CAPE NEWS

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Contents

From the Editor's Desk

Dear ISPAE Members,

Greetings from Team CAPE NEWS!
While we are struggling with hardships of lockdown and trying to keep ourselves safe and healthy, working as frontline warriors, we do have the challenge of normalising the situation as far as possible and maintaining routine and regularity in our daily lives.
In pursuit of this, we planned to come out with this issue of CAPE NEWS even if we had very few contributions due to obvious reasons. Finally, the members responded with enthusiasm, and we received bestowals in good numbers!
In this issue, we have included recommendations of various international societies on the management of children with endocrine disorders during the COVID pandemic, along with other standard sections of the CAPE NEWS.
Happy reading,
Stay safe and healthy!

Rakesh Kumar and team CAPE NEWS

Message from the ISPAE Office Bearers

Dear All,

These are testing and stressful times in the wake of Covid-19 pandemic. We hope you and your family are well and safe.
Our daily routine has changed because of the viral spread and the resulting lockdown, but we still have our duty to take care of our patients with whatever resources available to us. All of us have tried to do our best in this situation. One group of patients i.e. people with diabetes are vulnerable. Diabetes does not increase the risk of infection per se but can worsen the condition. ISPAE website has a link for management of covid and diabetes https://www.ispae.org.in/download_docs/Corona_Care_ISPAE_HINDI.pdf
The diabetes patient information page is at https://www.ispae.org.in/Diabetes.php

Continuing education is equally important for us medical professionals. We need to update our knowledge for good care of patients. ISPAE members on their own or along with IAP (central, state chapters or district chapters) have organized multiple webinars on important topics of pediatric endocrinology.

We need to lead by example by following all norms of physical distancing wearing face masks in public and avoiding gatherings. In addition, we need to educate all those who work with us or we come in contact with. This will be a great service to the community.

Take care and be safe

Leena Priyambada
Ahila Ayyavoo
Preeti Dabadghao

Hearty Welcome to New ISPAE Members

S.No	Name	Affiliation
1	Dr Suraj Gobain (MD Pediatrics)	St Augustine Hospital, Chapaguri, Bongaigaon, Assam.
2	Dr Khurshid Ahmed Bhat (DM Endo, SGPGI)	Endocrinologist, Kashmir Clinics, Srinagar, Kashmir

Message (Poem) from a child with T1D……

एक डॉक्टर हूँ मैं.....

एक डॉक्टर हूँ मैं ,
भगवान ना कहना मुझे ,
रोगियों के जीवन का -
साहारा हूँ मैं ।
एक डॉक्टर हूँ मैं ।

जात-धर्म पूछे बिना
उपचार करना धर्म है मेरा ,
स्वस्थ रहे यह संसार हमारा
यही सुबह का सुमिरन मेरा ।
एक डॉक्टर हूँ मैं ।

आदि काल से निभाता आ रहा
निस्वार्थ सेवा का धर्म मैं अपना ,
देश समाज की सेवा में मैं
कभी - कभी कर लेता हूँ -
स्वास्थ्य क्षीण मैं अपना ।
एक डॉक्टर हूँ मैं ।

शत्रु , मित्र, ऊंच, नीच
सबके दुखों का मैं हरनकारी,
खाँसी, जुखाम, सर्दी, बुखार,
हर स्थिति में मैं कल्याणकारी ।
एक डॉक्टर हूँ मैं ।

कभी आधी रात ,एक फोन से आई
पुकार पर
मैं नींद त्यागकर जाता हूँ ,
कभी किसी अनजाने की खातिर मैं
पूरी रात जागता हूँ ।
हाँ , एक डॉक्टर हूँ मैं ।

तुम्हारी मौत से लड़कर भी मैं ,
भगवान की उपाधि नहीं चाहता हूँ
इस सेवा के पथ पर चलकर मैं ,
सम्मान पाना चाहता हूँ ।
एक डॉक्टर हूँ मैं ।

भगवान राम के काल से –
सुषेण से लेकर
मानव काल के चरक सुश्रुत तक
निस्पक्ष सेवा करता आया हूँ ,
अब इस कोरोना की लड़ाई में
मैं हर दुखी को सुखी करने आया हूँ
एक डॉक्टर हूँ मैं ,
हाँ , एक डॉक्टर हूँ मैं ....

-दि[redacted]
(18 year, T1D for 7 years)

'D' has a condition called "H Syndrome" and T1D as part of the syndrome. He is under regular follow up Pediatric Endocrinology and Diabetes Unit at PGIMER, Chandigarh. He has a very caring and loving family. He has joined his B Tech course last year in a prestigious engineering Institute of the country.

ISPAE OBSERVERSHIP AWARDS 2019-20

Dr Mahesh Maheshwari, Professor, Pediatrics, AIIMS, Bhopal

Completed his

ISPAE Observership at Department of Endocrinology, SGPGI Lucknow

I recently completed my one-month ISPAE observership at the Department of Endocrinology, SGPGI, Lucknow from 17th February to 17th March 2020 under the guidance of Professor & Head Dr Eesh Bhatia, Professor Vijayalakshmi Bhatia, Professor Preeti Dabadghao and Dr Siddhnath Sudhansu.

The observership has given me the opportunity to learn clinical aspects of different endocrine disorders in children along with in depth academic discussion with the facultiy and other department colleagues. As the Institute runs four Pediatric Endocrinology clinics and one Diabetes clinic per week, with multidisciplinary support on an outpatient basis, it provides a high chance to see and manage lot of new and follow-up endocrine problems. Communication during counselling, education, training to children with diabetes and their parents, and meticulous record keeping are exemplary in SGPGI.

The Department has very a good in-house laboratory establishment and lab support. I observed and performed many hands-on hormonal assays during my training. I performed many dynamic tests in the pediatric endocrinology ward and learnt the interpretation of results in different clinical settings. During my training I also visited the Genetic Department and learnt the fundamentals of genetic testing. I also learnt the procedure and interpretation of results for bone density assessment in different bone metabolic disorders.

An important aspect of my observership was the academics. The Department regularly organizes teaching sessions with strong research-based knowledge. I actively participated in all bedside and intra-departmental teaching sessions, as well as the inter-departmental sessions with Pathology, Nuclear Medicine and Radiology. I discussed various research ideas with the faculty members and developed a plan for establishing the Pediatric Endocrinology division at AIIMS Bhopal.

