the trends in prediabetes and NAFLD among the youth are scarce. We aimed to analyze the trends in prediabetes and NAFLD among Korean youth from 2009 through 2018 and the relationship between prediabetes and NAFLD.

**Study Design:**

This cross-sectional study investigated the prevalence of prediabetes and NAFLD of 6,327 youths aged 10–18 years using data of the Korea National Health and Nutritional Examination Survey. We assessed the prevalence of prediabetes and NAFLD according to age-, sex-, and body mass index (BMI). Logistic regression analyses were performed to explain the relationship between prediabetes and NAFLD.

**Results:**

The prevalence of prediabetes increased from 5.14% to 10.46% and those of NAFLD increased from 8.17% to 12.05%, from 2009 to 2018 ( $p$  for trend  $< 0.001$  for prediabetes and  $p$  for trend = 0.001 for NAFLD, respectively). In addition, the prevalence of generalized and central obesity increased (all  $p$  for trend  $< 0.001$ ). In age-specific analyses, adverse trend in NAFLD was significant only in subjects aged 16–18 years ( $p$  for trend = 0.026) while the prevalence of prediabetes got worsen significantly in all age groups ( $p$  for trend  $< 0.001$  in subjects aged 10–12 years,  $p$  for trend = 0.002 in subjects aged 13–15 years,  $p$  for trend = 0.003 in subjects aged 16–18 years). In addition, adverse trends in obesity and central obesity were more apparent in subjects aged 16–18 years than those aged 10–15 years. In BMI-specific analyses, the prevalence of prediabetes and NAFLD increased significantly only in subjects with normal BMI ( $p$  for trend  $< 0.001$  for prediabetes and  $p$  for trend = 0.019 for NAFLD, respectively). In logistic regression, odds ratio of prediabetes for NAFLD was 1.85 (95% confidence interval, 1.37–2.52,  $p = 0.003$ ).

**Conclusions:**

Our results demonstrated adverse trend in generalized and central obesity, prediabetes, and NALFD among Korean youth. Moreover, the adverse trend in prediabetes and NAFLD was more apparent in the youth with normal BMI. These findings suggest that meticulous monitoring and management of prediabetes and NAFLD are required among youth, including normal BMI.

## **LOW MUSCLE MASS WITH OBESITY IS ASSOCIATED WITH METABOLIC SYNDROME IN ADOLESCENTS: A NATIONWIDE POPULATION-BASED STUDY**

Short running title: Appendicular skeletal muscle mass and metabolic syndrome

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Sources of Research Support: This study did not receive grants by any funding agency in the government, private, and not-for-profit sectors.

### **Background/Objectives:**

Skeletal muscle is a major site of insulin-mediated glucose utilization. Muscle mass is considered as important precursor to metabolic syndrome and insulin resistance in adults. We studied the association between low muscle mass with obesity (LMMO) and metabolic syndrome in Korean youth.

### **Subjects/Methods:**

The study included 1,319 participants aged 10–18 years from the 2009-2011 Korea National Health and Nutrition Examination Survey (KNHANES) data of children and adolescents. Low muscle mass (LMM) was defined as sex- and age-specific z-score of appendicular skeletal muscle mass divided by weight (ASM/Wt) <-1. Obesity was defined as >95% of body weight according to age and sex.

### **Results:**

The prevalence of LMMO was 4.9% for boys and 7.2% for girls. The LMMO group was more likely to develop metabolic syndrome (adjusted odds ratio [aOR] 40.5, [95% CI] 15.1 - 108.7), compared with obese (aOR 12.0, 95% CI 3.4 - 42.9) and LMM group (aOR 4.0, 95% CI 1.2 - 13.7). Similarly, in abdominal obesity, high blood pressure, elevated triglyceride, and low HDL-C, the risk was highest in LMMO compared to other groups. Insulin resistance increased risk in all LMM (aOR 2.4, 95% CI 1.6 - 3.7), obesity (aOR 15.8, 95% CI 8.3 - 30.2), and LMMO (aOR 10.9, 95% CI 6.0 - 19.7).

### **Conclusion:**

LMMO was more closely related to metabolic syndrome than obesity or LMM alone in adolescents. It is important to exercise to increase muscle mass along with weight since LMM alone can increase metabolic risk and insulin resistance.

Keywords: appendicular skeletal muscle; metabolic syndrome; insulin resistance; adolescents

## **CROSS-ORGANIZATIONAL, INTERNET-BASED DIABETES SELF MANAGEMENT EDUCATION AND PEER SUPPORT FOR YOUNG PEOPLE WITH TYPE ONE DIABETES IN ACCRA AND KUMASI, GHANA**

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Penpals United

### **Background:**

Effective mentorship programs and peer support for children with type one diabetes (t1d) encourage children to enter or remain in educational and other programs to ensure they are able to meet their future goals, to seek and be aware of mental health resources, and to prevent future medical complications from diabetes.

### **Introduction:**

The Penpals United (PPU) "Connect and Learn" project has empowered and educated young people living with diabetes in Accra and Kumasi, Ghana (Diabetes Youth Care, DYC) through sustainable, culturally and age relevant, internet based diabetes self management education and peer mentorship support. To achieve these results, PPU and DYC co-created an accessible online platform for young people to access, with videos, stories, comprehension checks, culturally relevant information, and other engaging content. Participants discussed material and their reactions throughout via an interactive WhatsApp group and video chatting platforms. PPU and DYC continuously evaluated and adapted the online platform based on user feedback. Young people who completed this course have become PPU-accredited Peer Leaders in their communities, and are thus able to provide psychosocial support to each other and to newly diagnosed children in their own communities.

### **Methodology:**

2 volunteers and/or diabetes educators in Ghana worked with PPU to create the online courses with culturally relevant information. These volunteers supported young leaders completing the courses and coordinated all facilitation on-the-ground. 45 young people completed the course. Evaluation included pre and post program surveys of approximately 20 Peer Leaders and other participants using online PPU modules. Analysis included mean comparisons using Excel.

### **Results:**

Peer leaders reported the following outcomes:

Correlation between (1) increase in comfort and confidence talking about diabetes and (2) how often in the past month they helped someone else who has diabetes

Decrease in the number of days missed at school or work due to diabetes

Decrease in the frequency of high blood glucose levels

Increase in frequency of blood glucose checking per day

Increase in frequency of counting carbohydrates

Increase in exercise frequency per week

Increase in confidence in leading a happy and successful life

Increase in hopefulness in future with diabetes

Increase in confidence in discussing diabetes with family

Increase in confidence in managing hypoglycemia and hyperglycemia

### **Conclusion:**

The capacity of young people with T1D to deliver peer support has increased, resulting in increased confidence in providing mentorship to other young people with T1D and to community members. Context-specific knowledge has improved knowledge and practice of T1D daily management.

### **Discussion:**

Culturally relevant and engaging DSME with peer to peer support models are effective in increasing young people with t1d's knowledge of, motivation to, and confidence in managing their disease.

## **EFFICACY OF GNRH AGONIST BY TWO DIFFERENT DOSAGE IN PATIENTS WITH CENTRAL PRECOCIOUS PUBERTY**

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### **Background**

The number of patients with central precocious puberty has been significantly increased recently, and proper treatment of CPP is important for both individuals and society. Previous studies showed GnRH agonist is an effective treatment choice for reducing psychological problems and improving the final adult height. It is important to use the proper dosage of GnRH agonist in the treatment of CPP, because excessive suppression of gonadotropin may reduce growth rate, and insufficient dose leads to inadequate HPA axis suppression. Currently, the effective dosage of GnRH agonist for the treatment of central precocious puberty is controversial, and therefore varies world widely. This study aims to evaluate the statural growth outcomes in girls with central precocious puberty who were treated with different doses of GnRH agonist, and estimate the most effective GnRH dose in CPP treatment.

### **Methods**

117 Girls with CPP who were treated with leuprolide acetate for at least 1 year at Severance hospital and Gangnam Severance hospital were enrolled. Among them, 17 patients were excluded due to insufficient data and pathologic causes of CPP such as brain tumor. 20 patients received treatment based on their weight, and the other 80 patients were treated with fixed dose of GnRH agonist. Independent t test was used to compare the final height, predicted adult height, and mid-parental height of the two groups.

### **Results**

There were no difference in the final adult heights in the two groups ( $161.1 \pm 4.730$  vs.  $159.8 \pm 5.439$ ,  $P=0.2981$ ), and height SDS for chronological age, and height SDS for bone age also showed the same results ( $0.160 \pm 0.91$  vs  $-0.109 \pm 1.1$ ,  $P=0.25280$ ). Additionally,  $\Delta$ height SDS for bone age showed no difference in the two groups.

### **Conclusions**

In this study, both groups showed effective suppression of bone age progression, and effective final height gain. The two groups also showed no difference in final adult height, height SDS for chronological and bone age, and the delta height SDS for bone age.

### GLUCAGON STIMULATION TEST

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#### Introduction

The diagnosis of growth hormone deficiency (GHD) is based on auxologic, clinical, anatomic and laboratory data.<sup>1-2</sup> When the diagnosis is not definite, Growth Hormone (GH) stimulation tests is indicated. Stimulation tests include the Insulin Tolerance Test (ITT), and tests using Glucagon, Arginine, Clonidine and L-dopa<sup>1-3</sup>. Two provocative stimuli are usually needed to limit false-positives whereas a sufficient GH response in one test rules out GHD in most cases.<sup>1-2</sup> The threshold level for a confirmatory diagnosis of GHD is arbitrary and suggested at 7 ng/mL depending on assays.<sup>1-2</sup> In Malaysia, frequently used tests are ITT and Glucagon Stimulation Test (GST). Our objectives were to compare the sensitivity, specificity, positive (PPV) and negative predictive value (NPV) between ITT and GST.

#### Methodology

Cross-sectional study involving 18 patients with short stature from 2016-2021 who underwent ITT and GST. Data were retrieved from the patients Electronic Medical Records. Sex-steroid priming was used for pre-pubertal patients age >10 years. For ITT, intravenous insulin 0.1 unit/kg (Actrapid) was used and GST intramuscular glucagon 30mcg/kg. Plasma GH levels were analysed using chemiluminiscent method (IDS-iSYS human Growth Assay).

#### Results

Twelve (67%) patients were diagnosed with GHD (median age 9.8, range 7-12 years). Seven were boys. Their mean height Standard Deviation Score (SDS) was  $-5.06 \pm 0.9$ , height velocity SDS  $4.9 \pm 1.8$ , IGF-1  $46.5 \pm 37.5$  ug/L and delay between chronological age (CA) and bone age (BA)  $4.1 \pm 1.5$  years (Greulich & Pyle method). Magnetic Resonance Imaging (MRI) of the Brain/Pituitary was abnormal in five (42%) patients. In the GHD group, mean lowest blood glucose for ITT was  $1.86 \pm 0.43$  mmol/L and GST  $3.44 \pm 0.48$  mmol/L ( $p < 0.001$ ). The mean peak plasma GH was higher in GST ( $2.18 \pm 1.59$  ug/L) compared to ITT ( $1.75 \pm 2.15$  ug/L), however was not statistically significant. All patients who were diagnosed with GHD had peak plasma GH levels  $< 7$  ug/L in both ITT and GST except for one patient who had a borderline value of 7.82 ug/L in ITT (2.78 ug/L in GST).

Six (33%) patients were concluded to be not GHD (median age 11.3, range 5.8-14.8 years). Their final diagnoses included prematurity, poor nutrition, constitutional and familial short stature. Their mean height SDS was  $-3.2 \pm 0.3$ , height velocity SDS  $3.8 \pm 3.3$ , IGF-1  $117.35 \pm 33.41$  ug/L and delay between CA and BA  $2.7 \pm 0.6$  years.

Three patients were screened false positive from ITT (peak GH 6.16, 6.57 and 3.87 ug/L despite adequate hypoglycaemia 2.1, 1.8, and 1.8 mmol/L). In comparison, their peak GH from GST were 13.5, 19.9 and 8.85 ug/L respectively. Their final diagnosis were familial short stature, born Very-Low-Birth-Weight and Small-For Gestational-Age with no catch-up growth.

#### Conclusion

ITT is often regarded as the gold standard in evaluation of the hypothalamic-pituitary-growth-axis, however based on our findings GST had better sensitivity (100% vs ITT 92%), specificity (100% vs ITT 50%), PPV (100% vs ITT 79%) and NPV (100% vs ITT 75%). While the sample size was small, the results suggest GST was comparable or even better than ITT.

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Genetics

## **CORRELATION ANALYSIS OF CLINICAL PHENOTYPE AND GENOTYPE OF RUBINSTEIN-TAYBI SYNDROME IN 49 CHINESE POPULATION**

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### **Background:**

Rubinstein-Taybi syndrome type 1 (RST1) is a rare genetic disease with big toe/thumb, special facial features and mental retardation as the main clinical manifestations. The incidence is about 1/100,000 to 125,000. In recent years Studies have found that mutations in different regions of the CREBBP gene are related to the severity of their clinical phenotypes, but there have not been reports on related systematic reviews and meta-analysis in the Chinese population.

### **Objective:**

Based on 4 unpublished cases in our department and a cohort of 45 reported RSTS1 cases in the Chinese population, to study the correlation between clinical phenotypes such as big toe/thumb, special facial features and mental retardation and CREBBP genotype.

### **Data source:**

Retrieved from 1963 to June 2021 China Knowledge Network, Wanfang Medical Network, PubMed database CREBBP gene caused RST1 in Chinese population case reports.

Inclusion criteria of study subjects: published case reports/cohort of RST1 patients, eligible patients are independent, CREBBP gene mutations and reports of clinical features.

Data extraction: Manually extract patient data from the text of the case report/series. A malformation score representing the severity of the clinical phenotype was calculated for each patient.

### **Data synthesis:**

49 patients published in the literature were selected for this study. More than 47 unique mutations were found in this cohort. The mutation is located in exons 30 and 31, and the severity of symptoms in most patients is not significantly different from other locations.

### **Conclusion:**

RTS1 is a complex disease with many possible mutations that affect the epigenetic changes of multiple system proteins throughout the body. By analyzing the cohort of reported CREBBP gene mutation cases, this study identified the most common clinical symptoms and hotspot mutation regions of RTS1 gene mutations in the Chinese population.

Keywords: Rubinstein-Taybi syndrome type 1; CREBBP gene mutation; Menke-Hennekam syndrome

## THE FIRST CASE OF DHX37 GENE MUTATION IN CHINESE POPULATION CAUSED 46, XY REVERSAL 11 CLINICAL FEATURES AND GENETIC ANALYSIS AND REVIEW

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### Abstract Purpose:

The DHX37 gene is a newly confirmed 46,XY sex-reversal pathogenic gene in 2019, and there is no report in the Chinese population. In this study, we help a case of 46, XY reversal pedigrees to clarify the genetic etiology and genetic counseling. Methods: To evaluate the detailed clinical symptoms and family history of the children and their families, take 2ml of peripheral blood from the children and their parents, perform whole exome sequencing, and verify the results with the Sanger method. Results: The proband, rearing as female gender, 6 years and 3 months old, the child was found to have abnormal external genitalia after birth, the nose bridge was relatively flat, scattered facial moles were seen on the face, the labia and groin were not touched, and the clitoris was enlarged like a penis. Hypospadias, pubic hair PH1 stage. AMH<0.01; FSH: 84.51mIU/ml, LH: 4.49mIU/ml, T<7.00ng/dl. Chromosome: 46, XY. A. Pelvic MRI: The uterus is located behind the bladder, and the ovaries are not clearly displayed; whole exome sequencing suggests: DHX37 gene c.2020C>T (p.R674W) heterozygous mutation, missense mutation, the mother is a heterozygous carrier, the father is no mutation in the locus, and the ACMG guidelines are rated as Likely pathogenic. Conclusion: The mutation of DHX37 gene causes 46,XY sex reversal to a newly discovered pathogenic gene in recent years. The clinical phenotype can be female, AMH and testosterone are obviously lowered, FSH is significantly higher, and the HCG provocation test is abnormal; the mother carrier may has no phenotype. The disease is inherited to male offspring. In clinic, children with 46,XY sex reversal and their parents need early genetic testing and genetic counseling.

Key words:DHX37 Gene Mutation ; 46,XY Sex Reversal;46,XY,Gonadal Agenesis

**UTILITY OF DRIED BLOOD SPOT SAMPLING WITH LC-MS/MS IN THE DIAGNOSIS OF 17-HYDROXYLASE DEFICIENCY IN AN ADOLESCENT.**

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**Background**

17-hydroxylase deficiency (17OHD) is a rare form of congenital adrenal hyperplasia (CAH), accounting for 1% of all cases of CAH. It is caused by mutations in the CYP17 gene, with an estimated incidence of 1 in 50,000 newborns<sup>1</sup>. There is defective biosynthesis of glucocorticoids and androgens, concurrently driving massive overproduction of mineralocorticoids which causes hypertension and hypokalemia<sup>2</sup>. It is a disorder of sex differentiation, with affected 46XY patients having ambiguous or female genitalia, and affected 46XX patients presenting with primary amenorrhea and lack of secondary sexual female characteristics<sup>3</sup>. Molecular genetic analysis to detect CYP17 gene mutations is time consuming and expensive for diagnosis, whereas advances in liquid chromatography tandem mass spectrometry (LC-MS/MS) allows for targeted steroid hormone analysis with a shorter turnaround time<sup>4</sup>.