This training program has increased my interest and knowledge in Pediatric Endocrinology. The guidance and learning I received will help me in strengthening the existing Pediatric Endocrinology services and starting the Pediatric Endocrinology division at AIIMS Bhopal. This training stimulated an unquenchable thirst for knowledge and the need to learn and grow constantly.

I am very grateful to my Institute for permitting me to attend this training and to my mentors for their guidance, support and amazing hospitality during my stay at SGPGI. It was a great opportunity to interact with young bright academic fellows and make them friends. Lastly, I would also like to thank ISPAE for giving me this opportunity as an ISPAE Observership Awardee 2019-20 for training in this premier institute. Such an opportunity as getting this Award is really a boost for interested faculty members in establishing Pediatric Endocrinology in their respective institutions.

Dr Mahesh Maheshwari, Professor of Pediatrics & In charge-Pediatric Endocrinology
AIIMS Bhopal (Madhya Pradesh). drmaheshkiran@gmail.com/9425428596

Excerpts from recent Guidelines

RECOMMENDATIONS FOR PEDIATRIC ENDOCRINE PATIENTS DURING COVID-19

Compiled by Dr Nikhil Lohiya, Consultant Pediatric Endocrinologist, Dr DY Patil Medical College, Hospital & Research Center, & Jupiter Hospital, Pune

ISPAD Summary of Recommendations Regarding COVID-19 in Children with Diabetes

https://www.ispad.org/news/494473/COVID-19-and-Children-with-Diabetes.html

Concern	Recommendation
How to contain the pandemic and prevent the infection?	• Wash your hands frequently with soap and water for 20 seconds or clean with alcohol-based hand rub. • Maintain social distancing (1 meter or 3 feet). • Cough or sneeze into tissue or elbow. • Avoid touching your face. • Sanitize surfaces frequently.
Should patients with diabetes attend school?	• It depends on the situation in your region. Follow local regulations and policies.
What should I tell my patient in case of symptoms?	• If your patient is feeling unwell, he/she should stay at home. Patients who have fever, cough and/or difficulty breathing, should seek medical attention and call in advance. Follow the directions of the local health authority.
How to control diabetes during illness?	General sick day diabetes management principles (modified from ISPAD Guidelines): • More frequent blood glucose and ketone (blood or urine) monitoring. • Aim for a blood glucose level between 4 and 10 mmol/L (70-180 mg/dL) and blood ketones below 0.6 mmol/L when the child is ill. • NEVER STOP INSULIN: If there is FEVER, insulin needs are usually higher. • Monitor and maintain hydration with adequate salt and water balance. • Treat underlying illness and symptoms (fever).
URGENT specialist advice with possible referral to emergency care must be obtained when:	• Fever or vomiting persist and/or weight loss continues, suggesting worsening hydration and potential circulatory compromise. • Fruity breath odor (acetone) persists or worsens / blood ketones remain elevated >1.5 mmol/L or urine ketones remain large, despite extra insulin and hydration. • The child or adolescent is becoming exhausted, confused, hyperventilating (Kussmaul breathing), or has severe abdominal pain.

While we wait for a specific treatment or vaccine against coronavirus, we should take good care of our patients. It is reassuring to remember that reports of COVID-19 infection suggest that it is less severe in children and adolescents.

ESPE- COVID-19 INFORMATION FOR CHILDREN AND ADOLESCENTS LIVING WITH ENDOCRINE CONDITIONS, INCLUDING TYPE 1 DIABETES MELLITUS

(Can be given as a handout to patients)

https://www.eurospe.org/news/item/14064/COVID-19-information-for-children-and-adolescents-living-with-endocrine-conditions-including-type-1-diabetes-mellitus

What is the risk: There are *no reliable data* suggesting that children with well-managed endocrine conditions (including type 1 diabetes mellitus) are at increased risk of getting infected or becoming severely ill with coronavirus (CV). Also, it is encouraging to know that CV illness generally has a milder course in children. However, poorly controlled diabetes mellitus can weaken immunity and thereby increase the risk of getting infected by the virus. There are some indications that otherwise healthy, but severely obese, children are at increased risk of greater lung involvement in a COVID-19 infection. New data is becoming available each day; in the meantime, parents and caregivers of children with endocrine conditions are advised to be vigilant to prevent COVID-19 infection by strict application of preventive measures.

How to minimise the risk: Wash hands frequently, maintain social distancing and implement protective measures at all times. This of course applies both to parents and caregivers, as well as children.

School and isolation: Children with diabetes and other endocrine conditions should follow local regulations regarding school and self-isolation. If home-based remote learning is an option, this mode of school attendance currently represents a safer approach for all children, including those with endocrine conditions.

In case of symptoms: Please call your physician (or the emergency telephone number), explain the symptoms and follow the official medical advice. For most mild cases, home rest in self-isolation is sufficient, but this decision should not be made solely by parents or caregivers. To repeat – please consult your physician and follow official medical advice.

Type 1 diabetes management during CV illness: Children with well-managed diabetes are expected to have the same course of illness as their peers. We recommend following the general advice for "sick day" management by the International Society for Pediatric and Adolescent Diabetes (ISPAD) and contacting your pediatric endocrinologist. Do not stop insulin treatment, increase the dose as needed, and frequently measure blood glucose and ketones.

Adrenal insufficiency management during CV illness: If the child becomes symptomatic, we recommend increasing the hydrocortisone dose, according to the general "sick day rules" in children with adrenal insufficiency due to congenital adrenal hyperplasia (CAH), panhypopituitarism (pituitary failure), Addison's disease, after long-term use of steroid medication, or any other cause. Follow your endocrinologist's standard advice on "sick day" management, and if unsure give an extra dose of hydrocortisone and immediately contact your endocrinologist or emergency care physician.

Other endocrine conditions during CV illness: In the case of CV illness in children with various other endocrine conditions, we expect the same course of illness as their peers and recommend following the usual management advice for sick children.

Insulin, hydrocortisone and other medications supply during the global outbreak: Although you should always have enough supplies of insulin/ hydrocortisone/ other medications for at least a week in advance, we do not recommend stocking up larger quantities of insulin or other medications, since this could endanger the supply chain and lead to regional or global shortages. At the present time, there have been no reports on the shortage of insulin or other medications. Please maintain the usual amount of back-up insulin/ medications and follow the local regulations and announcements.

Please bear in mind that our current knowledge on COVID-19 is limited by the lack of data, and further information and guidance will be provided as new data becomes available. Please stay connected and follow future updates from the WHO, ESPE and, for children with type 1 diabetes, from ISPAD.