**Clinical Case**

Our patient was a 14-year-old girl who presented to the General Paediatrics clinic with main complaints of absent pubertal changes. Her parents were non-consanguineous, and she was otherwise previously well with an unremarkable birth history. She had concomitant symptoms of primary nocturnal enuresis, and was referred onwards to the nephrologist. However, in the nephrology clinic, closer clinical examination revealed a prepubescent girl with blood pressure of 166/126 mm Hg. She was admitted to the ward for monitoring and evaluation of her hypertension, and referred to endocrinology due to absent puberty. Initial biochemistry revealed hypokalemic metabolic alkalosis (serum potassium level 2.7 mmol/L, bicarbonate 29 mmol/L, capillary blood pH 7.49), and primary gonadal failure (Follicle Stimulating Hormone 87.1 IU/L, Luteinizing Hormone 41 IU/L, undetectable estradiol levels). Pelvic ultrasonography revealed a blind-ended vaginal pouch, with absence of uterus and inability to visualize any gonads. An MRI Pelvis performed subsequently showed intra-abdominal gonads adjacent to the external iliac vessels. She had a bone age of 7 year 10 months old. A dried blood spot sample (DBS) was sent together with a serum sample for LC-MS/MS analysis. DBS-LCMS/MS revealed low 17-hydroxyprogesterone (17OHP) levels (10ng/dL) and serum LC-MS/MS revealed raised 11-deoxycorticosterone levels (419.5 ng/dL, normal range: <30 ng/dL), with low to undetectable values for cortisol, 11-deoxycortisol, 21-deoxycortisol, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and 17OHP. A short Synacthen test confirmed undetectable cortisol levels (<28nmol/L). These results came back within the same day of the test, and it was consistent with 17OHD. The patient was started on physiological hydrocortisone replacement, and chromosomal analysis returned a week later with a karyotype of 46, XY.ish Yp11.2(SRYx1). Early multidisciplinary involvement with counselling of the patient and her family was initiated.

**Conclusion**

This case shows integration of a detailed history, physical examination, biochemical correlation and utilization of DBS/serum LC-MS/MS for steroid profiling with a rapid turnaround time, which is invaluable for the clinician to diagnose, institute treatment and counsel the family in a timely manner. The clinical use of LC-MS/MS goes beyond neonatal newborn screening for classical CAH, extending to the quick evaluation and diagnosis of non-classical CAH in older children. Genetic analysis may only be required if the evaluation is still inconclusive, and remains useful for subsequent genetic counselling.

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Miscellaneous

## **NEUROPSYCHOLOGICAL PROFILE IN KOREAN GIRLS WITH TURNER SYNDROME**

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### **Introduction:**

Turner syndrome is genetic disorder associated with loss of part or all of one X chromosome in females. Patients with Turner syndrome have a unique neuropsychological profile, but clinical data on Korean patients are limited. This study analyzed the neuropsychological data of Korean Turner syndrome patients.

### **Methods:**

The patient group consisted of 20 patients diagnosed with Turner syndrome. Patient group were recruited April 2016 to May 2018 at the pediatric endocrinology clinic of the Severance Children's Hospital. The normal control group consisted of 13 subjects without chronic disease or any other medical disorder. Control group are recruited from December 2020 at the pediatric endocrinology clinic of the Severance Children's Hospital. The patient group and control group were females between 3 and 15 years of age. The test subjects underwent several neuropsychological tests. The t-test, wilcoxon rank-sum test, and chi-square test were used for analysis.

### **Results:**

In the K-WISC test results, the full scale IQ, Perceptual Reasoning Index, Working Memory Index, and Processing Speed Index scores in the patient group were statistically significantly lower than in the control group. Verbal Comprehension Index was not statistically different between the patient and control groups. The omission error and commission error scores for visual selective responses in the Comprehensive Attention Test results were statistically significantly lower in the patient group. In Social Maturity Scale test result, the social quotient was statistically significantly lower in the patient group (Patient  $97.32 \pm 11.62$ , control  $112.27 \pm 5.18$ , P-value  $< 0.001$ ). In PEDQL test result, the score of the patient group was statistically significantly lower in the interpersonal relationship (patient  $78.93 \pm 25.05$ , control  $95 \pm 8.94$ , P-value 0.0266).

### **Conclusion:**

Korean Turner syndrome patient have a specific neuropsychological profile. The results of this study enable clinicians to pay attention to neurocognitive and psychosocial functioning in the treatment of patients with Turner syndrome to improve the psychosocial functioning and quality of life of patients.

## **EFFECTIVENESS OF CARBOHYDRATE COUNTING EDUCATION IN CHILDREN AND ADOLESCENTS WITH TYPE I DIABETES**

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### **Background:**

The achievement and maintenance of normoglycemia is one of the most important goals to prevent both short and long-term complications in type 1 diabetes mellitus (T1DM). As carbohydrate acts as the primary macronutrient affecting postprandial glycemic response, carbohydrate counting is crucial in adjusting prandial insulin doses to preserve postprandial blood glucose within normal limits. The purpose of this study is to evaluate the effectiveness of carbohydrate counting education in children and adolescents with T1DM.

### **Methods:**

A retrospective chart review of 36 diagnosed T1DM patients who underwent carbohydrate counting education was conducted. All subjects were diagnosed with T1DM from January 2011 to June 2020, and were educated carbohydrate counting before July 2020 in pediatric endocrinology, Severance Children's Hospital, Seoul, Korea. We analyzed the data including clinical characteristics, education on carbohydrate counting, and glycated hemoglobin A1c (HbA1c) levels. Subgroup analysis was done in order to evaluate any difference in the effect of carbohydrate counting education.

### **Results:**

In 36 T1DM subjects educated, 50% were male, and mean age at the time of education was 17 years old. The mean HbA1c value for 1 year before education was 9.3 %, and a year after was 8.9 %, which is a decline of 0.4. In patients educated at elementary school and middle school age, an increase of 0.053 in HbA1C value was noted with the mean HbA1c level for 1 year before education as 9.507 +/- 0.489 % and after a year as 9.56 +/- 0.489 %. On the other hand, in subjects educated at high school and college age, decline of 0.671 was observed with the mean HbA1C value before and after education as 9.171 +/- 0.414 % and 8.5 +/- 0.414 %, respectively. The reduction in HbA1c after education, although not statistically significant, was higher in the high school-educated and university-educated group than in the other age groups.

### **Conclusions:**

From our study, the effect of carbohydrate counting education in T1DM patients was more pronounced in the older group. To optimize the educational effectiveness in all age groups, developing an appropriate education program designed for each age group may be helpful. With proper education, better blood glucose control can be expected to reduce complications and improve quality of life in T1DM patients.

## **BEHAVIOURAL AND EMOTIONAL PROBLEMS IN MALAYSIAN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN A SINGLE TERTIARY CENTRE**

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### **Introduction**

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder requiring a lifelong treatment regimen of insulin injections, diet and exercise. Studies which focus on psychological problems of T1DM patients are scarce in Malaysia. Hence this study was carried out to investigate the behavioral and emotional characteristics in Malaysian children and adolescents with T1DM as compared to healthy controls

### **Objectives**

Primary objective: To determine the behavioral and emotional characteristics of T1DM patients and healthy controls

Secondary objective: To determine the association between unfavourable behavioral and emotional characteristics with other factors (HbA1C, pubertal status).

### **Methodology**

This is a prospective cross-sectional observational study performed from July 2019 till July 2021 in a single tertiary centre in Malaysia. All children diagnosed with T1DM aged 6-18 years in Paediatric Endocrine Unit, Hospital Tunku Azizah Kuala Lumpur were identified. Control group consists of well children aged between 6-18 years. Children with underlying neurological/psychiatric conditions were excluded. Caregivers were to fill in a questionnaire - Child Behaviour Checklist (CBCL), which consists of 118 items. Statistical analysis performed with IBM SPSS statistics data editor.

### **Results**

A total of 83 samples are recruited of which 42 are in the study group while 41 in the control group. The mean age is 12.2 years (SD = 3.34) with male to female ratio 1:1.05. Ethnicity consists of Malay 72.2%, Chinese 14.5%, and Indian 13.3%. The demographic data between study group and control group are similar. Average years of illness is 4.83 years and mean HbA1c is 9.4%. Overall, T1DM children has higher mean internalizing (56.0 vs 45.4;  $p < 0.0005$ ), externalizing (51.1 vs 43.6;  $p < 0.0005$ ) and total (53.4 vs 42.1;  $p < 0.0005$ ) T-scores compare to the control group. There are higher proportions of children in the T1DM group who have clinical range of the CBCL scores, most noticeable in the category of anxious/depressed (19.0% vs 2.4%;  $p = 0.015$ ), withdrawn/depressed (19.0% vs 0;  $p = 0.003$ ), and somatic complaints (28.6% vs 0;  $p < 0.0005$ ). There is no association found between the metabolic control, duration of illness and pubertal status with CBCL score. On the other hand, female gender and older age of onset group seemed to score higher in CBCL but this is statistically insignificant.

### **Conclusion**

Psychosocial problems is a significant entity in children diagnosed with T1DM and need to be identified and addressed. Further study with a bigger sample size is required to establish the relationship between metabolic control, duration of illness and pubertal status with the psychosocial outcome.

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Growth

### **IDENTIFICATION OF IGF1R GENE VARIANTS IN SHORT CHILDREN BORN SMALL FOR GESTATIONAL AGE**

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#### **Introduction:**

In short stature children born small for gestational age (SGA-SS), IGF1R gene is one of important candidate genes in catch-up failure. Various deletions and single nucleotide variants of IGF1R have been reported. In this study, we aimed to find the prevalence of IGF1R gene mutation and to analyze their clinical characteristics.

#### **Method:**

Short stature children who met the following criteria were included: 1) Birth weight  $\leq$  10 percentile, and 2) Height at initial visit  $\leq$  3 percentile, and 3) IGF-1 SDS  $>$  0 or Height z-score  $<$  -2.5. Calculations of IGF-1 SDS and birth weight SDS were based on previous reports, Clin chem 2012;45:16-21 and Ann Pediatr Endocrinol Metab 2014;19:146-153, respectively. Deletions were detected using SALSA MLPA probemix kit P217-B2 IGF1R MRC Holland, Amsterdam, the Netherlands) and single nucleotide variants were analyzed by sanger sequencing of whole exon (#21) and exon-intron boundaries.

#### **Results:**

Mean age, birth weight SDS, height z-score, and BMI z-score of total 65 subjects were 8.0 years, -1.88, -2.83, and -0.52, respectively. Number of subjects whose birth weight  $\leq$  3 percentile was 25. Maximal value of IGF-1 SDS was 1.45. Family history of parental short stature ( $\leq$  3 percentile) was found in 18 subjects. Growth hormone stimulation test was undergone in 64 subjects. Peak GH level was 1.35-41.74 ng/mL and 25 subjects had peak GH level  $<$  10 ng/mL. A heterozygous deletion in 15q26.2q26.3 was found in one subject. She was 6.6 years old and her height z-score, BMI z-score, and birth weight SDS were -4.22, 2.36, and -3.23, respectively. She had no family history of parental short stature, peak GH level of 3.72 ng/mL, and IGF-1 SDS of -0.66. Various benign variants were found in direct sequencing but pathologic mutation or novel variant was not found.

#### **Conclusion:**

In this study, the prevalence of IGF1R mutation was 1.5% (1/65 subjects). Although clinical characteristics of SGA-SS subjects are various and heterogenous, IGF1-IGF1R axis is an important mechanism in SGA-SS, therefore, further investigation is needed.

**DENT DISEASE TYPE -1 A DIAGNOSTIC DILEMMA AND INDICATIONS FOR GH THERAPY**

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**Introduction:**

Dent disease type 1 is an inherited tubulopathy, more common in young males who present within a wide spectrum that encompasses rickets with short stature, night blindness, nephrocalcinosis, low molecular weight proteinuria, electrolyte abnormalities (especially calcium and phosphate) etc., all of which lead to eventual progression to renal failure, which based on the type of mutation (CLCN5)<sup>1</sup> can lead to end stage renal disease at a young age. Due to varied phenotypic presentations and also genetic heterogeneity, while masquerading as more commonly seen pediatric disorders, the mean age of diagnosis is delayed, (India and Europe was 8 years and 11 years respectively<sup>1,2</sup>).

**Clinical**

We present a retrospective review of a 15 year old male, with complaints of frothy urine, inability to feed and failure to thrive since 18 months of age. He was also severely stunted (<3rd centile) with delayed onset puberty. We would also like to report some previously unreported findings such as persistent hypercholesterolemia and dual renal biopsy patterns. The boy was definitively diagnosed after 13 years and subjected to multiple working diagnoses and the associated treatments, some of which included alternative forms of medicine.

**history:****Management:**

Post diagnosis, the boy was started on therapy which included thiazide diuretics, phosphate supplementation and statin therapy. A corrective osteotomy was performed for the genu valgum with good results. Due to poor compliance, follow up and appropriate dose titrations, frequent fluctuations in analytes were seen. The boy is now in stage G3a A1 of chronic kidney disease (KDIGO)<sup>3</sup>

**Conclusion:**

We would like to emphasize on the importance of having a high clinical suspicion and reaching a prompt early diagnosis of this disease in order to minimize the risk of misdiagnosis and treatment. This would help institute appropriate therapeutic modalities such as GH therapy<sup>4</sup> and genetic counselling, both of which were not offered to our patient. We also highlight evidence based guidelines for diagnosis and differentiation from other common disorders with similar clinical presentations.

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## **EFFECTS OF PRENATAL AND POSTNATAL ENVIRONMENTAL DISRUPTING CHEMICALS ON EARLY BREAST DEVELOPMENT IN 8-YEAR-OLD GIRLS: A PROSPECTIVE BIRTH COHORT STUDY**

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### **Background:**

The onset of puberty in girls has occurred earlier over the last decades. Environmental factors including endocrine-disrupting chemicals may affect puberty and reproduction. We investigated the relationship of prenatal and childhood chemical mixtures with early breast development (EBD) in 8-year-old girls from the prospective birth cohort.

### **Methods:**

From the Environment and Development of Children cohort study, data on Tanner stages for sexual maturation at 8-year-old visit were used. A total of 211 girls were included in this study, who had data on prenatal and childhood measurements of Cadmium (Cd), Mercury (Hg), Lead (Pb), bisphenol-A (BPA), 3-phenoxybenzoic acid (3-PBA), and three phthalate metabolites [mono (2-ethyl-5-hydroxyhexyl) phthalate, mono-(2-ethyl-5-oxohexyl) phthalate, and mono-n-butyl phthalate]. Breast detection before age 8y was defined as EBD. The relationship of single and mixed chemical exposures with EBD was assessed using logistic regression and Bayesian kernel machine regression (BKMR) models.

### **Results:**

EBD was found in 42 (19.9%). In logistic regression models, Cd (Adjusted odds ratio [aOR] = 4.6, 95% confidence interval [CI]: 1.7-12.5) and BPA (aOR = 0.7, 95% CI: 0.4-1.0) during pregnancy were associated with EBD, but any chemical exposure at age 8y was not related to EBD. In BKMR models including chemical mixtures during pregnancy, prenatal Cd exposure was the main contributor, in that prenatal Cd exposure significantly increased the risk for EBD when all other chemicals were set at 25th, 50th and 75th percentile. In BKMR models including chemical mixtures during pregnancy and childhood at age 8y, the positive relationship between prenatal Cd exposure and EBD was maintained, although the overall joint association was not significant.

### **Conclusions:**

Among prenatal chemical mixtures, Cd exposure was the main contributor to EBD in 8-year-old girls, although overall joint effects of prenatal and childhood chemical mixtures on EBD were not significant. The combined effects of chemical mixtures in a real world on pubertal development remain to be further determined.

## **EARLY RECOGNITION OF ENDOCRINE DEFICIENCIES IN CHILDREN WITH TRANSFUSION DEPENDENT THALASSEMIA MAJOR - EXPERIENCE OF A TERTIARY CARE CENTER FROM SOUTHERN INDIA**

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**Background:** With increased life expectancy, chronic endocrinopathies have been reported as commonest problems associated with transfusion dependent Thalassemia Major, secondary to hemosiderosis (1). Prevalence of commonest endocrinopathies like short stature and hypogonadism can be as high as 30-50% (2). Hence, role of early identification and prompt treatment of endocrine deficiencies is indispensable, especially when iron chelation is suboptimal (2)(3)(4).

### **Objective:**

This study was aimed to detect prevalence of endocrine deficiencies in transfusion dependent Thalassemia Major children aged > 5 years.

### **Materials & Methods:**

Thirty seven children (19 Male, 18 Female), more than 5 year of age, diagnosed with Thalassemia Major, who are transfusion dependent, undergoing treatment in Department of Paediatrics, Department of Paediatric Haematology and Oncology, Department of General Medicine, Kasturba Hospital Manipal, a constituent unit of Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India were included. After overnight fasting samples for fasting blood sugar, T4, TSH, cortisol, calcium, phosphorous, alkaline phosphatase, FSH, LH, testosterone/estradiol were collected. Anhydrous glucose (1.75 g/kg) was dissolved in a cup water and made to drink. Post glucose load sample was taken after 2 hours. If baseline cortisol is <20 µg/dl, stimulated sample collected 1 hour after 25 IU intramuscular Actom pralonagtum injection. PTH was tested in case of low corrected calcium or high phosphorous. Anthropometric parameters and results of hormonal studies were interpreted based on predefined criterias. This research activity was funded by APPES-CLAN equity grant.

### **Results:**

Mean (SD) age of participants was 15.62 (6.61) years with a male to female ratio of 1.05:1. Median (IQR) serum ferritin of study population was 2000 ng/ml (1010, 3237). Mean (SD) pre transfusion haemoglobin, transfusion index, dose of deferasirox were 7.05 g/dl (0.95), 137 (34.97) ml/kg/year, 15.68 mg/day (9.1) respectively. Except for delayed puberty, majority of endocrine abnormalities were asymptomatic. Only 2 with diabetes had hyperosmolar symptoms. Hypogonadism seen in 15/24 (62.5%) pubertal age group children was the commonest endocrine abnormality seen in study population, followed by short stature in 16/37 (43%). Impaired glucose metabolism was seen in 10/37 (27%), which included impaired fasting glucose 5/10 (50%), impaired glucose tolerance 3/10 (30%), diabetes mellitus 2/10 (20%). Adrenal insufficiency was noted in 9/37(25%) participants, all of them had subclinical secondary adrenal insufficiency except one who had primary adrenal insufficiency. Impaired thyroid function was seen in 5/37 (13%) children, among them 3 (60%) had subclinical hypothyroidism and 1 (20%) each had primary and secondary hypothyroidism respectively. Hypoparathyroidism was the least common endocrine abnormality seen in only 1 child. Earliest age to have any endocrine abnormality was 7 years (secondary adrenal insufficiency, impaired impaired fasting glucose). At least one endocrine deficiency was noted in 21/37 (56%) participants and multiple (≥2) endocrine deficiencies in 13/37 (35%).