Please wash your hands frequently, stay at home as much as possible and at least 1.5 meters away from non-family members.

MINI-REVIEW

Need for Hospital Visit during Covid-19 Pandemic– A brief guidance to the parents of children with hormone problems

Dr Sirisha Kusuma B, Consultant Pediatric Endocrinologist, Rainbow Children's Hospital, Madhapur & Hydernagar, Hyderabad.

The world has changed from the way we know it in the last couple of months due to the unprecedented Covid-19 pandemic. With a vaccine not yet on the horizon, social distancing is going to be the new normal for the foreseeable future. For the next few months, it is prudent to limit in-person hospital visits as much as possible for the safety of patients as well as healthcare workers. However, it is also important to know when NOT to hesitate to visit the emergency department.

Hormone problems are often chronic conditions and these children need to be in regular contact with their endocrinologist. Necessity brought by this pandemic opened new ways of doing so. Increasing numbers of hospitals and individual physicians are becoming available for video and teleconsultations, and most hospitals are open for emergencies even during lockdown. It is essential for parents to be vigilant, recognize and treat emergencies early, prevent them when possible, and finally know when to take their child to the hospital. Depending on the type of hormone problem the child has, here is some advice on how to prevent and respond to common emergencies.

1. TYPE 1 DIABETES

EMERGENCY: Persistently high blood glucose levels (> 250-300 mg/dl) especially when child is unwell (fever, vomiting, loose stools, stomach pain, lethargy/dull, or sleepy)

Check Ketones if you have blood ketone strips or urine ketodiastix.

- If blood ketones are > 0.6 mmol/L, or urine ketones are more than trace present, your child needs more Insulin.
- Check and see if your insulin is working or not. Regular insulin (e.g. Actrapid) and all newer (analog) insulins should be as clear as water, not cloudy or lumpy. NPH will be cloudy but not lumpy. Insulin will not work if it is frozen or kept in direct sunlight and heat. Change vial/pen if in doubt.
- Follow sick day rules as advised by your doctor, by giving extra liquids, and extra insulin every 3-4 hours. If not sure what to do, contact your doctor by video consult, WhatsApp consult or phone message.
- Check ketones every time child passes urine. If blood glucose continues to be high and ketones are moderate to strong positive, you need to visit the emergency room.

If ketones checking is not possible at home:

Try and follow sick day rules by giving extra insulin as advised by your doctor. Contact your doctor. Visit the emergency room if the child continues to have high blood glucose, is lethargic, dull, complaining of stomach pain, or has nausea or vomiting.

2. TYPE 1 DIABETES,

PHHI (persistent hyperinsulinemic hypoglycemia) and

CAH (Congenital adrenal hyperplasia) on HISONE replacement

EMERGENCY: Severe Hypoglycemia: Low blood sugar (<70 mg/dl) with drowsiness, unresponsive or seizures

If Inj. Glucagon available:

- Administer Inj. Glucagon (0.5 ml if the child weighs less than 25 kg, 1ml if the child weighs more than 25 kg) on the lateral thigh intramuscularly or subcutaneously.
- In 10-15 minutes, the child is expected to regain consciousness. Check blood glucose again and give a small snack (e.g. a glass of milk or a slice of bread). If the child continues to be not responsive, take him/her to the hospital immediately.

If Inj. Glucagon is not available at home:

Take the child to hospital immediately for IV glucose injection. DO NOT try to force sugar water into the child's mouth. While going to hospital, make a paste of glucose powder with a little water and rub this paste between child's gums and lips.

PREVENT HYPOGLYCEMIA IN ILLNESS:

If Type 1 Diabetes:

- Check blood glucose more frequently, especially if the child is not well (fever, loose stools, vomiting). If blood glucose is consistently less than 100 mg/dl, decrease insulin doses.
- If the child does not accept food, or vomits after taking the insulin dose, try to give sips of sugar containing liquids (ORS, fruit juice, thin lassi, diluted milk with sugar) to prevent hypoglycemia.
- Try to purchase Inj. Glucagon and keep stock at home.

If PHHI and on Tablet Diazoxide:

- Follow the same advice as above.
- Keep Inj. Glucagon at home as emergency medicine.

If CAH on Hisone tablets:

If the child is unwell (fever, vomiting or loose stools), **give STRESS DOSE of Hisone.** DO NOT FORGET. Stress dose is usually 3 times the usual dose of Hisone. If the child is on Floricort also, there is no need to increase the dose of Floricort.

If the child seems very dull, sleepy, if his/her hands and feet are cool to touch, he/she needs immediate Hydrocortisone injection. Take the child to nearest hospital.

- Try to purchase Inj. Hydrocortisone and keep it with you. Any local RMP can administer the injection on lateral thigh.

Dosing:

Up to age 3 years: 25 mg Hydrocortisone IM/IV
3-12 years: 50 mg Hydrocortisone IM/IV
> 12 years: 100 mg Hydrocortisone IM/IV

Further dosing every 6 hours if the child continues to be unwell (better to contact your doctor)

Up to 3 years: 10 mg IV/IM every 6 hours
3-6 years: 15mg IV/IM every 6 hours
More than 6 years: 25 mg IM/IV every 6 hours.

3. THYROID, PUBERTY & GROWTH and other disorders:

All children on thyroid medication, puberty medication (for early or delayed puberty), and growth medication should continue to take medication as usual. They **can postpone any routine 3 monthly doctor visits for a month or two.** If you run out of medicines, you can

purchase more, and continue same dose as before, till you see the doctor again. When possible and when needed, contact your doctor by **video consultation.**

For children with Type 1 Diabetes:
If you are facing trouble procuring the Insulins you can use some insulins interchangeably for a time period, e.g.: - Actrapid, Humulin-R, Humalog, Novorapid, Apidra and Fiasp can be used interchangeably as a temporary replacement
- Lantus, Basalog, and Tresiba can be used interchangeably as a temporary replacement.