### **Conclusions:**

Though endocrine abnormalities are asymptomatic to begin with, they are seen in > 50% of patients with transfusion dependent thalassemia and can appear as early as 7 years. Hence role of early screening and intervention is indispensable in improving quality of life and care, especially in resource limited setting with suboptimal chelation.

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**CLINICAL FEATURES, GENETIC DETECTION AND THERAPEUTIC RESPONSE TO RHGH OF CHILDREN WITH BORN SMALL FOR GESTATIONAL AGE: AN ANALYSIS OF 33 CASES**

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**Background:**

The causes of small for gestational age (SGA) are associated with genetic abnormalities. Genetic etiology that account for prenatal growth has not been thoroughly elucidated to date.

**Objective:**

To perform a genetic investigation of a group of SGA children with persistent short stature. rhGH treatment efficacy was evaluated between syndromic SGA patients and non-syndromic SGA patients.

**Methods:**

This study included thirty-three SGA children (17F/15M) with height standard deviation scores (HtSDS)  $\leq -2.0$  and unknown etiology from 2014 to 2021. Whole exome sequencing (WES) and/or MS-MLPA were performed on the enrolled patients sequentially to identify potential genetic etiologies. The medical records of 33 SGA patients treated with rhGH were evaluated retrospectively.

**Results:**

In total, 15/33 SGA children combining with intellectual disability, facial features and/or skeletal deformities, and 18/33 SGA children presented only short stature. A potential genetic etiology was identified in 14 (14/33, 42.4%) patients [13 by WES (92.8%), 1 by MS-MLPA (7.1%): ANCN (n = 2), ROR2, FGFR3, MAP2K1, PTPN11, SHOC2, SRCAP, FAM111A, GNPTAB, CHD7, 15q11.2del, Xp22.3-22.1del and loss of methylation on chromosome 11p15 (n=1 each). The diagnostic yield was 86.67% (13/15) and 5.56% (1/18) in syndromic SGA patients and isolated SGA patients, respectively ( $p < 0.0001$ ). In 15 syndromic SGA patients treated with rhGH, the mean HtSDS increased from  $(-3.18 \pm 0.95)$  before treatment to  $(-2.36 \pm 1.15)$  after treatment for  $(1.7 \pm 1.68)$  years ( $P < 0.05$ ). The height SDS change was positive correlated with treatment period ( $r = 0.6666$ ,  $p = 0.006$ ). In 18 isolated SGA patients treatment with rhGH, the mean HtSDS increased from  $(-2.88 \pm 0.92)$  before treatment to  $(-1.88 \pm 0.92)$  after treatment for  $(2.25 \pm 1.35)$  years ( $P < 0.05$ ). The HtSDS change was positive correlated with treatment period ( $r = 0.8542$ ,  $p < 0.0001$ ), and was negatively correlated with initial age of treatment ( $r = -0.5704$ ,  $p = 0.0134$ ). rhGH treatment significantly improved the HtSDS of isolated SGA patients than that of syndromic SGA patients (0.90 vs 1.48,  $p < 0.05$ ).

**Conclusion:**

Our study identified pathogenic or likely pathogenic genetic variants in 14 of 33 patients (42.4%). Patients with intellectual disability, facial dysmorphism and/or skeletal abnormalities are more likely to have a known genetic etiology. rhGH treatment significantly improved HtSDS in isolated SGA patients compared with syndromic SGA patients.

**COMPARISON OF METABOLIC PROFILE AND ANTHROPOMETRIC MEASUREMENTS AMONG OBESE CHILDREN WITH DIFFERENT GRADES OF FATTY LIVER DISEASE: AN EXPERIENCE IN BIRDEM GENERAL HOSPITAL**

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**Background:**

Fatty liver disease ranges from fatty infiltration alone to nonalcoholic steato- hepatitis, cirrhosis or hepatocellular carcinoma. It is a common comorbidity of childhood obesity.

**Objective:**

To determine the percentage of different grades of fatty liver disease and to compare metabolic profiles and anthropometric measurements among obese children with different grades of fatty liver disease.

**Materials****and****Methods:**

This cross sectional study included 79 obese children and adolescents of 8 to 18 years having simple obesity and attending the paediatric endocrine out patient department (OPD) of BIRDEM from 1<sup>st</sup> January 2018 to 30<sup>th</sup> June 2018. Body Mass Index (BMI)  $\geq$  95<sup>th</sup> centile for age and sex was used to diagnose obesity. Fasting blood samples were collected to measure SGPT and lipid profile. Real-time ultrasonographic examination of the liver was done to identify fatty liver disease with it's grading.

**Results:**

Among 79 children with simple obesity 24 (30.4%) had fatty liver disease. Majority had mild fatty liver disease (54.2%) followed by moderate one (41.6%). Fasting blood sugar ( $p=0.031$ ) and SGPT level ( $p=0.001$ ) were significantly higher among children and adolescents with fatty liver disease in comparison to children without it. When SGPT level and metabolic profile was compared between children with mild and moderate fatty liver disease, triglyceride level ( $p=0.033$ ) and diastolic hypertension ( $p=0.016$ ) was significantly higher in children having moderate fatty liver disease.

**Conclusion:**

Dyslipidemia with raised SGPT are important findings of liver dysfunction in obese children with fatty liver disease. Triglyceride level and diastolic blood pressure is higher with higher severity of fatty liver.

Key word: Obesity, fatty liver disease, SGPT, dyslipidemia.

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## **EFFICACY OF RANDOM URINE GONADOTROPIN LEVELS IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY ACCORDING TO GNRHA AGONIST TREATMENT: BEFORE, DURING, AND AFTER DISCONTINUATION**

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### **Introduction:**

The GnRH stimulation test(GnRHST) is the gold standard to evaluate central precocious puberty(CPP). However, the GnRHST requires invasive, expensive, repeated blood sampling for young patients. Three years ago, we reported that urinary gonadotropin(uLHFSH) concentration may be useful for the diagnosis and initial treatment monitoring in girls with CPP. We studied whether random uLHFSH could be an alternative tool after long-term treatment and treatment discontinuation in girls with CPP treated with GnRH agonist.

### **Methods:**

Both the GnRHST and urinary gonadotropin assay were performed in 80 girls with breast budding. The girls were classified as having CPP(peak LH  $\geq 5$  IU/L, N=50) or premature thelarche(PT)(peak LH < 5 IU/L, N=30) after the GnRHST. Auxological data and samples were collected and evaluated before treatment, every 6 months after treatment and at 6 months after treatment discontinuation, respectively, to evaluate the correlation and clinical aspects between serum and urine samples through segmented and time series analysis of the analysis set.

### **Results:**

42 girls with CPP were treated with GnRHa treatment more than two years. Among them, 17 patients were evaluated 6 months after treatment discontinuation. The age, bone age, BMI-SDS, Tanner stage-corrected LH concentration of serum( $0.27 \pm 0.05$  vs.  $0.08 \pm 0.06$ ,  $P=0.038$ ) and urine( $1.16 \pm 0.11$  IU/L vs.  $0.81 \pm 0.12$  IU/L,  $P=0.035$ ) sample was significantly higher in the CPP group than in the PT group, and showed positive correlation before GnRHa treatment( $r=0.660$ ,  $P<0.001$ ). However, urine FSH was no difference between the two groups. During GnRHa treatment, LH concentration of serum and urine was below the level of the PT group, but urine LH concentration increased back to 12 and 24 months of GnRHa treatment, indicating no difference from the initial urine LH concentration. The urine LH concentration( $1.04 \pm 0.52$  IU/L  $\Rightarrow$   $3.20 \pm 2.21$  IU/L,  $P=0.003$ ) was recovered significantly, but there was no statistical significance in urine FSH concentration. Serum and urinary LH concentration over the entire treatment period were positively correlated in girls with CPP( $R^2=0.180$ ,  $P<0.001$ ).

### **Conclusion:**

The measurement of noninvasive uLHFSH in girls with CPP was useful as an alternative test for monitoring the entire GnRH agonist treatment period as well as the diagnosis of CPP. However, the uLHFSH concentration tends to rise in contrast to the serum concentration during long-term treatment, which is thought to need further research.

Keywords: Central precocious puberty, Gonadotropin, Luteinizing hormone, Follicle stimulating hormone

## **CONGENITAL ADRENAL HYPERPLASIA IN CHILDREN: THE RELATIONSHIP BETWEEN PLASMA RENIN ACTIVITY WITH HYPERTENSION**

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### **Background:**

It is necessary to continuously be aware of hypertension incidence in 21-hydroxylase enzyme deficiency (21-OHD CAH) patients and its possible causes, even though hypertension is an uncommon manifestation of congenital adrenal hyperplasia due to 21-OHD CAH. Conflicting results regarding the role of plasma renin activity (PRA) levels have been suggested. The objective of this study is to assess the relationship between PRA with hypertension in 21-OHD CAH children.

### **Methods:**

This study design was cross-sectional. The subjects were divided into two groups, the hypertension and the non-hypertension groups, consisted of 21-OHD CAH children, aged >6 months to 18 years who already took hydrocortisone and- with or without fludrocortisone for at least 6 months. PRA levels were measured from all the subjects using the ELISA method.

### **Results:**

The prevalence of hypertension in 21-OHD CAH patients during the study period was 32%. There were 59.3% and 30.8% subjects with hypertension in salt-wasting and simple virilizing type, respectively. There was a significant mean difference in PRA levels between hypertension and non-hypertension groups in salt wasting patients ( $p=0,016$ ). The risk of hypertension in salt wasting patients with low PRA levels was 1,09 times after controlling for sex, 17-OHP levels, and the last fludrocortisone dose. We found a significant relationship between the last dose of hydrocortisone with the incidence of hypertension in salt wasting patients.

### **Conclusion:**

The risk of hypertension in salt wasting patients with low PRA levels was 1.09 times after being controlled for sex, 17 OHP level, and the last dose of fludrocortisone.

## EFFECTS OF GROWTH HORMONE COMBINED WITH GONADOTROPIN-RELEASING HORMONE AGONIST (GNRHA) CAN IMPROVE THE HEIGHT OF GIRLS WITH CENTRAL PRECOCIOUS PUBERTY

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### Background:

Central precocious puberty (CPP) is triggered by the early activation of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in inappropriate release of gonadotropin-releasing hormone (GnRH) and the onset of puberty. After years of clinical practice, GnRHa has become the standard treatment for CPP. However, some studies have shown that children with CPP can experience growth deceleration after GnRHa treatment, and ultimately fail to reach the ideal height. Therefore, GnRHa combined with rhGH may be a better choice for the treatment of CPP.

### Objective:

This study aimed to investigate the outcomes of gonadotropin-releasing hormone agonist (GnRHa) therapy with or without growth hormone (GH) therapy for girls with idiopathic central precocious puberty (CPP).

### Methods:

We conducted a retrospective analysis of CPP girls who attended the Pediatric Endocrinology Clinic of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology from January 1, 2017 to June 1, 2021. A total of 80 children with CPP girls aged 6-10 years old were treated for 30 months and were divided into the GnRHa group (group A, n=34), and the combined GnRHa/GH group (group B, n=46). All children were followed up every 3 months after treatment. They received regular tests including height, weight, and sex hormone levels, and pelvic B-ultrasound and bone age were measured every six months. The changes in height, weight, BMI, sex hormone levels and bone age were compared between the two groups.

### Results:

The initial CA was  $8.0 \pm 0.8$  years in group A, and  $8.7 \pm 0.9$  years in group B ( $P < 0.001$ ). There was no difference in height, weight, BMI, basic LH and FSH between the two groups before treatment, but the bone age had Statistical difference ( $9.2 \pm 1.1$  yrs vs.  $10.3 \pm 1.0$  yrs,  $P < 0.001$ ). After treatment, it was found that the height improvement of group B was significantly higher than that of group A at 9th, 12th, 18th, 24th, and 30th months ( $P < 0.001$ ). There was no statistical difference in body weight at each time point ( $P > 0.05$ ).

BMI was higher in group A than group B at each time point 12 months ago, which was statistically significant ( $P < 0.05$ ). However, there was no statistical difference at the 18th, 24th, and 30th months. There was no statistical difference between LH and FSH at each time point after treatment ( $P > 0.05$ ). There was a significant statistical difference between the two groups in terms of bone age before treatment ( $9.2 \pm 1.1$  yrs vs  $10.3 \pm 1.0$  yrs,  $P < 0.001$ ,  $t = 3.815$ ), there was no statistical difference at each time point after treatment ( $P > 0.05$ ).

### Conclusion:

Growth hormone combined with gonadotropin-releasing hormone agonist (GnRHa) can have more additional height gain than the GnRHa-alone group. And long-term treatment does not increase body weight, BMI and bone age progression.

## DEVELOPMENT AND VERIFICATION OF A DIAGNOSTIC PREDICTION MODEL FOR GIRLS WITH CENTRAL PRECOCIOUS PUBERTY

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### Objective

To explore the application of prediction model in the diagnosis of central precocious puberty (CPP) in girls.

### Methods

A total of 1107 girls with precocious puberty (PP) who had completed the gonadotropin-releasing hormone (GnRH) stimulation test were included in the model development group. They were admitted to the Department of Endocrinology, Fuzhou Children's Hospital of Fujian Medical University from January 2014 to April 2020 with the onset age ranged from 4 to 8 years. A total of 321 PP girls admitted in the same hospital with the same inclusion criteria from May 2020 to July 2021 were included to construct the model verification group. Physical examination, serum luteinizing hormone (LH), follicle stimulating hormone (FSH), bone age (BA) and pelvic ultrasound results were collected. R software was used for model development, verification and display, including: 1. Model development: Using data of the model development group, predictors were screened by Lasso regression analysis, and prediction models were established by Logistic regression. 2. Model verification: Cook distance test was used to test the strong influence points, spline function was used to test the linear relationship between predictor and outcome, and variance inflation factor (VIF) was used to verify multicollinearity. By drawing the correction curve between the predicted result and the actual result, the consistency test was carried out. The receiver operating characteristic (ROC) curve of the model was drawn to evaluate the prediction ability of the model, and the maximum ROC index was calculated. The k-fold cross-validation method (k=10) was used for internal verification of the final model. The model verification group data were used to verify model differentiation and calibration externally. 3. Model display: "DynNom" R package was used to draw dynamic column map and build a web calculator to display the model.

### Results

Among 1107 children with PP in the model development group, 537 (48.5%) were positive for GnRH stimulation test and diagnosed as CPP, while 570 (51.5%) were negative for GnRH stimulation test and CPP was excluded. In the model verification group, 146 (45.5%) of 321 children with PP were diagnosed with CPP, and 175 (54.5%) were excluded from CPP diagnosis. The model development results are as follows: 1. Model development: The Logistic prediction model was established as follows:  $LN [P/(1-P)] = -5.508 + 1.579 \times \text{LH base value (" Middle ")} + 2.861 \times \text{LH base value (" High ")} + 1.191 \times \text{Uterine volume} + 0.316 \times \text{BA} + 0.371 \times \text{Course of disease (" Middle ")} + 0.430 \times \text{Course of disease (" Long ")} + 0.285 \times \text{Tannar stage of breast (" B > 2 ")}.$  2. Model verification: It is verified that there is no strong influence point in the model, there is no multicollinearity among the predictors, and there is good consistency between the prediction results of the model and the actual results. The continuous variable BA had a linear relationship with the outcome, and the uterine volume had a nearly linear monotonic relationship with the outcome. Internal verification shows that the model shows a good degree of differentiation and calibration. The area under the ROC curve of the model was 0.858. When the cut-off point of prediction was 0.476, the Yuden index was the largest, and the sensitivity and specificity of the model were 72.6% and 86.7%. When the prediction cut-off point is adjusted to 0.75, the specificity and sensitivity of the model can reach 95.09% and 50.47%, which can guide clinical diagnosis. External verification shows that the area under the ROC curve is 0.910, and the prediction accuracy is 88.48% at the same prediction cut-off point. The model also shows good differentiation and calibration degree for external data. 3. Model display: the model calculator can be accessed through the website url: <https://wuwenyong.shinyapps.io/dynnomapp>.

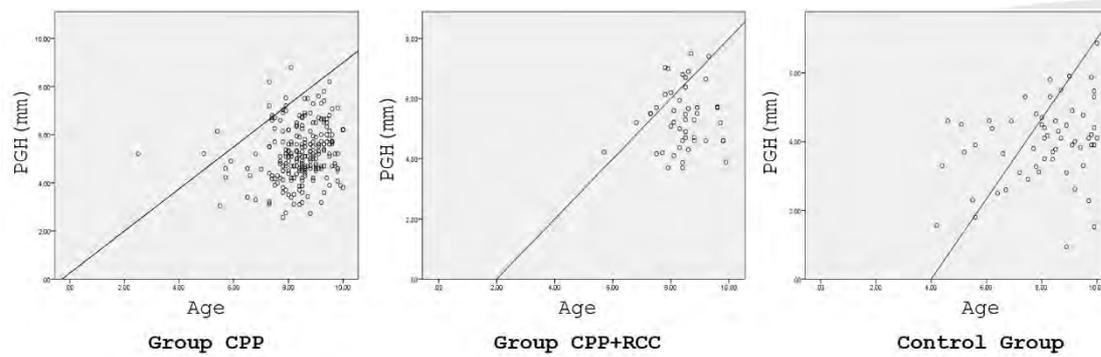
**Conclusion**

The model is suitable for PP girls aged from 4 to 8 years, and has good diagnostic prediction ability. Different cut-off points can make the model have different application value.