Here is a list of numbers to contact to get Insulin supply

FOR CIRCULATION ON BEHALF OF RSSDI: PLEASE CONTACT THESE NUMBERS FOR INSULIN SUPPLIES ANYWHERE IN THE COUNTRY. THEY WILL HELP PERSONS WITH DIABETES. KINDLY ENSURE THEY SHOULD CONTACT COMPANIES WHOSE INSULIN THEY ARE ON

COMPANY	CONTACT PERSON	HELPLINE PHONE NO.	WHATSAPP NO.	EMAIL
BIOCON	DR.PRAVEEN	18004257667	9820068508	livingpatientcentricity@biocon.com
CIPLA	HELPLINE REPRESENTATIVE	9099306000	GIVE A MISSED CALL TO THE CALL CENTRE	www.myinsulincare.com
KOYE	SUHAIL MOTLEKAR	9133711055	9833403524	suhail.motlekar@koye.com
LILLY	PRABHAT BHATIA	18001230021	COMPLETE COMMUNICATIONS ON HELPLINE	lillypsp@hcah.in
LUPIN	SOBHAN PAUL	98230655003	9830655003	sobhanpaul@lupin.com
NOVO	HELPLINE REPRESENTATIVE	18001039527	8040303200	INagree@novonordisk.com
SANOFI	DR FAHEEM	1800222295	9892623290	Medinfo.india@sanofi.com
WOCKHARDT	MAHENDRA SAGGU	8863949494/8862949494	9930079275	msaggu@wockhardt.com/diasolhelp@squer.co.in

TEAM RSSDI

Case Report 1

Diagnosing Hyperinsulinism/Hyperammonemia (HI/HA) Syndrome masquerading as Childhood Epileptic Encephalopathy with Intractable Seizures: Game changer in management!

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Abstract: A 4yo girl born of non-consanguineous parentage presented with poorly controlled seizures since the age of 11 months. There was global developmental delay with no focal neurological signs or neuro-cutaneous markers. She was diagnosed as having idiopathic West syndrome and epileptic encephalopathy at two different neurological centers and had been on five anti-epileptic drugs prior to her current visit. While blood counts and routine chemistries were normal, past work up had revealed hyperammonemia with normal levels of amino acids and acylcarnitine on tandem mass spectrometry. Chromosomal analysis was 46XX with no evidence of micro-deletion and methylation disorders. MRI brain had shown moderate thinning of corpus callosum while EEG showed generalized slowing. At her current presentation she was seen to have increasing frequency of myoclonic jerks which progressed to generalised tonic clonic seizures. On evaluation, she was noted to have an incidental venous plasma glucose of 22 mg/dl and an inappropriately elevated Insulin (9.7 mU/L) and C-peptide (1.71 ng/ml) levels at the time of hypoglycemia. Thyroid and adrenal hormones were normal. Structural (CT scan) and functional imaging (^{68}Ga-DOTANOC PET/CT) of the pancreas showed bulky body and tail of pancreas without focal lesions. Clinical exome sequencing confirmed the presence of heterozygous mutation in exon11 of *GLUD1* (glutamate dehydrogenase) gene (p.Ser498Leu), a well-known cause of congenital hyperinsulinism-hyperammonemia (HI/HA) syndrome. The child was treated with diazoxide (6 mg/kg/d in divided doses) and uncooked corn starch, with moderate restriction of dietary protein. At follow up after10 months, the child is seizure-free with no episodes of hypoglycemia, and her anti-epileptic medicines have been tapered to one medication (levetiracetam). We thus report congenital hyperinsulinism as a rare but important cause of “uncontrolled seizures” and “childhood epileptic encephalopathy” with remarkable response of hypoglycemia and seizures to diazoxide and dietary modifications.

Key-words: Congenital hyperinsulinism, hyperammonemia, hypoglycemia, seizure, epileptic encephalopathy

Key messagages

1. Hyperinsulinism/Hyperammonemia syndrome is a well-known cause of congenital hyperinsulism caused by mutation in the *GLUD1* (glutamate dehydrogenase) gene.
2. This disorder, unlike other congenital hyperinsulinism syndromes, presents later at an average age of 4-11 months; seizures are an important feature of presentation.

3. This disorder is exquisitely responsive to diazoxide and dietary modification in controlling hypoglycemia and seizures.

Introduction

The term “epileptic encephalopathy” describes a heterogeneous group of epilepsy syndromes associated with severe cognitive and behavioral disturbances. These disorders vary in their age of onset, developmental outcome, etiologies, neuropsychological deficits, electroencephalographic (EEG) patterns, seizure types, and prognosis, and may have a significant impact on neurological development (1, 2). The epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and can worsen over time (3). A common feature is that these disorders are usually refractory to standard anti-epileptic drugs (AEDs). As a result, more aggressive use of AEDs is needed in suppressing inter-ictal epileptiform discharges. A secondary etiology of these epilepsy syndromes should be carefully looked into, particularly metabolic causes. We report a case of congenital hyperinsulinism masquerading as epileptic encephalopathy syndrome with refractory seizures unresponsive to multiple AEDs.

Case History

A 4yo girl presented to our Neurology outpatient clinic with history of recurrent myoclonic jerks and an episode of generalised tonic clonic seizure (GTCS). The child was born to non-consanguineous parents through in-vitro fertilization techniques and was delivered by cesarean section (indication: polyhydramnios) at 36 weeks. Birth weight was 2.2 kg and she cried immediately after birth. There were no major neonatal events except for physiological jaundice. The child was noted to have global developmental delay by age 6 months, and started having seizures from 11 months of age. The semiology included staring look, blinking of eyes, jerky movements of all four limbs, lip smacking and associated post-ictal drowsiness, with clustering of events at night. MRI brain at that time showed moderate thinning of the corpus callosum, mild supra-tentorial white matter and diffuse gray matter volume loss, with relative sparing of the occipital lobes. The child was diagnosed as cryptogenic West Syndrome at one year of age, at a tertiary referral center, and started on levetiracetam, valproate and clonazepam, but had poor control of seizures (once in 7-10 days). At two years of age, she was diagnosed as having cryptogenic generalized epilepsy syndrome at another center; even on levetiracetam, valproate and clobazam, she had weekly episodes of myoclonic jerks, some progressing to GTCS. A repeat EEG at the age of 3 years was reported elsewhere, as sharp slow wave bursts that are mainly generalised, some from left temporal lobes, suggesting a predominantly generalized and rarely left temporal seizures. So, zonisamide and oxcarbazepine were added to her regimen. Clinical examination at age 2 and 4 years of age revealed flat feet, broad based gait, with no focal neurological deficits. Power and tone of extremities were normal with no clinical neuro-cutaneous markers. Serum ammonia done on two occasions were 252 and 232 (Normal: <30) µmol/L. Liver function