## INFLUENCE OF RATHKE'S CLEFT CYST ON PITUITARY HEIGHT AND SEVERITY OF ILLNESS IN CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY

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### Background

Rathke's cleft cyst(RCC) is often detected on head MRI in children with central precocious puberty(CPP).

### Objective

To investigate whether RCC has influence on the imaging characteristics of pituitary gland in children with central precocious puberty.

### Methods

Clinical data and cranial MRI of the CPP patients diagnosed in the Department of Endocrinology of Children's Hospital of Shanghai in 2020 were retrospectively studied, including the coronal height diameter of pituitary gland, and the correlation with the severity of illness was evaluated.

### Results

There were 232 children with in the CPP group and 60 children in the control group. There was no significant difference in pituitary gland height (PGH) between CPP patients with and without RCC ( $P=0.493$ ). In the CPP group and the control group, there was a linear correlation between age and PGH ( $P=0.008$  and  $P=0.026$ ), respectively, while the linear correlation between age and PGH in CPP patients with RCC was not statistically significant ( $P=0.608$ ), but it did not affect its clinical characteristics.

### Conclusion

The PGH of CPP patients increases linearly with age, and RCC affects the changing rule. Therefore, clinical follow-up evaluation is recommended.

## **THE EFFECT OF GROWTH HORMONE THERAPY ON LINEAR GROWTH IN CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA)**

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### **Background:**

Children who are born small for gestation (SGA) and fail to demonstrate catch-up growth by 4 years of age are treated with recombinant human growth hormone (rhGH) to achieve catch-up growth, maintain a normal height velocity and achieve a final adult height within their normal target range. The current study was done to analyse the short-term efficacy of rhGH treatment in children born SGA.

### **Methods:**

A retrospective single-centre observational study was conducted at a tertiary paediatric endocrine centre. Children born SGA with failure to show catch-up growth and who received rhGH therapy (50 mcg/kg/day) were included in this study.

These subjects were regularly monitored for their anthropometry, rhGH dose adjustment and any adverse effects of the therapy. The Change in Height SDS (Ht. SDS) and Predicted Adult Height SDS (PAH SDS) at the end of 1 and 2 years of treatment were statistically analysed.

### **Results:**

A total of 27 children (13 girls and 14 boys) were enrolled in the study. The mean age of starting the rhGH therapy was 10.16 years (5 years – 15.4 years) with a mean bone age of 9.31 years (2.5 years – 12.5 years). 17 children were pubertal at the time of onset of rhGH therapy.

The mean Ht.SDS of the subjects improved by +0.59 SDS (N=27) at end of first year and by +1.02 SDS (N=18) at end of second year. Similarly, the mean predicted adult height also improved from -1.98 SDS (N=24) to -1.02 SDS (N=25) at end of first year and to -0.67 SDS (N=15) at end of second year with a DPAH SDS of +0.96 SD and +1.913 SD respectively. Some of the subjects have not completed 2 years of rhGH therapy.

### **Conclusions:**

rhGH therapy in children born SGA, results in catch-up growth and improves their predicted adult height, despite late onset of therapy (during puberty). As the study duration was short, a long follow up is needed to determine the effect of rhGH therapy on the final adult height.

## **EXPERIENCES OF DIABETES MANAGEMENT AND INTERVENTION DURING COVID-19 PANDEMIC IN CHILDREN AND CAREGIVERS OF TYPE 1 DIABETES MELLITUS (T1DM) IN INDONESIA**

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### **Objectives**

Children with chronic diseases are the most vulnerable population and affected the most by COVID-19 pandemic, particularly in resource-limited countries. Children and adolescents with type 1 diabetes mellitus (T1DM) have been facing great challenges in managing their diabetes daily, related to diabetes essentials such as insulin, glucose strips, and access to adequate diabetes education and healthcare. This study was conducted to assess their experiences in managing diabetes during COVID-19 pandemic. The information obtained may be useful for formulating future guidance about the best diabetes intervention methods during restrictions.

### **Methods**

A cross-sectional survey-based study was conducted online and in the pediatric outpatient unit in Endocrinology Clinic Cipto Mangunkusumo General Hospital, Jakarta, Indonesia from June 2020 until December 2020. Data was collected from 148 adolescents with T1DM or their caregivers on a structured questionnaire. The questionnaire was divided into three parts; information about demographics, diabetes management and its complications, and conditions related to COVID-19.

### **Results**

There were 148 respondents (23 adolescents, 111 parents, and 14 relatives or caregivers of T1DM patients) who filled in the questionnaires with only 131 respondents completing all parts. The median age of patients was 13 years old with the majority of them (50.7%) being female. During the pandemic, the median of A1c was 8.2% and diabetes-related complications that occurred were frequent hyperglycemia (23%), hypoglycemia (14.2%), and diabetic ketoacidosis (8.1%). Most respondents lived in Java island, particularly Jakarta (51.4%), West Java (28.4%), and Banten (14.2%). The majority of T1DM patients (89.9%) had their medication covered by governmental insurance. Seventy-three percent of respondents had the opinion that T1DM patients would have more severe COVID-19 symptoms if being infected; 82.6% were concerned about being infected by COVID-19. Seventy-eight percent of respondents were living in areas with restrictions; however, 49.6% were exempted from the regulations. About 89.9% of respondents had access to information about specific diabetes management during the pandemic, mostly from doctors (61.2%) and communication group chat (54.1%). Ninety-four respondents were able to do routine visits to the hospital and 102 continued insulin as prescribed. Twenty-three respondents were lacking access to basal insulin, 12 to bolus insulin, and 32 respondents to glucose strips. The most common psychological problems during the pandemic were irritability (29.1%), distress (12.9%), anxiety (12.1%), and depression (11.3%). About 40% of respondents stated that they need psychological support. Forty percent of respondents had COVID-19-related symptoms during the pandemic.

### **Conclusions**

COVID-19 pandemic has arisen new challenges of diabetes management in children and adolescents with T1DM, particularly those living in resources-limited settings. Patients' compliance or routine visits, access to insulin and glucose strips, access to information about specific diabetes management during the pandemic, and psychological aspects have been affected. Information about COVID-19 prevention, specific diabetes management during the pandemic, and psychological support must be prioritized in routine visits or in other dedicated sessions using technology such as telemedicine, group empowerment, and social media.

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**PHENOTYPIC CHARACTERISTICS OF 46XY AND 45X/46XY TESTICULAR DYSGENESIS**

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**Introduction:**

Disorders/differences of sex development (DSD) are a heterogeneous group of conditions<sup>1</sup>. Incomplete testicular differentiation results in genital ambiguity and may be found in subjects who have either 46,XY or 45,X/46,XY karyotypes with a variety of phenotype. Studies focussing on the clinical features of patients with partial gonadal dysgenesis (PGD) and mixed gonadal dysgenesis (MGD) are rare.<sup>2</sup>

**Methods:**

The aim of this study was to investigate the clinical, biochemical and gonadal histological characteristics of patients with MGD and PGD. Medical records from all patients with a diagnosis of MGD and PGD who were seen in our centre between 2011 and 2021 were reviewed. Patients' clinical presentation, karyotypes, height, hormonal profiles, imaging and histology of the gonads were evaluated.

**Results:**

A total of twenty – three patients fulfilled the inclusion criteria; MGD (12 patients), PGD (11 patients). There was no significant difference in the median age of presentation between the two groups. The mean birth weight in the MGD group was lower than the PGD group ( $2.8 \pm 0.5$  vs  $3.1 \pm 0.4$  kg) however did not achieve statistical significance. There was no differences regarding parental consanguinity, dysmorphic features, delayed neuromotor development, renal or cardiac malformations. Short stature (height Z -score < -2SD) was a feature of 50% of patients with MGD as compared to no patients with PGD ( $p < 0.001$ ). The mean height Z score at the last visit was lower in the MGD group ( $-1.53 \pm 1.27$ m) as compared to the PGD group ( $-0.87 \pm 0.59$ m) although this was not statistically significant.

At first visit majority of patients in the MGD group (75% vs 45.5%,  $p < 0.05$ ) had not been assigned gender. After a definitive diagnosis these patients were more likely to be assigned male. The degree of genital ambiguity assessed by the EMS and EGS score did not show any significance between groups. There was also no significant difference with the location of gonads between the groups. However in the MGD group a uterus was more likely to be present (83.3% vs 18.2%,  $p < 0.001$ ) and there was a greater degree of asymmetry as assessed by gonadal palpation ( $p < 0.001$ ).

Gonadal hormone function in the postnatal period revealed a significantly lower serum testosterone in the PGD group ( $p < 0.036$ ). The HCG tests performed before 1 year did not reach the set threshold in 4/7 patients in MGD group and 6/8 patients in PGD group ( $p = NS$ ). Gonads were removed in 9/24 of patients with MGD (37.5%) and 2/22 of those with PGD (9%) ( $p < 0.001$ ). Histology of gonads did not reveal significance difference between groups varying between streak gonads to dysgenetic testis.

**Conclusions:**

In conclusion, the results of this study indicate that the main differences between MGD and PGD are related to growth and the presence of Mullerian structures. Phenotypes of the patients vary greatly and clinical management should be individualized.

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## **POST RAMADAN HYPERGLYCAEMIA WAS COMMON IN YOUNG PEOPLE WITH DIABETES WHO FASTED DURING THE COVID -19 PANDEMIC LOCKDOWN OF 2020 IN BANGLADESH**

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BIRDEM

### **Objective:**

Muslim people with T1DM should be actively discouraged from fasting during the COVID-19 pandemic, as diabetes has emerged as a significant risk factor for adverse outcomes of COVID-19 infection. We report the experience of young patients with type 1, type 2 and other types diabetes who fasted during Ramadan 2020 at the time of the COVID-19 pandemic time lockdown.

### **Research Design and Methods:**

A Post- Ramadan survey was designed for young patients who fasted during Ramadan in 2020 during COVID pandemic time. The study was conducted to compared the basal characteristics and other parameters in children and adolescents (< 18 years), with young adults (> 18 years) with diabetes at Paediatric Diabetes Center in BIRDEM in Bangladesh.

### **Results:**

Among the study participants, a significantly higher number of participants were in older age group who fasted for more than 15 days ( $p=.045$ ). A considerable proportion (30.7%) of patients developed mild hypoglycaemia, and only eight patients (2.6%) developed moderate to severe hypoglycemia. There was significant reduction of post Ramadan basal insulin dose in both groups ( $p =0.001$ ). Although increased bolus insulin dose requirements were observed in older age group, but decreased requirement was observed in younger age group during Ramadan ( $p =0.001$ ). Post Ramadan median HbA1C in both groups was increased with marked increase in older age group compared to younger age group though it did not reach the statistical significance. ( $p=0.239$ )

### **Conclusions:**

COVID-19 pandemic had minor impact on fasting during Ramadan in our cohort, they could fast safely with less complications during Ramadan. Our data supports Ramadan focused diabetes education with ample self-care, young people with diabetes can fast safely during Ramadan.

## **THE EFFECT OF GROWTH HORMONE THERAPY ON LINEAR GROWTH IN CHILDREN WITH IDIOPATHIC SHORT STATURE**

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### **Background:**

Idiopathic short stature (ISS) is a recognised but a controversial indication for height augmentation with recombinant human growth hormone (rhGH). The current study was done to analyse the short-term efficacy of the rhGH treatment in ISS.

### **Methods:**

A retrospective single-centre observational study was conducted at a tertiary paediatric endocrine centre. Children who were diagnosed with ISS and were treated with rhGH therapy for at least 1 year were included in this study. The subjects were treated at a dose of 0.05 mg/kg/day. They were regularly monitored for any adverse effects on the therapy. The anthropometric characteristics at the baseline and at the end of 1 year treatment were statistically analysed.

### **Results:**

A total of 22 children were enrolled in this study, out of which 11 were girls and 11 were boys. The mean age of starting the rhGH therapy was 11.4 years (6 years – 14.5 years). Post rhGH therapy, the mean growth velocity increased by 3.8 cm from the pre-treatment period. The mean Ht.SDS of the subjects improved by +0.51 SDS (+0.14 - +1.13 SDS) and the mean predicted adult height also improved from -1.71 to -0.98 with a DPAH SDS of +0.73.

### **Conclusions:**

The use of rhGH therapy in children with ISS improves short-term linear growth and increases PAH. As the study duration was short, a long follow up is needed to determine the

## **FACTORS ASSOCIATED WITH GROWTH HORMONE TREATMENT RESPONSIVENESS IN NOONAN SYNDROME**

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### **Background**

Noonan syndrome is a congenital malformation syndrome which accompanies short stature, and growth hormone (GH) therapy was approved in 2017.

### **Purpose**

The purpose of this study was to investigate the factors associated with the response of Noonan syndrome to GH treatment.

### **Methods and Results**

Of the 19 patients with Noonan syndrome treated with GH at the Department of Endocrinology and Metabolism of our hospital from May 1, 2011 to April 30, 2021, we examined 18 patients, excluding one patient who died after the start of treatment. The growth rate SDS of the 18 patients was 3.798 (2.497-4.865) one year after the start of treatment, the  $\Delta$  height SDS was 0.645 (0.44-1.13) one year after the start of treatment, and the  $\Delta$  IGF-1 SDS was 1.19 (0.66-1.62) before and one month after the start of treatment. Of the 18 patients, 12 had one or more loading tests; 3 had a low response to one or more loading tests, and the remaining 9 had no GH secretion deficiency, but there was no difference in growth rate SDS at 1 year of treatment between patients with and without GH secretion deficiency. Of the 18 patients, 10 had mutations in PTPN11, 1 had a mutation in SOS 1, 1 had a mutation in RAF1, and 6 had unknown mutations. There was no difference in growth rate SDS at the first year of treatment between patients with and without PTPN11 mutation. 12 patients started treatment before the age of 8 years and 6 patients started treatment after the age of 8 years, and the former had higher  $\Delta$  height SDS at the first year of treatment (1.045 vs. 0.39,  $P < 0.01$ ).

### **Discussion**

In Noonan syndrome, increase in growth rate was expected by GH treatment regardless of the presence or absence of GH secretory failure. Although there are various reports on gene mutation and response to treatment, in this study, no difference was apparent in the presence or absence of PTPN11 mutation. Although we did not find an association between low response to the loading test and response to treatment, as with GH secretion deficiency in general population, the younger the age at which treatment is initiated, the greater the expected increase in growth rate and height after initiation of treatment.

### **Conclusions**

Factors associated with GH treatment responsiveness in Noonan syndrome were investigated. It is necessary to accumulate more cases for further analysis.

## **A CASE OF SCN8A-RELATED EPILEPTIC ENCEPHALOPATHY COMPLICATED BY MULTIPLE FRACTURES**

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Children with severe motor and intellectual disabilities can have bone fractures, but are rarely complicated by multiple fractures in infancy. The SCN8A mutation is known to cause epileptic encephalopathy, and in some reports, osteoporosis and fractures. A male neonate was born at 37 weeks and 3 days of gestation with a weight of 2976 g after uncomplicated pregnancy. On day 0, he showed irritability, tremor, and myoclonus, and from the second day after birth, breath-holding spell with facial flushing, rigidity, bradycardia, and hypoxia appeared. At one month of age, an electroencephalography showed multifocal paroxysm and abnormal background activity, and he was diagnosed as having epilepsy. Anti-epileptic drugs were started, but bradycardia and hypoxia during breath-holding spells were continued, and the patient underwent tracheostomy and mechanical ventilation was started at 3 months of age. At the age of 4 months, X-ray test revealed multiple fractures and post-fracture healing, and findings of osteoporosis (L2-4 BMD 0.228 g/cm<sup>2</sup>) were also noted; blood tests showed that Ca, P, ALP, and 25OH vitamin D were within normal limits. Pamidronate was administered at 6 months of age, but was temporarily discontinued due to worsening of renal function. At 11 months of age, pathogenic variant in SCN8A was revealed by whole-exome sequencing. The multiple fractures were occurred with epileptic seizures, based on osteoporosis associated with the SCN8A mutation. At 13 months of age, a new bone fracture was found and pamidronate was restarted. Since then, the bone resorption markers have been decreasing and frequency of bone fractures has been improved. Although the mechanism of osteoporosis in this disease has not been clarified, it has been reported that bone resorption is accelerated and bisphosphonates are useful for fracture prevention. Screening for fractures and bone density should be considered in patients with SCN8A-related disorders.

**ENDOCRINE DISORDERS IN THALASSEMIA:AN INDIAN PERSPECTIVE**

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**Background:**

Thalassemia is the most common hereditary disorder worldwide. The patient's' survival is dependent on lifetime blood transfusion which leads to iron overload and its toxicity on various organs including endocrine glands. Undiagnosed endocrinopathies is associated with increased morbidity and impaired quality of life. Data is scant from India on the burden of endocrinopathies in children with thalassemia. This study aimed to determine the burden and predictors of short stature, delayed puberty, thyroid and adrenal disorders.

**Methods:**

We analysed 142 consecutive patients thalassemia major or intermedia, attending the out patient services of a tertiary care hospital and screened them for endocrinopathies between January 2016 till July 2021. We analysed the burden of endocrinopathies with regards to serum ferritin levels.

**Results:**

Most common endocrinopathy was short stature, followed by hypogonadism, hypothyroidism and hypocortisolism (Table-1). Occurrence of endocrinopathies was significantly higher in patients in highest quartiles of serum ferritin as compared to the lower quartiles. Hypergonadotropic hypogonadism was more common than hypogonadotropic hypogonadism (Table-1). Thalassemia intermedia or major per se was not an independent predictor of endocrinopathies. Serum ferritin (iron overload status) was the primary predictor of occurrence of endocrinopathies.

**Conclusion:**

Endocrinopathies are common in children with thalassemia, and frequent go unrecognized, contributing to significant morbidity. Serum ferritin is a good predictor of endocrinopathies in thalassemia. Maintaining a good chelation viz. maintaining a low serum ferritin has an important role in reducing the burden of endocrinopathies in children with thalassemia.