tests were normal (ALT: 26 U/L; AST: 25 U/L). Serum Lactate was 22.1 (normal: 4.5-19.8) mg/dl. Karyotyping was 46XX with no microdeletion at 15q11 and normal SNRPN gene methylation (ruling out Angelman syndrome). In view of the elevated ammonia, she was screened for inborn errors of metabolism (IEM) twice with estimation of amino acids and acylcarnitine by tandem mass spectrometry by using dried blood spot on S&S 903 filter paper. No significant abnormality was detected to suggest IEM. When she presented to our institution, she had an incidental finding of hypoglycemia on routine chemistry with a plasma glucose of 22 mg/dl. Urine ketones were negative. Serum creatinine kinase was 87 (normal: 26 -192) U/L. Serum ammonia was elevated at 160 (normal: 11-32) µmol/L. Hormone tests in the critical sample during the hypoglycemia revealed TSH 0.481 µIU/ml, fT4 1.36 ng/dl, growth hormone (GH) 0.69 ng/ml and cortisol 29 µg/dl. Serum insulin and C-peptide were inappropriately elevated (Table 1), consistent with hyperinsulinemic hypoglycemia. Analysis of urinary excretion of organic acids revealed mild to moderate elevations of 2-propyl hydroxyglutaric acid (VPA) at 15.85% (normal: 0%) and 4-OH-Benzoic-2 at 31.49% (normal: <22.38%). EEG for classification of epilepsy syndrome showed generalized slowing with no epileptiform discharges. A ^{68}Ga-DOTANOC-PET/CT showed bulky pancreas with no focal somatostatin receptor expression. Clinical exome sequencing reported a heterozygous mutation on exon 11 of *GLUD1* gene (p.Ser498Leu), a pathogenic variant causing the hyperinsulinemia-hyperammonemia (HI/HA) syndrome. The child was treated with diazoxide 6 mg/kg/d in divided doses, uncooked corn starch (2 scoops thrice daily) and AEDs were tapered. Her daily protein intake was reduced to 0.5 g/kg/day. Currently, after 10 months of follow up, she has been seizure-free with no hypoglycemic episodes, and only on levetiracetam which is also being tapered down.

Table 1: Hormones measured in the critical blood samples (at the time of hypoglycemia)

Venous plasma glucose (mg/dl)	Serum insulin (mU/L)	Serum C-peptide (ng/ml)	Serum cortisol (µg/dl)	Serum GH (ng/ml)	Serum TSH (mIU/L)
22	9.7	1.71	29	0.69	0.481
45	15.6	1.68			
29	11.5	1.94	12.3		

Discussion

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and infants. It is a genetic disorder with both familial and sporadic forms, characterized by dysregulation of insulin secretion (4-6). Despite its genetic cause, some cases do not present at birth. Early recognition, diagnosis, and treatment are necessary to prevent or minimize neurologic damage from recurrent or prolonged episodes of hypoglycemia. In normal children, when the plasma glucose concentration decreases below

60 mg/dL, insulin secretion is suppressed. In children with CHI, insulin is inappropriately released even during periods of hypoglycemia because this relationship is disturbed, due to mutations resulting either in abnormal function, or in regulation of the ATP-dependent potassium (KATP) channel of the pancreatic beta cells (Figure 1) (7).

While mutations in *ABCC8* and *KCNJ11* genes are responsible for >50% of cases, *GLUD1* gene is affected in 5% of cases of CHI. *GLUD1* mutations cause a gain of function in glutamate dehydrogenase (GDH), an enzyme that catalyzes the conversion of glutamate to alpha-ketoglutarate and ammonia (Figure 1), resulting in increased insulin secretion and hyperammonemia. The insulin secretion is triggered by dietary protein, and particularly leucine, which is an allosteric activator of GDH (7,8). It also increases the production of gamma-hydroxybutyrate which inhibits the secretion of glucagon in a paracrine fashion. Unlike mutations in *ABCC8* and *KCNJ11*, mutations in *GLUD1* present later, at an average age of 4-11 months. The birth weights of children with *GLUD1* mutations are usually normal (unlike macrosomia seen in *ABCC8* & *KCNJ11* mutations) and hypoglycemic episodes are less severe. Most of these children have diet independent hyperammonemia, thus the term 'protein-induced hypoglycemia'. Serum ammonia levels are moderate (3-5 fold high; 95-320 µmol/L) and do not cause cerebral dysfunction. Seizures in *GLUD1* mutations can be a result of hypoglycemia, as well as an independent entity as there are GDH receptors in the brain, resulting in hyper-excitability (9,10). Absence seizures and myoclonic jerks are the usual clinical manifestations, occurring during the fasting state or after high protein meals, and are usually refractory to traditional AEDs. However, CHI related to *GLUD1* mutations is very responsive to diazoxide and dietary protein restriction, with reduction in episodes of hypoglycemia and the doses of AEDs. This is in contrast to CHI related to *ABCC8* and *KCNJ11* mutations which are generally diazoxide unresponsive. There is one anecdotal report of spontaneous resolution of CHI related to a *GLUD1* mutation in a child by 8 years (11). Hence, it is critical to get metabolic work up in children with syndromes of epileptic encephalopathy and particularly be alerted to HI/HA syndrome if there is hyperammonemia in the preliminary work up.

Two interesting aspects in our case also merit attention. Serum GH level at the time of hypoglycemia was quite low, suggesting GH deficiency. However, the child's growth curve and current height were normal (10-25th centile); hence, we feel this low GH could be related to the negative feedback from hyperinsulinism. The other notable lab abnormality was an elevated urine organic acid (2-propyl hydroxyglutaric acid), which is elevated in patients with CHI related to enzyme hydroxyacyl-coenzyme A dehydrogenase (HADH), previously known as short-chain L-3-hydroxyacyl CoA dehydrogenase (SCHAD). This enzyme is involved in fatty acid beta-oxidation and linked with GDH (Figure 1) and hence *GLUD-1* mutation can affect activity of HADH and result in mild to moderate organic aciduria.

Conclusion: We present a case of HI/HA syndrome, caused by mutation in the *GLUD1* gene who presented as a case of intractable seizures and epileptic encephalopathy. The disorder is exquisitely responsive to diazoxide and dietary modification, serving as effective management of hypoglycemia and seizures.