**Table-1: Endocrinopathies in thalassemia based on serum ferritin levels**

PARAMETER	QUARTILES OF FERRITIN				P-VALUE
	QUARTILE-1 (n=24)	QUARTILE-2 (n=47)	QUARTILE-3 (n=47)	QUARTILE-4 (n=24)	
	[759-2000]	[2000-4250]	[4250-5000]	[5000-6000]	
Age	15.5±4.81	12.5±2.78	14.7±0.85	22.0±1.06	0.723
Height	150±16.5	135±14.4	145.7±3.8	152±4.2	0.002
Weight	36.2±8.7	28.5±6.7	38.2±7.2	45.3±4.06	<0.001
BMI (kg/m <sup>2</sup> )	15.8±0.39	15.4±0.39	17.9±2.8	19.5±0.65	0.001
SHORT STATURE (n)	12	46	47	16	<0.001
HEIGHT SDS (median/range)	-0.91 ±.10	-2.36±.95	-2.09±.43	-3.39±.84	<0.001
WEIGHT SDS	-.99±.61	-1.03±.51	-.88±.48	-1.47±.45	0.080
DELAYED PUBERTY (n)	3	6	15	23	<0.001
Hypergonadotropic hypogonadism (n)	0	3	4	3	-
Hypogonadotropic hypogonadism (n)	2	0	6	11	-
Hypothyroidism (n)	0	0	1	3	-
Hypoadrenalism (n)	0	0	0	3	-
TSH (mU/ml)	1.61±1.04	3.2±.95	3.3±1.33	2.6±.72	0.001

Free T4 (ng/dl)	1.35±.05	3.2±.95	1.1±.25	.96±.09	0.003
IGF-1 (ng/ml)	345±83.38	248.25±83.5	182.2±107.56	215±2.13	<0.001
8am CORTISOL (mcg/dl)	17.65±2.61	16.55±2.63	16.8±1.87	18.05±2.08	0.420
LH (U/L)	2±1.49	1.2±1.21	1.1±.56	17.6±17.4	<0.001
FSH (U/L)	2.4±2.13	2.4±2.08	2±1.75	24.2±21.15	<0.001
Hemoglobin (g/L) (mean/SD)	8.5±1.2	8.7±.85	8.7±.25	8.5±.53	0.558
FBG (MG/DL)	89±1.06	87±3.1	79.5±11.08	82±.00	0.004
Calcium (mg/dl)	9.1±.37	9.3±.35	9.12±0.44	8.2±.00	<0.001

SDS: standard deviation score; all values expressed as mean± standard deviation; P<0.05 considered statistically significant

## **WHETHER OR NOT IS THERE A CORRELATION BETWEEN BIRTH SIZE AND PENILE LENGTH?**

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### **Background:**

Penile elongation is caused by the action of testosterone. Testosterone levels in the blood are elevated during three periods: fetal life, early postnatal mini-puberty, and puberty. It has been reported that boys born as Small-for-Gestational Age (SGA) have significantly lower testosterone levels during mini-puberty compared to boys born as Appropriate-for-Gestational Age (AGA), which may result in differences in mean penile length. However, there have been few reports on whether there is a correlation between body size at birth and penile length.

### **Purpose:**

To compare penile length in boys born as non-SGA and SGA.

### **Methods:**

Eight hundred and twenty-eight cases (805 non-SGA, 23 SGA) born at our hospital between December 2010 and November 2013 without any apparent serious underlying disease and who agreed to participate in the Maternal and Child Health Cohort Study were included in the study. Penile length was measured over time from 3 months to 7 years of age, and the results were compared between the two groups. The mean body size at birth for non-SGA children was 49.4 cm in height and 3.04 kg in weight, and 43.8 cm in height and 2.17 kg in weight for SGA children. The penile length to birth height ratio at 3 months of age was 0.068 for non-SGA children and 0.073 for SGA children. The following are the mean values (cm  $\pm$  SD) of penile length in the order of non-SGA births/ SGA births; 3 months 3.38  $\pm$  0.58/3.19  $\pm$  0.55, 6 months 3.40  $\pm$  0.61/3.32  $\pm$  0.58, 9 months 3.48  $\pm$  0.68/3.32  $\pm$  0.73, 1 year 3.47  $\pm$  0.68/3.54  $\pm$  0.70, 2 years 3.51 $\pm$ 0.70/3.21 $\pm$ 0.70, 3 years 3.72 $\pm$ 0.71/4.03 $\pm$ 0.92, 5 years 4.14 $\pm$ 0.89/4.06 $\pm$ 1.08, 6 years 4.17 $\pm$ 0.97/4.61 $\pm$ 0.87, and 7 years 3.96 $\pm$ 0.58/3.70 $\pm$ 0.24. There was no significant difference between the means of the two groups at any age (t-test, P>0.05).

### **Discussion:**

Although testosterone levels in mini puberty are said to be significantly different between non-SGA and SGA births, there was no significant difference in penile length between the two groups in this study. One limitation of this study is that the sample size of SGA children was smaller than that of non-SGA children, which may have prevented a significant difference.

### **Conclusion:**

The results suggest that penile length is not correlated with body size at birth.

## **HYPERGLYCEMIC HYPEROSMOLARITY STATE IN AN ADOLESCENT FEMALE WITH CENTRAL DIABETES INSIPIDUS AND TYPE 2 DIABETES MELLITUS AFTER SUPRASellar TUMOR SURGERY**

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### **Background:**

Hyperglycemic hyperosmolar syndrome (HHS) is an acute complication with a high mortality rate in diabetic patients, but its occurrence in young age is rare. In diabetic patients complicated with central diabetes insipidus, water-electrolyte management is more difficult when the diabetic control is not adequate.

### **Case presentation:**

The patient is an 18-year-old girl with severe obesity, combined pituitary hormone deficiency, and central diabetes insipidus after suprasellar germ cell tumor removal at the age of 7 years. She developed type 2 diabetes mellitus at the age of 14 and was taking metformin and sitagliptin. 53 days before admission, her HbA1c was 7.2%. She forgot to take desmopressin orally disintegrating tablets 2 days before admission. She presented to the emergency room with headache. On admission, routine laboratory tests showed HbA1c 10.5%, Na 161mmol/l, blood glucose 669mg/dl, venous pH 7.306, HCO<sub>3</sub><sup>-</sup> 20.8mmol/l, total ketone body 1037μmol/l, plasma osmolality 359mOsm/l, urine ketone negative. She was diagnosed with HHS. Dehydration correction with Ringer's solution acetate and continuous intravenous insulin were started. The maximum total daily insulin dose was 2.3 U/kg/day, which was gradually decreased and continuous insulin infusion was discontinued on the 13th day. The patient was switched to insulin degludec and liraglutide injection. Flash glucose monitoring with FreeStyle LibreLink was introduced, and discharged on the 16th sick day to outpatient treatment.

### **Conclusion:**

One of the factors that may have contributed to the development of HHS in this patient was poor adherence to desmopressin orally disintegrating tablets. The introduction of FreeStyle LibreLink has made it easier for the family and medical workers to monitor blood glucose changes. In addition, although this patient has difficulty in controlling her weight, the use of GLP-1 agonists for hypothalamic obesity is expected to reduce her BMI.

## Diabetes

### A Family with A Novel Termination Mutation in Hepatic Nuclear Factor 1 $\alpha$ In Maturity-Onset Diabetes of The Young Type 3

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#### Introduction:

Maturity-onset diabetes of the young (MODY) is an early onset, genetically heterogenous and autosomal dominant form of monogenic diabetes-mellitus. It leads to impaired insulin secretion and affects 1-2% of all diabetic patients. The pancreatic autoantibodies are absent and is often associated with extra-pancreatic manifestations. We report an Indian-family due to a novel (c.618G>A,p.Trp206Ter) mutation in HNF1 $\alpha$  gene (MODY-3). This kind of non-sense mutation has been previously described as unresponsive to sulphonylurea therapy.

#### Case

A 7-year-old girl presented with osmotic symptoms. She was diagnosed with type1 DM based on her age of presentation, clinical examination, biochemical parameters [fasting blood glucose(293 mg/dl),HbA1c(13.3%)] and history of type1 diabetes in her mother. She was started on basal-bolus insulin regimen with improvement in her HbA1c(8.4%). Her GAD-65 antibody was negative. Her 11-year-old brother on screening had a FBG(191 mg/dl) and HbA1c(10.5%) in the absence of osmotic symptoms. On further inquiry, mother was on a very low total-daily-dose of insulin for a type1 diabetic. Suspecting MODY, a genetic panel was sent which found a heterogenous nonsense variation in exon 3 of HNF1A gene resulting in premature truncation of the protein at codon 206. Subsequently both the siblings were started on sulphonylureas showing a significant improvement in their HbA1c(6.8% and 6.3% respectively).

#### Presentation:

#### Conclusion:

MODY is often misdiagnosed as either type-1 or type-2 diabetes depending upon the initial age of presentation. In contrast to previous case report, this mutation showed a good response to sulphonylurea therapy.

## **FREE, BIOAVAILABLE 25-HYDROXYVITAMIN D LEVELS AND ITS ASSOCIATION WITH DIABETIC KETOACIDOSIS AT DIAGNOSIS IN CHILDREN WITH TYPE 1 DIABETES MELLITUS**

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### **Backgrounds:**

Considering the role of vitamin D in insulin secretion and immune modulation, low 25-hydroxyvitamin D (25OHD) levels may contribute to risk for type 1 diabetes (T1DM). Few studies on free and bioavailable 25OHD not bound to vitamin D binding protein (VDBP), biologically active forms, have been conducted in T1DM. We compared total, free, bioavailable 25OHD levels, VDBP and its genotypes between T1DM patients and control. We also investigated the relationships of vitamin D metabolites with clinical and biochemical presentation at T1DM diagnosis.

### **Methods:**

This retrospective, cross-sectional study included 87 children with T1DM (40 boys,  $8.0 \pm 3.7$  years) and 87 age and sex-matched healthy controls (43 boys,  $9.1 \pm 2.1$  years). A multiplex liquid chromatography-tandem mass spectrometry assay was used to simultaneously measure vitamin D metabolites. The free and bioavailable 25OHD levels were calculated using the formula by Bikle.

### **Results:**

T1DM patients had lower levels of total 25OHD ( $16.9 \pm 6.1$  vs.  $20.2 \pm 6.5$  ng/mL,  $p=0.001$ ) and VDBP ( $143.9 \pm 30.1$  vs.  $226.0 \pm 37.4$  ug/mL,  $p<0.001$ ), but higher free 25OHD levels ( $8.6 \pm 4.4$  vs.  $6.6 \pm 2.3$  pg/mL,  $p<0.001$ ) than controls. The proportion of VDBP genotype did not differ between T1DM patients and controls. T1DM patients presented with diabetic ketoacidosis (DKA) at diagnosis showed lower levels of total ( $15.3 \pm 4.9$  vs.  $18.5 \pm 6.7$  ng/mL,  $p=0.016$ ), free ( $8.2 \pm 5.0$  vs.  $9.1 \pm 3.9$  pg/mL,  $p=0.059$ ), and bioavailable 25OHD ( $2.5 \pm 1.4$  vs.  $3.0 \pm 1.3$  ng/mL,  $p=0.010$ ) than those without DKA, without significant difference in free and bioavailable 25OHD levels between T1DM patients presented with DKA and controls. The lower the total, free, and bioavailable 25OHD levels at T1DM diagnosis, the lower the pH and HCO<sub>3</sub>. However, the relationship of vitamin D metabolites or VDBP genotype with DKA or pH, serum C-peptide, and positivity of autoantibodies at diagnosis was not significant.

### **Conclusions:**

Increased levels of free 25OHD were found in T1DM patients compared to healthy children, with significantly higher levels in T1DM patients without DKA at diagnosis. Considering the relationship of low free 25OHD levels with acidosis at diagnosis, it needs to be further investigated whether free 25OHD plays a protective role in metabolic deterioration in T1DM patients.

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General Paediatric

### **CLINICAL PREDICTORS OF ACUTE KIDNEY INJURY IN CHILDREN WITH ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS: A TERTIARY CENTRE EXPERIENCE**

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#### **Introduction:**

Acute post-streptococcal glomerulonephritis (APSGN) in the paediatric population remains a major health burden to the health care system in developing countries. Acute kidney injury (AKI) is not an uncommon complication of APSGN. This study aimed to look at the prevalence, clinical predictors and duration of AKI, among children with APSGN.

#### **Methods:**

A 10-year retrospective review of medical records of patients with APSGN, aged between 12 months to 18 years, admitted to a tertiary hospital. Multiple logistic regression analysis was used to identify predictors for AKI, and Kaplan-Meier survival analysis was used to determine the median time of AKI resolution in paediatric APSGN.

#### **Results:**

Four hundred children were included in the study. There was a male predominance (n = 262 (65.5%). The prevalence of AKI in the cohort was 21.7% (n = 86) (95% CI: 17.6-25.8). Older age and gross haematuria were identified as significant predictors for AKI in APSGN (p = 0.006 and p <0.001 respectively). The median time of AKI resolution in paediatric APSGN was 18.0 days (IQR = 15.3-20.7).

#### **Conclusion:**

In children with APSGN, AKI was common and its median duration was 18 days. Older age at presentation and gross haematuria were significant predictors for AKI to develop.

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## CLINICAL PROFILES AND OUTCOMES OF RENAL SCARRING AMONG CHILDREN UNDERWENT DIMERCAPTOSUCCINIC ACID RENAL SCAN IN A TERTIARY HOSPITAL

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### Introduction:

Pyelonephritis in children under 5 years of age leads quite often to renal scarring, which is an established risk factor for hypertension, proteinuria and chronic kidney disease (CKD).<sup>(1,2)</sup> Factors that may predispose to renal scarring include congenital anomalies of kidney and urinary tract (CAKUT), comprising of VUR, horseshoe kidney, duplex kidney, or any obstruction of the urinary system.<sup>(3)</sup> Dimercaptosuccinic acid (DMSA) renal scan has been universally used to detect renal scarring. It can also help to determine the relative function of kidneys.<sup>(4,5)</sup> Hypertension has been demonstrated in children as early as 8 years after detection of renal scarring.<sup>(6)</sup> Nevertheless, there are limited studies on looking at the time taken to develop other complications of renal scarring like CKD and proteinuria.

### Objectives:

The aim of this study were to determine the proportion, risk factors and outcomes of renal scarring among children in a tertiary centre, Kelantan, to study the association between risk factors and development of renal scarring and to determine the association between risk factors and outcomes of renal scarring.

### Methodology:

This was a cross-sectional study conducted in Hospital USM, Kubang Kerian which is a tertiary teaching hospital located on the east coast of peninsular Malaysia. All records of children less than 18 years old that were referred for DMSA renal scan beginning from the 1st January 2008 until 31st December 2019 were reviewed. Records with inadequate data were excluded. The medical records retrieved were reviewed retrospectively to identify risk factors of renal scarring and follow-up records were reviewed to determine the renal outcomes in patients with scarring.

Results: Out of 92 children referred for DMSA scan, half were detected to have renal scarring. There was a significant association between VUR and DMSA abnormalities (p-value=0.007). Forty-two out of forty-eight children with renal scarring had underlying VUR. Fourteen (33.3%) of them had low grade and twenty-eight (66.7%) had high-grade VUR. More than half of children with VUR (n=36) presented with recurrent UTIs while another 23 children had no documented history of recurrent UTI. Non-E.coli organisms (75.0%) seemed to be the main cause of renal scarring. Common isolates were Klebsiella pneumonia (n=8, 44.4%) and Pseudomonas aeruginosa (n=4, 22.2%). Seventy-eight percent of children with recurrent UTIs secondary to VUR were on prophylactic antibiotics and more than 50% of children had renal scarring despite on prophylactic antibiotics. CKD (27.1%) and hypertension (12.5%) were the commonest complications seen in children with renal scarring. The median duration between diagnosis of the complications and detection of renal scarring was 1 year. Five children (10.4%) developed proteinuria after the detection of renal scarring. There was no significant association between risk factors and outcomes of renal scarring in our population.

### Conclusion:

A high proportion of children undergoing DMSA scans had renal scarring and early development of serious complications was not uncommon.

## **IN SITU SIMULATION WITH HIGH-FIDELITY PAEDIATRIC MANIKINS AT REGIONAL HOSPITALS IN PENANG**

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### **Background**

In Situ simulation, defined as a team-based simulation strategy involving interdisciplinary healthcare team members working in their own environment on patient care units is not commonly carried out locally in Malaysia. High-fidelity manikins are expensive and not many centres can afford it and there are only a handful of certified healthcare simulation educators (CHSE) in Malaysia.

### **Objective**

To assess the feasibility of running high quality, team-based in situ paediatric simulation at the regional hospitals in Penang with a high-fidelity manikin in a mobile team and a Certified Healthcare Simulation Educator(CHSE).

### **Methods**

Allied Health Centre of Excellence ( AHCoE ), an organisation with some of the latest state-of-the-art healthcare simulation facilities allocated an educational fund to support the regional private hospitals in Penang in running in situ simulation at the hospitals to create awareness of the impact of healthcare simulation on patient safety. AHCoE also provided assistance and support from their technical team and the mock code simulation was facilitated by a CHSE. The hospital administrators and their respective head of paediatric departments of the private hospitals in Penang were offered this opportunity.

The teams of participants were made up of nurses and physicians. Participants are briefed on the scenario they will encounter, their surroundings, and the high-fidelity patient simulator they would work on. The simulation ran about 10 minutes. The scenario was an in situ simulation involved a paediatric patient that was decompensating rapidly in the Paediatric Emergency Room (ER). Interventions was expected to be done in an organized and effective way to turn the case around. The learners then went through a facilitated debriefing session by the CHSE when everyone came together and talks about what happened in the scenario. They received a feedback/summary on equipment needs and processes that can be improved. After completing the simulated clinical experience, the participants were requested to submit a validated evaluation form, the Simulation Effectiveness Tool-Modified (SET-M)<sup>1</sup>.

### **Results**

A total of 32 participants ( 5 physicians and 27 registered nurses ) from 5 private hospitals in Penang participated in this exercise. The SET-M evaluation was very positive as more than 95 % of the participants strongly agreed that the simulation scenarios increase their confidence in their assessment skills and they had the opportunity to practice clinical decision making skills. More than 90% of them strongly agreed that debriefing contributed to learning and was a constructive evaluation of the simulation.

### **Conclusion**

This is a pioneer project in Malaysia with a mobile simulation team and a high-fidelity manikin. The experience from the participants was very encouraging with lots of positive feedback and the participants were more confident in their assessment and clinical skills. This is a feasible approach for regional hospitals with limited resources in healthcare simulation.

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## QUALITY OF LIFE (QOL) ASSESSMENT IN INFLAMMATORY BOWEL DISEASE IN MALAYSIAN CHILDREN

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### Background:

Inflammatory bowel disease (IBD), a chronic, relapsing inflammation of the gastrointestinal tract, can potentially impair the quality of life (QoL) of affected children. We aimed to evaluate factors affecting QoL in Malaysian children with IBD.

### Methods:

In this cross-sectional study, children aged between 8-17 years old with a confirmed diagnosis of paediatric IBD > 6 months were recruited. IMPACT-III questionnaires was used to assess the QoL. Sociodemographic data and disease-related information were collected.

### Results:

75 children [UC: n=44, CD: n=41; mean ( $\pm$ S.D.) age at interview 12.8 ( $\pm$ 2.7) years] were interviewed. A higher weight-for-age z-score or BMI-for-age-z-score were weakly correlated with a better body image domain score ( $r=0.261$ ,  $p=0.023$  and  $r=0.235$ ,  $p=0.042$ ), respectively. The mean ( $\pm$ SD) IMPACT-III score was negatively affected by the disease activities (71.84 $\pm$ 13.60 [mild] vs. 65.46 $\pm$ 10.89 [moderate] vs. 46.29 $\pm$ 14.52 [severe];  $p<0.001$ ). Diagnosis at a younger age ( $r = -0.31$ ,  $p = 0.007$ ) and a longer duration of disease ( $r, = 0.286$ ,  $p = 0.013$ ) was associated with a better QoL, respectively while a history of hospitalization (63.96 $\pm$ 13.95 vs. 74.10 $\pm$ 12.24,  $p=0.034$ ) and a higher number of admissions ( $r= -0.352$ ,  $p=0.041$ ) were associated with lower QoL score, respectively. No significant difference in QoL was observed between children with UC and CD ( $p=0.195$ ).

### Conclusions:

QoL in paediatric IBD was adversely affected by a more severe and longer duration of disease and a younger age at onset. Control of disease activity and maintaining long-term remission could help to improve the QoL in children with IBD.

(244 words)

Keywords: Inflammatory bowel disease, ulcerative colitis, Crohn's disease, quality of life, IMPACT-III

## **DO CARETAKERS OF PAEDIATRIC PATIENT WITH CHRONIC KIDNEY DISEASE SUFFER FROM BURNOUT?**

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### **Introduction**

Caring for children with chronic kidney disease (CKD) is challenging since CKD imposed multiple psychosocial impact not only to patient but also to caretakers. This study aimed to determine the prevalence of burnout and its associated factors among caretakers of paediatric patient with CKD. We also want to know the correlation between caretaker's strain and burnout.

### **Methods**

This was a cross-sectional study that involved caretakers of children with CKD. They were recruited from a university hospital in Kelantan, Malaysia. Self-administered questionnaire in Malay language comprised of Demographic Information Form, Copenhagen Burnout Inventory (CBI-M) and Caregiver Strain Index (CSI-M) was used. Data was analysed using SPSS version 24.

### **Results**

Eighty-eight caretakers participated in this study. The mean age of caretakers was 42 years old, majority were female (72.4%), Malay (99.0%) and Muslim (99.0%). The mean age of children with CKD was 11 years old, most of them were on medication (69%) and mean duration of illness was 4.6 years. The prevalence of burnout in all domains among the caretakers was 5.7%. Eight caretakers had personal burnout (9.1%) while five (5.7%) had client-related and work-related burnout respectively. Multiple linear regression showed association of duration since the initial diagnosis and total ward admission within six months with total burnout score. Pearson correlation revealed a positive and fair correlation between strain and burnout.

### **Conclusion**

Prevalence of burnout among caretakers was generally low, but personal burnout outnumbered other domains. Children with longer duration of illness and frequent ward admission are the important factors leading to burnout among caretakers. A higher number of caretakers having significant strain indicated that there were concerns among caretakers that might contribute to burnout later.

Keywords: caretaker, burnout, strain, children, chronic kidney disease.

**CONGENITAL RADIAL DYSPLASIA**

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Radial dysplasia of newborn is a rare congenital incidence in which it accounts for less than 1% of the births worldwide. Being the most common congenital longitudinal deficiency, it is usually associated with multiple congenital syndromes such as VACTERL syndrome, TAR syndrome, Holt-Oram syndrome, Fanconi anemia and VATER syndrome. Here we present a case of a newborn who was diagnosed to have radial club hand postnatally.

A term baby boy was born with bilateral aplastic thumbs and short forearms, Type IV Bayne and Klug classification. X rays of bilateral upper limbs showed absence of radial bones and only four metacarpals and phalanges on each side. No maternal history of consumption of medications or supplementations antenatally while his family history was unremarkable in terms of congenital disorder and consanguinity. Child was born without other dysmorphism and was developmentally normal up to age. Blood investigations as well as imaging revealed normal findings, ruling out other associated congenital anomalies. He was referred for early intervention programs (EIP) for limb function training and is still under our Paediatrics follow up for growth and development monitoring.

Radial longitudinal deficiency is uncommon and is important to work up for other associations. Though this atypical presentation is isolated, it requires multidisciplinary management to ensure that the child has a good well-being generally and able to function near normal in terms of gross and fine motor.

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General Paediatric

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**ANALYSIS OF SURVIVAL AND PROGNOSTIC FACTORS OF ACUTE LYMPHOBLASTIC LEUKAEMIA USING A SINGLE TREATMENT REGIMEN: A UNICENTRIC STUDY FROM HOSPITAL UNIVERSITI SAINS MALAYSIA, KELANTAN**

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**Introduction:**

The overall survival for paediatric acute lymphoblastic leukaemia (ALL) has shown a remarkable improvement in the past decades. We aimed to evaluate the clinical presentations, the overall survival and identify prognostic factors of poor disease outcome among children with ALL treated with UKALL regime.

**Methods:**

This retrospective study involved data transcription from medical records of children diagnosed with ALL and received UKALL protocol regime in Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia from January 1st, 2008 till December 31st, 2017. Eligible records were identified from patient registry in paediatric oncology unit and subsequent medical records were individually traced. Kaplan-Meier analyses with log-ranks were performed to determine the 2-year and 5-year survival rates. Multivariate analysis with simple and multiple Cox regression were performed to determine prognostic factors of poor disease outcome.

**Results:**

A total of 110 patients were included. Majority presented with fever (81.8%), lethargy (49.1%), pallor (43.6%), and arthralgia (26.4%). The overall survival analyses at 2-year and 5-year were at 80.0% and 72.7%, respectively. The mean survival rate was 76.8 months (95% CI: 68.9-84.8). Modelling with multiple Cox regression showed that TWCC of  $50 \times 10^9/L$  and above ( $p=0.013$ ), and history of relapse ( $p=0.001$ ) significantly predicted poor survival outcome among children with ALL.

**Conclusion:**

Our study showed patients presented with common clinical features of acute leukaemia. Our reported overall survival analysis was considered fair for developing countries. Additionally, hyperleukocytosis, leucocytosis and relapse of disease predicted poor survival outcome.

**PP 9**

General Paediatric

**VERTICAL TRANSMISSION OF SARS-COV-2**

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SARS-Cov-2, also known as COVID-19 infection, has plagued the world, beginning at the end of 2019 in Wuhan, China and evolved to become pandemic around the world until present. Globally, as of August 2021, there have been 200 million confirmed cases of COVID-19 reported, of which approximately 1.3 million of confirmed COVID -19 cases have been reported in Malaysia. As the infection progress with cases of infection and death multiplied, substantial evidence supports that route of transmission of the disease was direct person-to-person respiratory transmission and possibly by the route of airborne.

From recent cohort studies, approximately 2% of infant born to pregnant women infected with SARS-CoV-2 during the late trimester tested positive in the first 24-96 hours of birth. Therefore concerns regarding possibility of vertical transmission of the disease arise. We report a case of possible vertical transmission of SARS-Cov—2 in a newborn that came to us at 19 hours of life.

**SUBCLINICAL HYPOTHYROIDISM, FACTORS AFFECTING TIME TO TSH NORMALISATION.**

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**Objective:**

To prospectively analyse the median time for TSH to normalise and to evaluate the prognostic factors affecting time to TSH normalisation in infants and children with Subclinical hypothyroidism (SH).

**Method:**

We recruited 116 participants (infants and children up to 3 years of age) with subclinical hypothyroidism who are otherwise well, infants of mothers with autoimmune thyroiditis and Down Syndrome. This study involved our paediatric ward (inpatient) and Paediatric Endocrinology Clinic (outpatient) Hospital Universiti Sains Malaysia (Hospital USM). Kaplan-Meier survival analysis was used to determine the median time of TSH to normalise. Finally, a Cox Proportional Hazards Regression was used to explore the prognostic factors that were associated with the median time for TSH normalisation.

**Results:**

During the study, 108 (98%) out of 116 patients with subclinical hypothyroidism had TSH normalisation at a median time of 4.0 weeks. Overall, patients whom were term at birth; median (95 % CI): 4 (3.3,4.6) , appropriate for gestational age (AGA); [4 (3.3,4.6)] and birth weight of  $\geq 2.5$  kg; [4 (3.3,4.6)] had median time of TSH normalisation earlier compared to patients whom were born preterm; [12 (0.0,27.1)], small for gestational age (SGA); [8 (4.7, 11.2)] and birth weight of  $< 2.5$ kg; [8 (1.1,14.8)]. Significant predictors for factors associated with TSH normalisation based on simple Cox regression analysis with  $p < 0.25$ , were age at diagnosis; CrudeHR( 95% CI): 0.985 (0.96,1.0),birth weight; [1.883 (1.0,3.4)], SGA; [0.531 (0.28,1.0)], AGA; [2.409 (1.0,3.8)] and gestational; [0.430 (0.2,0.7)], Down syndrome; 2.845,(0.68, 11.8),and maternal autoimmune thyroiditis; [0.618 (0.32,1.19)]. However only preterm gestation was significant predictor for TSH level to normalise; Adjusted HR(95%CI): 0.389(0.2,0.75), ( $p=0.005$ ) from multiple Cox regression analysis.

**Conclusion:**

Premature is a significant predictor for TSH level to normalise and 61.1% less likely to have a normal level of TSH.

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**PAEDIATRIC SELLAR AND SUPRASellar TUMOURS: CLINICAL CHARACTERISTICS, ENDOCRINOLOGICAL OUTCOME AND MORBIDITY FROM A SINGLE TERTIARY CENTRE IN KUALA LUMPUR, MALAYSIA**

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**Introduction:**

The clinical features, endocrinological outcome, and morbidity of both sellar and suprasellar tumors in children vary with different types of histology, site, and the extent of tumors, as well as the treatment approach. We herein report children with suprasellar tumors treated at our center.

**Methods:**

Data were collected by retrospective review of medical records from January 2015 to December 2020. These patients were identified from the pediatric endocrine clinic.

**Results:**

A total of 34 children with sellar and suprasellar tumors were included. The mean age of presentation was 6.58 (2-13) years old with male to female ratio 3:2. All patients had tissue diagnosis with the most common histology being adamantinomatous craniopharyngioma 55.9% (n=19), followed by germ cells tumour (GCT) 23.5% (n=8), pilocytic astrocytoma 17.6% (n=6) and glioma 2.9% (n=1). The mean duration of follow-up was 6.2 (0.6-15.5) years. One patient with craniopharyngioma had lost to follow-up. All patients were alive by the time of the report. The majority of patients, 67.6% presented with raised ICP symptoms (headache, vomiting, altered consciousness or convulsions), 47.1% with eye symptoms (blurring of vision, hemianopia or nystagmus), 11.8% with symptoms of polyuria and polydipsia resembling cranial diabetes insipidus, 5.9% with short stature and 8.8% with precocious puberty. 52.9% of patients (n=18) had required emergency VP shunt insertion prior to definitive treatment. Surgical resection (transcranial approach) was the definitive treatment in 79.4% of patients (n=27), while either chemotherapy or radiotherapy was given for the remaining 17.6% of patients that do not require surgery. 1 patient with craniopharyngioma was undecided for surgical resection. Among those who performed surgery (n=27), 33.3% had required adjuvant radiotherapy, 7.4% required both chemotherapy and radiotherapy, 3.7% required repeated surgery and 55.5% do not require further intervention but on follow-up and radiological surveillance. 85.2% of them were reported to be having residual while 14.2% do not have residual. Recurrence was reported in 11.1% of patients who had undergone surgical intervention.

All the survivors were reported to have significant morbidity; 61.7% have moderate to severe visual impairment (ranging from hemianopia to total visual loss) while 14.7% with neurological deficits (ranging from unilateral hemiparesis to spastic quadriplegia). All of them have at least two pituitary hormones deficiency. Cranial diabetes insipidus (DI) was reported in 88.2% (n=30), while 91.2% (n=31) had TSH deficiency, 88.2% (n=30) had ACTH deficiency on hydrocortisone replacement (18 patients being confirmed with glucagon stimulation test, GST), 52.9% (n=18) with biochemically proven GH deficiency (peaked GH level <10ug/L), and as to far 29.4% (n=10) with gonadotrophin deficiency, requiring pubertal induction. GH therapy was given to 4 patients, of which 3 patients had GCT and 1 with craniopharyngioma. GH therapy was stopped in the patient with craniopharyngioma after 3 months, due to tumor recurrence. There were also another 3 patients with precocious puberty, not related to disease progression. The incidence of severe hypothalamic obesity (BMI SDS >2.5) among survivors are 14.7% (n=5), in comparison with those overweight (BMI SDS 2-2.5) 26.5% (n=9) and normal BMI (BMI SDS <2) 58.8% (n=20). As for overall (n=34), mean weight SDS was -0.06 (SD 1.8), mean height SDS -2.28 (SD 1.7), and mean BMI SDS +1.39 (SD 1.36). Metabolic complications arising from obesity were not reported due to the relatively short duration of follow-up.

**Conclusions:**

Despite significant improvement in the management and survival of pediatric sellar and suprasellar tumors in children, the morbidity and endocrinological complications relating to multiple pituitary hormones deficiency, hypothalamic dysfunction with obesity, and the long-term metabolic outcome still require further research.

## **A CASE REPORT OF VICI SYNDROME: A RARE CONGENITAL DISORDER OF AUTOPHAGY**

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### **Introduction:**

Vici syndrome is one of the rare congenital disorders of autophagy, arising from mutation of EPG5 gene. It is a multi-systemic autosomal recessive disorder, characterised by oculocutaneous albinism, corpus callosum agenesis, cataract, cardiomyopathy, and immunodeficiency. We report an infant with Vici syndrome, who suffered from recurrent severe infections and refractory immune thrombocytopenia.

### **Case Presentation:**

Our subject, a baby boy who was born term, was a product of a consanguineous marriage of the Indian ethnicity. He suffered from cutaneous albinism, immunodeficiency with recurrent infections, absent of corpus callosum with severe neurological impairment, hypertrophic cardiomyopathy, and bilateral cataracts. Diagnosis of Vici syndrome was confirmed by genetic testing, which showed homozygous mutation in EPG5. The condition was further complicated by severe refractory immune thrombocytopenia, which failed to respond to intravenous immunoglobulin and oral prednisolone. He succumbed to his illness after contracting a severe nosocomial pneumonia, spiralling down to acute respiratory failure at one year old.

### **Conclusion:**

To date, this is the first Vici syndrome reported from Malaysia. There is no known cure for Vici syndrome, and the management is solely supportive, with poor prognosis. Its association with immune thrombocytopenia was not widely described, with unclear mechanism. We suggest further investigational studies to determine the association between immune thrombocytopenia and Vici syndrome, and exploring treatment options.

## CONGENITAL BILATERAL ISOLATED RADIAL DYSPLASIA

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Radial dysplasia of newborn is a rare congenital incidence in which it accounts for less than 1% of births worldwide. Being the most common congenital longitudinal deficiency, it is usually associated with multiple congenital syndromes such as VACTERL syndrome, TAR syndrome, Holt-Oram syndrome, Fanconi anemia and VATER syndrome. Here we present a case of a newborn who was diagnosed to have radial club hand postnatally.

A term baby boy was born with left aplastic thumb, left hypoplastic little finger and right hypoplastic thumb with bilateral short forearms, Type I and Type II Bayne-Klug classification respectively. Radiographs of left upper limb revealed presence of only three metacarpals, hypoplastic 5th phalanges and absence of 1st phalange with short radius while right upper limb showed shortened right radial bone with absence of 1st metacarpal bone and hypoplastic 1st phalanges. Carpal bones were unable to be identified well as the bones were not fully ossified yet. No maternal history of consumption of medications or supplementations antenatally while his family history was unremarkable in terms of congenital disorder and consanguinity. Child was born without other dysmorphism and was developmentally normal up to age. Blood investigations as well as imaging revealed normal findings, ruling out other associated congenital anomalies. He was referred for early intervention programs (EIP) for limb function training and is still under Paediatrics follow up for growth and development monitoring. Radial longitudinal deficiency is uncommon and is important to work up for other associations. Though this atypical presentation is isolated, it requires multidisciplinary management to ensure that the child has a good well-being generally and able to function near normal in terms of gross and fine motor.