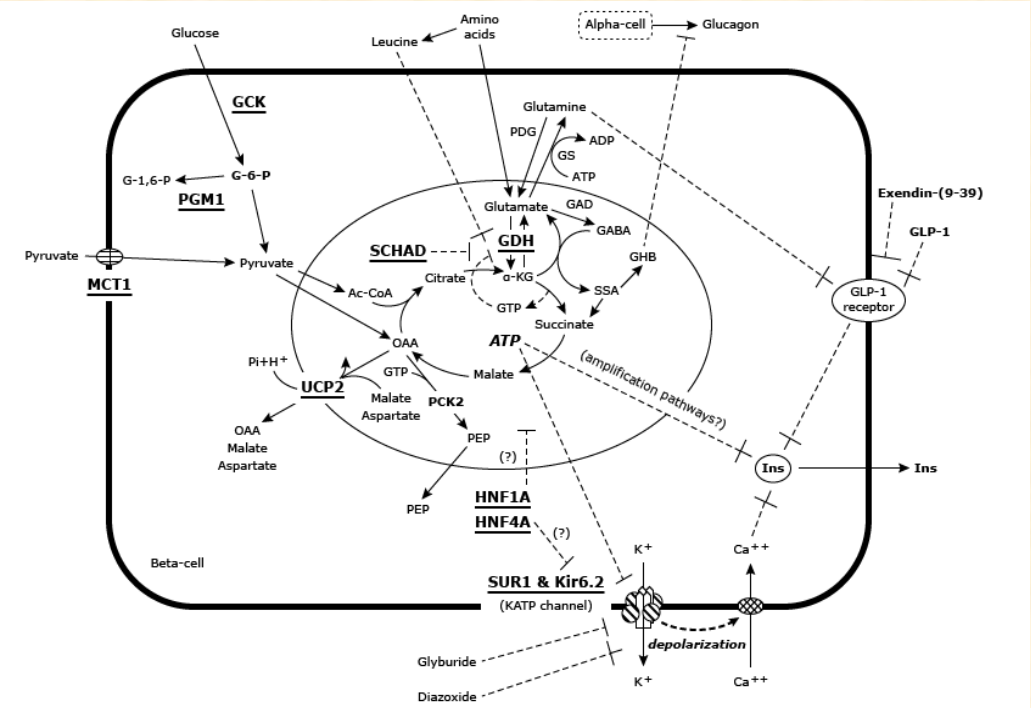

Diagram of β-cell fuel-mediated insulin secretion showing 11 genes currently associated with congenital HI (bold and underlined). Glucose oxidation stimulates insulin secretion via a "triggering pathway" by inhibiting ATP-sensitive KATP channels, leading to plasma membrane depolarization, activation of voltage-gated calcium channels, elevation of cytosolic calcium, and release of insulin from stored granules. Insulin secretion is also promoted by various "amplification pathways" once cytosolic calcium is elevated, eg, by mitochondria-derived signals or by membrane receptors such as the GLP-1 receptor. Amino acids stimulate insulin secretion through several mechanisms, especially leucine, which allosterically activates GDH enzymatic activity to increase oxidative deamination of glutamate to α-KG; GDH activity is allosterically inhibited by GTP and by the SCHAD enzyme protein. During glucose-stimulated insulin secretion, the rise in α-KG increases flux through a gamma amino butyric acid shunt and generates γ-hydroxybutyrate (GHB), which is released as a paracrine inhibitor of glucagon secretion from α-cells. HI-associated genes include: *GCK* (glucokinase), *PGM1* (phosphoglucomutase 1), *MCT1* (monocarboxylate transporter 1), *UCP2* (uncoupling protein 2), *SCHAD* (short-chain 3-hydroxyacyl-CoA dehydrogenase), *GDH* (glutamate dehydrogenase), *HNF1A* (hepatocyte nuclear factor 1A), *HNFA* (hepatocyte nuclear factor 4A), *SUR1* (sulfonylurea receptor 1), *Kir6.2* (inwardly rectifying potassium channel 6.2).
G-1,6-P: glucose 1,6 diphosphate; G-6-P: glucose 6 phosphate; Ac-CoA: acyl coenzyme A; Pi: inorganic phosphate; PDG: phosphate-dependent glutaminase; ADP: adenosine diphosphate; ATP: adenosine triphosphate; GS: glutamine synthetase; GTP: guanosine triphosphate; PCK2: phosphoenolpyruvate carboxykinase 2; PEP: phosphoenolpyruvate; OAA: oxaloacetate; α-KG: alpha-ketoglutarate; GAD: glutamic acid decarboxylase; GABA: gamma-aminobutyrate; GHB: gamma-hydroxybutyrate; SSA: succinic semialdehyde; Ins: insulin; KATP: ATP-dependent potassium (channel); GLP-1: glucagon-like peptide-1; K^+: potassium ion; H^+: hydrogen ion; Ca^{++}: calcium ion.

Figure 1: Pancreatic beta cell pathways of insulin secretion (Reproduced the image from Ref.7)

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Case Report 2

A tale of three siblings: Congenital hypothyroidism due to thyroid dyshormonogenesis

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BACKGROUND:

Congenital hypothyroidism (CH) is the commonest cause of preventable mental retardation. While majority of cases are caused due to problems with thyroid gland development and migration (dysgenesis), 15% are caused by disorders of thyroid hormone biosynthesis (dyshormonogenesis). Both form of disorders results in primary hypothyroidism. Whereas CH due to dysgenesis is usually sporadic, dyshormonogenesis is transmitted in autosomal recessive manner. A complete diagnostic work-up for CH is important as it could provide information of the cause. Further, it is important to understand the nature of illness (permanent/ transient), for genetic counselling, the treatment, risk of transmission to offsprings and to decide early screening of siblings (as in India with no universal screening for CH). A report of 3 siblings with congenital hypothyroidism due to thyroid dyshormonogenesis is presented.

CASE REPORT

Three siblings (out of five), born out of non-consanguineous marriage, were diagnosed as having congenital hypothyroidism.

Sib1: The elder sibling,13-year-old boy, 3rd by birth order, was diagnosed to have hypothyroidism at 6 months of age due to poor activity and delayed milestones. He was started on levo-thyroxine but was not given treatment on regular basis by parents. When child presented to our centre, he was off therapy for last 1year, had symptoms of lethargy, constipation, and puffiness of face. He was short, had delayed bone age (10 years) and was pre-pubertal.

Sib 2: An 8-year-old girl, 4th in birth order. She had similar complaints few months after birth, but she was not tested for hypothyroidism at that time. She was investigated at 4 years of age and was started on thyroxine treatment. Treatment was unfortunately discontinued by parents for last 2 years. She had mental retardation, was prepubertal and short.