### Terms:

radial club hand, radial dysplasia, radial longitudinal deficiency, radial ray deficiency

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## THYROID DISORDERS IN DOWN'S SYNDROME IN A CHILDREN'S HOSPITAL

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### Introduction

Down's syndrome (DS) remains to be one of the commonest chromosomal disorders. Thyroid disorders are well-recognised in infants and children with DS. We aim to characterise thyroid disorders found in a group of children with DS.

### Methodology

All DS children who were being followed-up under the Paediatric Clinic of Sabah Women and Children Hospital, Kota Kinabalu, Malaysia from March to May 2021 were identified. Diagnosis of DS was established by genetic confirmation and/ or typical clinical features. The clinical data and thyroid function tests were reviewed. Thyroid dysfunction is classified into 5 subsets: Congenital hypothyroidism, primary hypothyroidism, central hypothyroidism, subclinical hypothyroidism, and hyperthyroidism. Decision to treat the thyroid dysfunction was determined by attending clinicians.

### Results

A total of 64 patients with DS were identified. 48 patients (75%) had genetics confirmation. 32 patients (50%) had thyroid disorders, with a mean age of onset of  $1.3 \pm 1.2$  years old. 14 (43.8%) of those with thyroid disorders were diagnosed before the age of 6-month old. A majority of them have subclinical hypothyroidism (71.9%), followed by congenital hypothyroidism (12.5%), primary hypothyroidism (9.4%) and central hypothyroidism (6.2%). None had hyperthyroidism. 25 (78.1%) of those with thyroid disorders were started on thyroxine treatment, and the mean starting dose was  $5.1 \pm 3.4$  mcg/kg/day. A lesser cardiac complication was noted among the DS patients with thyroid disorder, compared to those without thyroid disorder (62.5% vs 87.5%,  $P=0.021$ ). However, no statistically significance was found in regards to association with gastrointestinal complications (71.2% vs 68.8%,  $P=0.578$ ).

### Conclusions

Our cohort shows a high prevalence of hypothyroidism among DS children. Majority of them are treated with thyroxine. A better understanding and careful evaluation of the thyroid status in DS children is important to avoid over or under treatment.

**POST COVID COMPLICATIONS: MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C). A LOCAL EXPERIENCE**

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**Introduction**

Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (MIS-C) is a novel condition that was first reported in early 2020. Information regarding its incidence is limited in Malaysia. We present a case series that describes the clinical characteristics and outcomes of patients diagnosed with MIS-C in Hospital Melaka over a period of 6 months from January to June 2021.

**Discussion**

MIS-C is characterized by persistent fever, single or multi organ dysfunction, cardio-circulatory manifestations with increased inflammatory biomarkers and evidence of recent or concurrent COVID-19 infection. It shares common features with other paediatric inflammatory conditions such as Kawasaki disease and Toxic Shock Syndrome. All our patients meet definitional criteria for MIS-C/PMIS by WHO. Three out of five of our patients present with shock and required inotropic support. Only one required mechanical ventilation and had multiorgan failure. Development of laboratory markers or diagnostic methods to distinguish MIS-C from severe COVID-19 illness and other hyperinflammatory conditions is critical for early and prompt diagnosis and treatment. Despite potential severity of disease, there is no mortality in our center and short term recovery is good after treatment with immunomodulators.

**Conclusion**

As the COVID-19 pandemic spreads, causing a third peak and a more sustained transmission across Malaysia, pediatricians should maintain a high index of suspicion for MIS-C, in children presenting with evidence of systemic inflammation and recent or concurrent SARS-COV-2 infection, as early recognition and prompt referral to critical care is essential.

### **PHACOMATOSIS PIGMENTOVASCULARIS: A CASE REPORT**

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#### **Introduction:**

Phacomatosis pigmentovascularis (PPV) is a group of rare congenital malformation characterized by vascular and skin pigmentary lesion of various degree. Due to its rare occurrence and existence, only limited number of cases have been reported making it a diagnostical and management conundrum. PPV is divided into 5 types with wide arrays in cutaneous and extracutaneous involvement. A complete biochemical and radiological workup with multidisciplinary review need to be done for management.

#### **Case presentation:**

We report a 3 month-old girl in a non-consanguineous parent. At birth she had multiple cutaneous manifestation throughout her face and body which prompt an initial diagnosis of Sturge-Werber syndrome (SWS). However, she presented with infantile spasm at 2 month of age with MRI features of gross brain anomaly making the diagnosis of SWS alone a far-fetched. We concluded for possible PPV in association with SWS due to presence of both cutaneous and extracutaneous features: right sided facial and limb hemihypertrophy with port wine stain, nevus anemicus involving the face and the right upper and lower limb, melanocytosis of sclera, extensor infantile spasm and MRI features of cerebral atrophy and dysgenesis of corpus. Child was started with oral vigabatrin for seizure control. She is currently on our regular follow up for seizure control and general developmental review.

#### **Conclusion:**

A thorough clinical examination with complete imaging modalities are needed in diagnosis of PPV and its systemic component. Due to its rarity, further cases need to be reported to predict the disease course, genetic predispositions and progression especially involving its neurological manifestation.

## NEONATAL OUTCOMES OF PREGNANCIES COMPLICATED BY MATERNAL HYPERTHYROIDISM

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### Objective:

We aim to study the proportion of infants born to maternal hyperthyroidism, their clinical, hormonal status, median time and factors affecting time for serum free T4, TSH normalization.

### Methodology:

A cross-sectional study recruited 170 inborn admitted to Neonatal Intensive Care Unit (NICU), Hospital Universiti Sains Malaysia (HUSM) from January 2013 until December 2018. We analyzed their baseline demographic and clinical characteristic, maternal treatment, autoantibodies level and thyroid function. Finally, we analyzed the newborn's thyroid function and thyroid autoantibodies.

### Results:

The proportion of newborns with maternal hyperthyroidism were 0.8% (170/ 20198). Seven (4.1%) developed overt hyperthyroidism, 4 (2.4%) had thyroid storm and 102 (60%) had abnormal TFT. The overall median time for TFT normalization was 30 days (95% CI): (27.1, 32.8). Cox Proportional Hazard revealed normal TFT on day 3-5, crude HR: 95% CI: 4.918 (2.11, 11.44) and day 15: 3.496 (1.61, 7.58) were significant variables affecting time of normalization.

### Conclusion:

Most infants with maternal hyperthyroidism had a benign course with median normalization time of 30 days. If the repeated TFT at day 3-5 and day 15 were normal, the likelihood to have subsequent TFT normalization were 4.9 and 3.4 times respectively compared to infants with abnormal results.

Keywords: Infant of mother with maternal hyperthyroidism, maternal hyperthyroidism, Graves' disease (GD), thyroid function test

## **CONGENITAL HYPERINSULINISM: GENETIC RESULTS, TREATMENT AND OUTCOMES. FOLLOW-UP OF A CASE SERIES AT A PAEDIATRIC ENDOCRINE CENTRE IN MALAYSIA**

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### **Introduction**

Hyperinsulinaemic hypoglycaemia (HH), the most common cause of persistent hypoketotic hypoglycaemia in neonate and infants, is a heterogeneous condition caused by dysregulated insulin secretion. Prompt diagnosis of HH and treatment is essential to prevent hypoglycaemic-related brain injury.<sup>1</sup> Transient forms of HH are associated with birth asphyxia, intrauterine growth-retardation, maternal diabetes mellitus or overgrowth syndromes such as Beckwith-Wiedemann syndrome.<sup>2,3</sup> Genetic forms congenital hyperinsulinism (CHI) is caused by mutation in the genes involved in the regulation of insulin secretion.<sup>3,4</sup>

### **Objectives And Methods**

We describe the presentation, genetic results, treatment and outcomes of eleven patients (median age of three on follow-up, age range from 1 to 14 years old) with CHI referred to our centre.

### **Results**

All presented with symptomatic non-ketotic hypoglycaemia at birth to 3 months old. Six had seizures. Diagnosis was suggested by a high glucose delivery rate  $> 10\text{mg/kg/min}$  at presentation and confirmed by detectable/elevated insulin levels on critical sampling. 6 patients (60%) were born with normal birth weight and 4 were large for gestational age. Genetic study was sent to Exeter Laboratory, United Kingdom for nine patients. Seven had positive results (5 ABBC8 gene, 1 KCNJ11, 1 GLUD-1) while two were negative for the common mutations tested. All patients were initially on diazoxide and hydrochlorothiazide. Seven were diazoxide-unresponsive but were able to maintain their blood glucose levels  $>3.5\text{mmol/L}$  on discharge with subcutaneous (SC) injections of short-acting somatostatin analogue (octreotide), dose range  $10\text{-}30\text{mcg/kg/day}$  divided four times daily. One patient was switched to long-acting SC Octreotide LAR  $10\text{mg}$  4-weekly at the age of 6 years and is doing well. Three patients had a focal form of disease suggested by the genetic results. Two underwent pancreatectomies in an overseas centre due to the unavailability of  $^{18}\text{F}$  DOPA PET scan locally.

On follow-up, 5 (45%) had episodes of documented blood glucose below the target range of  $<4.0\text{mmol/L}$  at home but were noted to be infrequent and asymptomatic. Four (36%) had suboptimal neurodevelopment outcome evidenced by global developmental delay, periventricular leukomalacia on MRI, epilepsy, and special education. Three (27%) have feeding issues requiring nasogastric feeding. Three (27%) had poor weight (BMI  $< -2$  SDS) attributed to poor dietary intake while one was obese (BMI  $> +2$  SDS) due to excess calories. All had normal growth (adjusted for mid-parental height SDS). Three patients referred from other states subsequently defaulted follow-up.

### **Conclusion**

Management of CHI is challenging especially those who are diazoxide-resistant. Prompt recognition and treatment to prevent hypoglycaemia is essential to prevent adverse neurodevelopmental outcome, which was observed in almost half of our cohort. Molecular diagnosis plays an important role in guiding treatment options and prognostication. The need for ongoing treatment in the absence of gene mutations in two of our patients suggests that there may be other novel genetic mechanisms. Surgical management for focal disease is limited in our local settings because of unavailability of  $^{18}\text{F}$ -DOPA PET scan.

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## VITAMIN D DEFICIENCY RICKETS IN THREE TODDLERS FOLLOWING COVID-19 PANDEMIC LOCKDOWN

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### Introduction

Nutritional rickets is a worldwide problem which has been increasingly reported in both high and low income countries. The highest burden of the disease however is reported in Asia, Africa and Middle East due to sun avoidance or dietary calcium deficiency. Three toddlers aged 1-2 years of age presented in March to April this year with bony deformities following one year of national Covid-19 pandemic lockdown since March 2020.

### Case presentation

Patient 1, aged 15 months old had bilateral wrist swelling for 1 month while patient 2, aged 20 months old and patient 3, aged 12 months old were noted to have leg bowing for 2 months. All 3 patients were breastfed till presentation without formula milk supplementation. Weaning occurred at 4-6 months of age but the complementary diet was deficient in micronutrients and calorie intake. Patient 1 and patient 3 were picky eaters and both toddlers had faltering growth. Patient 2 had atopic eczema since 3 months of age and was on a restrictive diet devoid of cow's milk, meat and dairy products. All 3 patients and their nursing mothers were mostly confined indoors with minimal sun exposure during the pandemic lockdown. Physical examination revealed frontal bossing, rachitic rosary and bowing of both lower limbs in all 3 patients. Bone metabolic profile confirmed vitamin D deficiency rickets evidenced by normal serum calcium, low serum phosphate, raised alkaline phosphatase, raised parathyroid hormone and low 25-hydroxyvitamin D levels. Bilateral wrist and knee X-Rays revealed splaying, fraying and cupping of radial, ulnar, femur and tibial metaphyseal ends. Splaying and fraying were also seen in the distal anterior ribs of the chest X-Rays. Patient 1 and patient 2 had concurrent iron deficiency anaemia. All three patients responded well to 2000-3000IU vitamin D3 and calcium supplementation for 3-6 months duration. In addition, patient 1 and patient 2 required iron supplements for 6 months.

### Conclusion

Vitamin D deficiency rickets appears to be an increasing problem in breastfed toddlers with the implementation of the prolonged movement control order. Picky eaters and young children on restrictive diets are particularly at risk of dietary micronutrient deficiencies. Early recognition of these at-risk groups during this pandemic is crucial so that early vitamin D supplementation can be commenced to prevent development of nutritional rickets.

## **SYNDROME OF INAPPROPRIATE ANTIDIURESIS(SIAD) IN CHILDREN: REPORT OF FOUR CASES**

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### **Background**

Chronic hyponatremia in children remains a challenge in terms of diagnosis and management. The syndrome of inappropriate antidiuresis (SIAD), is a disorder of sodium and water balance characterized by urinary dilution impairment and hypotonic hyponatremia, in the absence of renal disease or any identifiable non-osmotic stimulus to induce antidiuretic hormone (ADH) release. It is a diagnosis of exclusion and can have a genetic basis. We present here 4 members from 2 families who had hypotonic hyponatremia with relevant biochemical changes of SIAD.

### **Case Presentations**

The first 2 cases are a set of first cousins. Case 1 presented at 9 years old with clinical seizure and his cousin had incidental detection of hyponatraemia during an admission for otitis media at 2 years old. Both had global developmental delay and work-ups revealed no obvious diagnosis. The 3rd and 4th case are biological brothers. Case 3 also presented with clinical seizures at 3 years old while his older brother was detected a month later with acute gastroenteritis at age of 4 years old. Development was normal for the last two cases. There was no clear risk factor such as cerebral or pulmonary disorders, malignancies or drugs to explain the chronic hyponatraemia. All of them were euvolemia at presentation. Their biochemical profiles demonstrated features of SIAD, including isolated severe hyponatraemia (110 — 125 mmol/l) without hyperkalaemia, with low serum osmolality, inappropriate high urine osmolality and increased urine sodium excretion. All patients were treated with sodium supplement. Fludrocortisone was given at initial phase and managed to be wean off in Case 2 while at reducing dose for the other three cases. Genetic study was not available.

### **Conclusion**

SIAD itself is rarely encountered in children. A high index of suspicion is important in cases of chronic hyponatraemia, especially when no obvious aetiology can be found.

**RETROSPECTIVE STUDY ON PAEDIATRIC PATIENTS VISITING DOGBITE CLINIC IN HOSPITAL MIRI : A 3-YEAR PRELIMINARY REPORT (2019-2021)**

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Rabies is a fatal and vaccine-preventable viral disease that occurs in more than 150 countries and territories.<sup>1</sup> Usually, the virus is transmitted by a bite from an infected animal with dogs as the main source of human rabies deaths, contributing up to 99% of all rabies transmissions to humans. Sarawak has been endemic of rabies cases since July 2017 with the first reported death involving two children on 4 July 2017 in Serian Division.<sup>2</sup>

**Methodology:**

This is a descriptive retrospective study of the paediatric patients who attended Dog Bite Clinic (DBC) Hospital Miri from January 2019 until June 2021. Data was obtained from registry and documented forms in the DBC. The patient pool consists of children age less than 12 years old who were bitten or scratched or both by dog or cat or other animals such as monkey. Patient demographics, perpetrator ownership and vaccination status, risk assessment, treatments and well-being of the patients post 1 year of event were reviewed in this study.

**Result:**

A total of 709 patients from 1 year to 12 year old (424 boys, 285 girls, median age 6.5 years) were included in this study. Total number of attending children has reduced drastically from year 2019 to 2021. Perpetrator were mainly dogs and cats with 54.2% of patients were injured by dog while another 44.9% were bitten/scratched by cats. Own pet accounts for 80.39% of the cases. Among these animals, only 15.5% were vaccinated with another 68.7 % were unvaccinated and 15.8% unsure vaccination status. Provoked injury happened in 73.5% of the cases as 20.3% were unprovoked and 6.2% unsure mechanism. Risk assessment of the wound was categorized into 1 (2.3%), 2 (55.9%) and 3 (41.8%). For immediate management post-bite, only 5.1% of the patients had their wounds rinsed under running tap water for 15 minutes or more. Post exposure prophylaxis in the form of rabies vaccine were administered to 48.7% of the victims as scheduled, while only 2.3% of cases required Rabies Immuno Globulin (RIG) after discussion with paediatrician. 79% of the patients were prescribed with antibiotic. These children were followed up for a year at DBC or via phone review. Out of 482 children reviewed at 1 year, most of them are doing well (58.3%) while another 41.7% unsure health status. To date, there is neither positive human rabies case reported nor mortality occurred among our patients.

**Conclusions:**

This study is limited by a few factors such as knowledge of the attending doctors, unsure of positive rabies animals that has bitten the child. Bias and overtreatment of animal bite may contribute to the high usage of antibiotics and post exposure prophylaxis. Regular update and education of new doctors and local community is needed to improve the immediate care which confers most effectiveness in rabies prevention.

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## NEONATAL GRAVE'S DISEASE

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### Introduction:

Active Grave's disease in pregnant mothers may lead to neonates with hypothyroidism or hyperthyroidism. Neonatal hyperthyroidism occurs in 1-5% of infants born to mother with Grave's hyperthyroidism.

### Case Report:

Here we report a case of neonatal grave's disease in a neonate born to mother with Grave's disease. Mother was diagnosed with Grave's disease at 29 weeks and 5 days POA as she was symptomatic. Her TSH receptor antibody was 12.4 IU/L, and she was started on T. Carbimazole and T. propranolol during her pregnancy. Her Free T4 (FT4) prior to delivery was still high at 30.4 pmol/L and her Thyroid Stimulating Hormone (TSH) was <0.01 mU/L. Baby's cord TSH was 0.01 mU/L with FT4 of 30.64 pmol/L. Her Thyroid function test was repeated at day 6 of life, of which FT4 was increasing to 53.9 pmol/L and TSH was < 0.01 mU/L. She was then noted to have static weight with intermittent tachycardia and fever which was attributed to hyperthyroidism as her repeated FT4 was increasing in trend. She was started on Syrup Carbimazole at 0.2mg/kg/dose. Syrup Carbimazole was withheld after 5 days as repeated FT4 had dropped drastically to 29.1 pmol/L. This was then restarted after 1 week at a lower dose of 0.1mg/kg/dose as repeated TFT showed an increasing FT4. Subsequently, she was doing well under our follow up and Syrup carbimazole was weaned down gradually.