Sib 3: An 18-month-old boy, 5th in birth order. He was diagnosed to have hypothyroidism at 15 months of age due to delayed milestones. He was getting regular treatment since diagnosis and was well controlled. Parents find him more active now and has started achieving milestones, though he still has delayed development.

Table 1. Thyroid related laboratory investigations of three siblings

	Sib 1 **(at presentation)**	Sib 2 **(at presentation)**	Sib 3 **(at diagnosis)**
TSH	301. 9 mIU/L	213 mIU/L	> 100 mIU/L
Free T4	< 0.4 ng/dL	< 0.4 ng/dL	< 0.4 ng/dL
Tc Scan	Uptake 0%- s/o athyreosis	Uptake 0.2%- s/o athyreosis	Not done
USG neck	Isthmus and both thyroid lobes show normal size and echotexture	Isthmus and both thyroid lobes show normal size and echotexture	Both thyroid lobes and isthmus are normal in size and echotexture

Figure 1. Clinical photograph of 3 sibs.

Figure 2. Tc-99m pertechnetate thyroid scan of Sib 1 and Sib 2 showing no thyroid uptake (tissue) in the neck or ectopic sites.

The etiological work up was done for both elder siblings, as they were off drugs when they presented. The younger sibling, 18-month-old boy, was on treatment, so nuclear imaging was not possible. The Technetium (Tc-99m pertechnetate) scan was s/o athyreosis, with no uptake in thyroid bed, though salivary glands were seen. But USG neck was s/o normal thyroid lobes. This led to possibility of Sodium iodine symporter defect or TSH receptor defect. Further tests will be required to prove the specific defect in these siblings.

DISCUSSION

Congenital hypothyroidism is the most common inborn endocrine disorder, with a prevalence of 1 in 2000-4000 new-borns. It is a common cause of preventable mental retardation. Majority (85%) of cases are caused by problems with thyroid gland development and migration (dysgenesis), and are usually sporadic, 15% are caused by disorder of thyroid hormone biosynthesis (dyshormonogenesis), inherited in an autosomal recessive fashion(1).

The etiological classification is based on clinical and biochemical evaluation. Useful tests being, measurement of serum TSH, thyroxine (T4), triiodothyronine (T3), thyroglobulin (TG), ultrasound and scintigraphy, using ^{99m} pertechnetate or, preferably ^{123}I, and when indicated, the perchlorate discharge test. A complete diagnostic work up is important to identify the etiology, to decide the need for genetic work up (which will further help to decide whether a genetic counselling is required) , the nature – permanent or transient (if transient and euthyroid now, can lead to hypothyroidism when increased demand for thyroid hormone synthesis), also a potential impact on treatment (some may need only iodide supplementation, whereas others require levo-thyroxine (LT4) therapy).

Scintigraphy may show no uptake despite the presence of a eutopic thyroid gland with excess iodine intake (through exposure, eg- from antiseptic preparations), maternal TSH receptor blocking antibodies , TSH suppression from LT 4 treatment, and inactivating mutations in the TSH receptor and the sodium/ iodide symporter (NIS) (2).

From the history, examination and investigations of the siblings in this case, it is suggestive of either NIS defect or TSH receptor defect. The technetium scan showed no uptake, but salivary glands were visualized. USG neck, showed normal lobes of thyroid.

The ability to concentrate iodide actively is a characteristic feature of the thyroid gland and several other tissues. This function is mediated through sodium iodide symporter (NIS, a protein located in the basolateral membrane of thyrocyte). NIS is a member of of the SLC5A transporter family. A defect in NIS can result in hypothyroidism, the severity of which is variable, depending on the degree of loss of function of the mutant NIS and by the amount of iodine supply. The laboratory hallmarks of the condition are markedly reduced or absent thyroidal uptake of radio iodide or pertechnetate (even the salivary glands/ gastric uptake is not seen), reduced I- saliva to plasma ratio (S/P) (normally its above 25), thyroglobulin (TG) levels which may be high , restoration of euthyroid state by treatment with pharmacologic doses of iodide (1-5 mg/day). Currently, the definitive diagnosis is based on the identification of a mutation in the NIS gene. This is inherited in autosomal recessive manner (3).

TSH exerts its activity by binding to the extra cellular domain of TSH receptor (TSH-R). It mediates the effects of TSH in thyroid development, growth, and thyroid hormone synthesis. Inactivating mutation in TSH receptor, will lead to hypothyroidism, with no uptake on scintigraphy. But on USG, the thyroid gland is usually hypoplastic. It is expected that this subtype out of all those conditions causing dyshormonogenesis, will not result in goitre. This is transmitted in autosomal recessive manner. Autosomal dominant form of partial resistance to TSH has been demonstrated in families. The thyroglobulin maybe normal or high this condition. The sequencing of TSH –R gene should confirm the diagnosis (4).

The further etiological work up (genetic) would have been important for the diagnosis in these children, as it would have helped in confirming the specific accurate diagnosis. Early diagnosis in next sibling can help preventing mental retardation. (Newborn screening is not

yet done routinely in many parts of the country). Detailed etiological work up can further help to counsel parents- regarding nature of illness, whether the CH is transient or permanent, and to decide if iodide supplementation would help in treatment, if NIS defect is confirmed.

The story of these 3 siblings also highlights the poor awareness on the part of parents (and society at large), and poor compliance. The universal newborn screening for CH (if available) could have made difference in the life of these siblings.

CONCLUSIONS: Congenital hypothyroidism, being a common endocrine disorder and satisfying all the criteria to be included in the newborn screening program, which is not done routinely yet in many parts of the country. Many children and families are bearing the brunt due to mental retardation because of delayed diagnosis. The etiological work up is very important to decide the need for genetic tests, which will further help to decide whether a genetic counselling is required, the nature – permanent or transient (if transient, and euthyroid now, can lead to hypothyroidism when increased demand for thyroid hormone synthesis occurs), and also, a potential impact on treatment - as some may need only iodide supplementation, whereas the rest need levo-thyroxine therapy. Especially in those cases, where we suspect NIS defect, iodide treatment being a possibility (or an add on with levo-thyroxine). Also, if the elder one is diagnosed earlier, the siblings would have been screened earlier (as newborn screening is yet not done routinely in many parts of India).