### Discussion:

There are many factors affecting incidence of neonatal hyperthyroidism, mainly being level of maternal serum thyrotropin. In our patient, mother had high TSH receptor antibody at 3rd trimester, specifically 5 times more than the upper limit, which predisposed our baby to neonatal hyperthyroidism. Symptoms of hyperthyroidism may develop between 10 to 20 days of life such as in our patient, symptoms developed at day 10 of life.

### Conclusion

All babies born to mothers with hyperthyroidism should be screened with a high index of suspicion. TSH receptor autoantibody should be taken if possible, or Thyroid Function Test at day 3-5 of life and again at day 10-14 of life to ensure that thyroid disorders are not missed in these babies.

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## **BIOCHEMICALLY NORMAL ADRENAL PHEOCHROMOCYTOMA FOLLOWING EXTENSIVE CENTRAL NECROSIS IN AN ADOLESCENT WITH VON HIPPEL-LINDAU GENE MUTATION**

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### **Background:**

Pheochromocytomas are rare in children, with a spectrum of clinical presentation such as hypertension, headache, tachycardia and diaphoresis. The diagnosis is usually established from a raised urinary or plasma catecholamine or their metabolites. A large majority of the paediatric pheochromocytoma cases are associated with genetic syndromes such as familial paraganglioma, multiple endocrine neoplasia type 2 and von Hippel-Lindau disease.

### **Case presentation:**

We present a previously well 11-year-old girl who manifested with a hypertensive crisis secondary to an adrenal tumour but with unexpectedly normal urinary metanephrine and catecholamine results. She was short of breath, pale and tachycardic on presentation. An urgent ultrasound to investigate the hypertension showed a well-defined hypoechoic solid lesion at the left renal hilar region with no internal vascularity or calcification. Abdominal computed tomography confirmed a well-defined encapsulated, non-enhancing hypodense soft tissue with a pronounced enhancement of the peripheral rim of viable tumour tissue described as the 'ring sign'. She improved spontaneously following the crisis and blood pressure was controlled with single anti-hypertensive agent (prazosin). She underwent laparoscopic left anterior adrenalectomy four months later. Intra and post-operatively were uneventful and haemodynamically stable. The histopathological study confirmed a pheochromocytoma with large central necrosis and a Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) of 4. Her genetic screening reported a pathogenic von Hippel-Lindau (VHL) gene mutation. On follow-up, she was normotensive without treatment, surveillance urine metanephrines and whole body scan detected no other tumours or evidence of metastatic lesions.

### **Conclusion:**

Following the catecholamine crisis, an acute infarct occurred, resulting in extensive tumour necrosis and subsequent rapid remission of symptoms and paradoxically normal biochemical markers. Although not unheard of in adults, we believe this is the first reported case of a spontaneous extensive necrosis resulting in a biochemically normal pheochromocytoma in an adolescent.

## **SPINAL MUSCULAR ATROPHY TYPE 0 - MORE OF A CURSE THAN A BLESSED BUNDLE OF JOY**

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Spinal muscular atrophy (SMA) is one of the most common autosomal recessive disease, neurodegenerative, and characterized by progressive symmetrical muscle weakness, affecting approximately 1 in 10,000 live births. The disease is conventionally classified into four phenotypes. This case report describes a rare phenotype of very severe SMA in a newborn with immediate clinical presentation at birth, SMA type 0. More research should be dedicated to investigate the genetic determinants of its widely variable phenotypes.

### **Case Report:**

This newborn was the second male child of non-consanguineous parents. He was born with good Apgar score 9/10 via vaginal delivery at 39 weeks with a healthy weight of 2990g. Although alert and well saturated under room air, he was extremely floppy thus admitted to neonatal intensive care unit for further assessment. Mother is a 29-year old, para 2, antenatally uneventful, with another living male child, currently 3 years of age and growing well. He appeared comfortable at rest, not dysmorphic, pink, alert, with obvious paucity of movements over all limbs. He had head lag with absence of deep tendon reflexes and poor tone. Other systemic examinations were unremarkable. Cranial ultrasound showed normal appearance of brain and ventricles with no signs of hemorrhage, chest radiograph revealed no obvious pathology. He had normal thyroid function test, creatinine kinase, metabolic screen of amino acids and acylcarnitine were unremarkable. MRI Brain normal study, with no signs of hypoxic ischemic encephalopathy. Genetic studies showed there was homozygous deletion of SMN1 gene. The diagnosis was fully explained to parents and the baby was discharged to the local hospice for compassionate care after which he rapidly deteriorated and passed away at age 4 months.

### **Discussion:**

SMA type 0 variant has a fatal course, with most dying by age 3 months. Unlike most SMA infants diagnosed at a later infantile period presenting with pneumonia and incidentally found to be neurologically floppy, SMA type 0 presents soon after birth, at times even intrapartum whereby mother complaints of obvious cessation of fetal movements. Our infant has 2 copies of SMN2 from the genetic study, however, considering the characteristics were evidenced since birth confirms the diagnosis of the lethal form. In conclusion, a strikingly alert infant with profound hypotonia presenting immediately at birth affirms the most severe form, SMA type 0.

## CHALLENGES IN MANAGING CONGENITAL HYPERINSULINISM IN A DISTRICT HOSPITAL: A CASE REPORT

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### Introduction:

With the advance technology, genetic study such as next generation sequencing test or whole exome sequencing has made diagnosis easier and faster for critically ill children. However, in a developing country without the luxury of appropriate laboratory support, clinical diagnosis remains the mainstay of management. This case illustrates the challenges in managing a rare disease in a district hospital.

### Case:

DD was a two-month-old Iban boy who presented with fever and seizure episode. DXT taken on arrival at emergency department was 0.8 mmol/L. He was treated for meningitis, and we had difficulty maintaining normoglycemia even though he was not septic. He required hypertonic glucose infusion up to D20% with the highest GIR of 19.3mg/kg/min. Various methods were attempted which include kept him nil per oral with high dextrosity drip, giving infusional feeding, adding polycose in the feeding, giving high feeding volume. Until day 5 of admission, we had difficulty getting intravenous access, IM glucagon was given. His blood glucose responded well to glucagon. Hence, glucagon infusion was resumed once IV line was obtained. His critical sampling did not correspond with congenital hyperinsulinism, as the blood taken during DXT 1.1mmol/L showed RBS: 4.6mmol/L, C-peptide: 1691 pmol/L, serum insulin: 18.2 mIU/L, random cortisol: 48.1 nmol/L. Diagnosis of congenital hyperinsulinism was made based on clinical response to glucagon after discussion with paediatric endocrinologist at another tertiary center. Child was kept for 2 months to ensure proper understanding of hypoglycemia education plan. DD was discharged with oral diazoxide but he was readmitted a next day upon finding out that the mother did not take his medication on discharge and they did not have a refrigerator to keep glucagon for emergency use. DD was kept in ward for another month to sort out social issue and to reinforce parental education. 3 weeks after discharge, he was brought in dead after having 3 days of fever and seizures at home. DXT was ranging 1—3 mmol/L. Post-mortem was performed. As his blood test sent to Exeter lab was negative, pancreatic tissue was taken and sent to Exeter lab which result is still pending.

### Conclusion:

This case has posed much challenges from inexperience of the treating physician on managing congenital hyperinsulinism to educating the parents. With the limitation of healthcare facilities in a district hospital, much effort was invested in getting opinion from the expert, accessing to medication and laboratory support in order to manage this child. Perhaps with the improvement in healthcare system, earlier diagnosis and intervention could be offered.

## **EFFECTS OF COVID-19 ON GLYCAEMIC CONTROL IN YOUNG PEOPLE WITH TYPE 1 DIABETES MELLITUS IN MIRI GENERAL HOSPITAL**

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### **Introduction:**

The emergence of severe acute respiratory syndrome coronavirus 2 (COVID-19) in China in December 2019 and the declaration of a pandemic by the World Health Organisation (WHO) by March 2020 led to national lockdowns in most countries globally<sup>1,2</sup>. Closures of schools with limited outdoor activities resulted in marked changes in patients' routines. Currently in Malaysia, schools and various establishments are gradually re-opening. Our study aims to evaluate the impact of lockdown on young people's diabetic control.

### **Methodology:**

This retrospective study involved eight patients with mean age of  $12.61 \pm 4.22$  years who were under follow-up in the outpatient paediatric clinic in Miri General Hospital for Type 1 Diabetes Mellitus (T1DM). A standardised questionnaire regarding lifestyle changes and feasibility of insulin administration was carried out among these patients who were contacted via telephone. Glycated haemoglobin (HbA1c) levels before the lockdown for year 2019 and during the lockdown from years 2020 to 2021 were compared.

### **Results:**

Half of the group (group A) showed improvement in their HbA1c levels. The other half (group B) showed worsening glycaemic control. For group A, the average HbA1c before lockdown was 10% and after lockdown was 9%. For group B the average HbA1c was 8.3% before the lockdown and 8.8% after the lockdown. Fifty percent of the patients found it more convenient to administer insulin during the pandemic, however of that only 25% had better glycaemic control (p-value: 1). Despite having more time at home, none of them exercised more and 62.5% had poorer eating habits. However, the pre- and post-lockdown differences in HbA1c in relation to these two factors were not statistically significant (p value: 0.537) in this study. Seventy-five percent were stressed about attending follow-up due to the fear of contracting COVID-19.

### **Conclusion:**

During the COVID-19 pandemic, many patients experience stress and have more unhealthy habits. Though this study did not show that lockdown was associated with a significant deterioration in glycaemic control in the short-term, more attention should be paid to stress and lifestyle factor management in patients with T1DM as the pandemic is still ongoing.

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## **EPIDEMIOLOGY OF CONGENITAL HYPOTHYROIDISM AND MANAGEMENT PLANS IN SOUTHERN KELANTAN : A REGIONAL COHORT STUDY**

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### **Background:**

Congenital Hypothyroidism (CH) is the commonest treatable condition for mental retardation if started treatment early within 2-4 weeks. Malaysia has started our own newborn TSH screening programme since 1998. Objectives: The aim of this study was to evaluate CH patients diagnosed in our paediatrics clinics of our region, evaluating their demographics, percentage of transient hypothyroidism and different treatment strategies.

### **Methods:**

In a retrospective cohort, patients under follow up in Paediatrics clinic Hospital Sultan Ismail Petra, Kuala Krai and Hospital Machang in the year of 2021 ( 80 patients ) for CH were reviewed. Collected data consisted of patients' demographics, clinical characteristics, biochemical and clinical parameters for starting thyroxine, treatment initiation timing and requirement of thyroxine beyond 3 years of age. In addition, thyroid ultrasonography scans and radioisotope scans results are evaluated as well.

### **Results:**

80 patients (45% females, 55% males; median age 2.68 years) were included in this study. Median age of starting treatment is 28 days old, with mean TSH upon starting 20.22 mIU/l. We identified the majority of our patients are diagnosed following prolonged jaundice workup (56.3%). Mean dose of levothyroxine started was 7.5 mcg/kg/day with median of 23 days to achieve normal TFT. Among the 37/80 patients are above 3 years old, and 9/37 could be off thyroxine giving a percentage of 24.3% transient hypothyroidism in our cohort. We have performed 26 thyroid ultrasounds and 50% are hypoplastic gland, 7.7% thyroid agenesis and 42.3% are normal. Of the 4 radioisotope scans we did for the patients, only 1 was ectopic thyroid gland while the others were normal scans.

### **Conclusions:**

Clinicians must be updated with the latest guidelines on diagnosing and treatment of CH. Future studies need to be carried out to capture the incidence of CH in the region and linear growth or intellectual abilities of patients with CH.

## OVERVIEW OF PAEDIATRIC PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA IN HOSPITAL SULTAN ISMAIL JOHOR BAHRU

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### Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder involving impaired synthesis of cortisol from cholesterol by the adrenal cortex.[1] There are two major phenotypes, classic and non-classical CAH.[1] The commonest cause of CAH is 21-hydroxylase deficiency (21-OHD), accounting for more than 95% of cases.[1] The incidence of CAH is approximately 1 in 10,000 - 15,000 livebirths.[1] Classic CAH can be divided into "salt losing" (75%) and "simple virilising" (25%).[1] Salt losing CAH often presents with adrenal crisis in newborn while simple virilising CAH often presents with ambiguous genitalia. Non classical CAH usually presents later in life with hyperandrogenism features.[1]

### Methodology

This is a cross-sectional descriptive study of all patients with CAH under paediatric clinic in Hospital Sultan Ismail Johor Bahru. Retrospective data on gender, ethnicity, age of onset, types of CAH, clinical presentation, complications, family history and treatment were collected from the patients' medical records. All cases were reviewed by paediatric endocrine team, Hospital Putrajaya.

### Results

There are 16 patients with CAH included in the study. There were 10 male patients (63%) and 8 female patients (37%). Majority are Malays at 81% and 19% are Chinese. The mean age of patients were 9.3 years (5 months – 19 years). The median age of onset was 1 month (1 week - 6 years old). 12 cases (75%) are classic salt losing CAH and 4 cases (25%) are simple virilising CAH. All salt losing CAH cases presented at age below 3 months with 10 cases (83.3%) presented during neonatal period. Seven cases (44%) have positive family history. Seven cases (44%) had ambiguous genitalia and 6 cases (38%) had hyperpigmented skin. All salt losing CAH presented with salt losing/adrenal crisis and 1 simple virilising CAH case presented with adrenal crisis at 6 years old. Fourteen (87.5%) had 17-hydroxy progesterone >60 nmol/L at diagnosis. Fourteen patients (87.5%) are on Hydrocortisone and Fludrocortisone and 2 patients on Prednisolone. Complications include short stature (8 cases, 50%), advanced bone age (6 cases, 37.5%), metabolic syndrome (3 cases, 18.8%), testicular adrenal rest tumor (2 cases, 12.5%) and precocious puberty (1 case, 6.3%).

### Discussion

Salt losing can lead to adrenal crisis which is life threatening and should be suspected in any ill patients with persistent electrolytes abnormalities and hypoglycaemia especially in presence of ambiguous genitalia or hyperpigmented skin. Early referral to paediatric endocrinologist is essential. Prenatal counselling, genetic testing and close monitoring of subsequent sibling are recommended in cases of positive family history. CAH patients need close monitoring with emphasize on compliance of treatment to reduce complications. Newborn screening for CAH is desirable in Malaysia as many cases presented with salt losing and diagnosis was delayed.[2]

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## MY BABY GREW A TAIL: A CASE REPORT

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### Introduction

Extragenital germ cell tumours (GCTs) are GCTs arising outside the testes or the ovaries. Sacrococcygeal teratoma (SCT) is a neonatal neoplasia affecting one in every 27000 live births. SCT is predominantly seen in the female with one-to-four ratio. SCT is mostly benign, but it can recur as malignant teratoma.

### Case report:

We report a baby girl born term at 39 weeks via spontaneous vaginal delivery with a birth weight of 3.22 kg. Antenatally, the mother had Gestational Diabetes. She was referred for undetected mass antenatally at the coccygeal region with respiratory distress.

Initially she was treated for Congenital Pneumonia and was able to wean off oxygen at 32 hours of life. She had a mass measuring 3cmx3cm with membranous sac, less than 1 cm from the anal verge. Clinically, there were no dysmorphism and other systemic examinations were normal.

Full blood count on admission revealed Haemoglobin 20.3g/L, Platelets 358 x 10<sup>9</sup>, and Total white count 22.3 x 10<sup>4</sup>. C-Reactive Protein (CRP) was <5 mg/dL. Blood Culture showed no growth.

Renal profile revealed urea 1.8 mmol/L, potassium 4.2 mmol/L, sodium 137 mmol/L, and creatinine 28 µmol/L. Liver function test showed aspartate aminotransferase (AST) 40 U/L, alanine aminotransferase (ALT) 25 U/L, alkaline phosphatase (ALP) 250 U/L, total protein 55 g/L, albumin 35 g/L, total bilirubin 218.1 µmol/L and direct bilirubin 12.9 µmol/L.

Serum alpha-feto protein (AFP) done at Day 1 and Day 7 of life were > 2479.00 IU/mL and 25228.00 IU/mL respectively.

Ultrasound (USG) Abdomen, Pelvic and Spine revealed a well-defined predominantly cystic mass with solid components from the left para-midline gluteal region. It measured 1.8cm x 3.3cm x 4.3cm (AP x W x CC) with no communication seen with the sacral bone or spinal canal.

Echocardiography revealed Patent Ductus Arteriosus of 1.3 mm. Screening Ultrasound Cranium was normal. She was reviewed by the paediatric surgeon and a repeated USG Abdomen, Pelvic and Spine revealed a pedunculated left paramedian external mass with predominantly cystic component seen in the buttock region. It measured approximately 1.3cm x 3.8cm x 3.9cm (AP x W x CC) with presence of septation within the mass.

Surgical resection of the tumor with coccygectomy was done with findings of pedunculated tumor arising from the coccyx, measuring 6x4cm with part of tumor ruptured. HPE revealed mature teratoma.

### Discussion:

Early diagnosis of SCT antenatally will help in fetal monitoring, planning of delivery and early surgical resection. Traumatic delivery should be avoided as SCT is a highly vascular tumour. Continuous follow-up post resection should be done for the following three years as the rate of recurrence is 4%. Level of AFP should be monitored serially and by eight to nine months post resection, the level should be reducing to normal adult level. With sudden increase of AFP level and no mass seen at the previous resection site, imaging is warranted.

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