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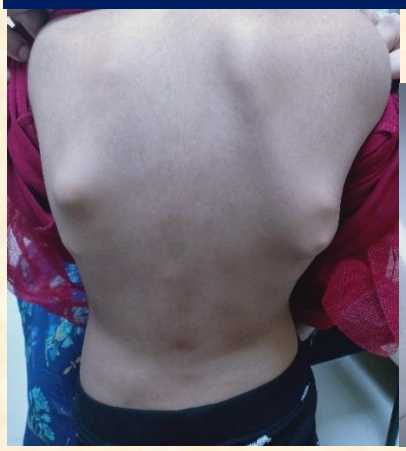
PHOTO QUIZ

Dr. Subramanian Kannan, Department of Endocrinology, Narayana Hrudhayalaya Hospitals, Bangalore



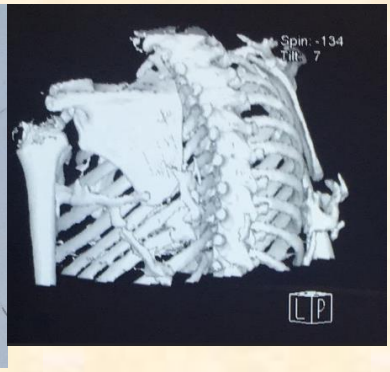


Figure 1 **Figure 2** **Figure 3**

Question:

A 5-year-old girl born to non-consanguineous parents, was brought for multiple hard swellings in the back and arm. Parents noted that she was apparently healthy till about 12 months back, when she started developing soft swellings in the back below the scapular area; after some days the swelling would become as hard as a stone. Similar swellings occurred in the inner aspect of her arms as well (Figure 1). While these lesions were initially painful, they became painless once they turned hard. A CT scan revealed densely calcified lesions in the subcutaneous aspect of posterior chest wall with bony peduncles; the largest lesion was below the right scapula (Figure 2). Similar lesions were also noted around the knee joints and toes, with short great toes with hallux valgus deformity (Figure 3).

Answer on the last page

Pedendoscan

Dr Nikhil Lohiya, Consultant Pediatric Endocrinologist, Dr DY Patil Medical College, Hospital & Research Center, & Jupiter Hospital, Pune

1. Gonadal Tissue Cryopreservation for Children with Differences of Sex Development

Johnson EK, Finlayson C, Finney EL, Harris CJ, Tan SY, Laronda MM, et. al. Gonadal Tissue Cryopreservation for Children with Differences of Sex Development. Hormone Research in Paediatrics. 2019;92(2):84-91.

About the Study: In this **retrospective** observational study, the authors offered Gonadal Tissue Cryopreservation (GTC) to patients with DSD undergoing prophylactic gonadectomy, after extensive multidisciplinary counseling. For those who elected to attempt GTC, data were abstracted, including: DSD diagnosis, age at gonadectomy, indication for gonadectomy, pathology results, and final decision about long-term gonadal tissue storage. Among **10 patients** enrolled for GTC, **5 had Germ Cells (GCs) present**. These 5 patients had ovotesticular DSD (13 months), mixed gonadal dysgenesis (17 months), partial gonadal dysgenesis (3 years), partial androgen insensitivity syndrome (11 years), and mixed gonadal dysgenesis (12 years). Four of these 5 patients elected for GTC; 1 did not, citing immature gametes not matching the gender identity. From this, the authors concluded that GTC at the time of gonadectomy for patients with DSD is feasible. **In many patients, GCs are present**. While questions remain about the timing of gonadectomy, quality of GCs, and future success of the use of the tissue based on technological advancement, GTC represents a novel approach to experimental fertility preservation (FP) for individuals with DSD.

Critical Appraisal: The study question of FP is relevant in children with DSD. The study design was also practical, as any other experimental design may not work here (probably a focused observational study would make for a stronger study) due to ethical restrictions. The study satisfies the aim to report experiences of patients with DSD who elected to attempt GTC at the time of prophylactic gonadectomy. The authors have discussed ethical concerns with regard to fostering false hopes in the context of an experimental procedure, risk of genetic transmission of a DSD to offspring, cost, and desire for autonomous patient decision-making. They discussed all these issues with the families offered GTC, and recommend the same before doing GTC. The authors have also discussed the limitations of a small sample, with disparate diagnoses, genetic profiles and ages. They point out that definite conclusions can not be drawn regarding predictive factors for presence of GCs, quality of GCs, or optimal age for preservation. They leave key questions for future research - Which DSD diagnoses are likely to have FP? Do younger children with DSD have GCs in their gonads more frequently? Are GCs of high enough quality to be used to produce a biological child with future assisted reproductive technologies? How should concerns about genetic transmission of a DSD

condition to offspring be handled? What is the best way to address concerns about false hope of the future ability of gonadal tissue to produce a biological child?

Can it be applied in our setting? Considering the Indian scenario, the dream of GCT is far-fetched. GTC is still an experimental area with several grey areas, needing considerable infrastructure and expertise, to be considered only in an experienced center with a multi-disciplinary team, after crossing the hurdle from the local Ethics Board.

2. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity.

Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C et. al. A randomized, controlled trial of liraglutide for adolescents with obesity. New England Journal of Medicine. 2020 Mar 31.

About the Study: This was a randomized, double-blind trial, consisting of a 56-week treatment period and a 26-week follow-up period. The authors enrolled adolescents (12 to <18 years of age) with obesity and a poor response to lifestyle therapy alone. Participants were randomly assigned (1:1) to receive either liraglutide (3.0 mg) or placebo subcutaneously once daily, in addition to lifestyle therapy. The primary end point was the change from baseline in the body-mass index standard-deviation score (BMI SDS) at week 56. Of 299 participants screened, 251 underwent randomization - 125 participants in the liraglutide arm and 126 in the placebo arm. At week 56, treatment was completed by 101 participants (80.8%) in the liraglutide group and 100 participants (79.4%) in the placebo group. Liraglutide was superior to placebo in the change in BMI SDS from baseline to week 56 (estimated difference, −0.22; 95% confidence interval [CI], −0.37 to −0.08; P = 0.002). A reduction in BMI of at least 5% was observed in 51 of 113 (43.3%) participants in the liraglutide group vs. 20 of 105 participants in the placebo group (18.7%), with a reduction in BMI of at least 10% observed in 33 and 9, respectively (26.1% vs. 8.1%). A greater reduction was observed with liraglutide for BMI (estimated difference, −4.64 percentage points) and for body weight (estimated difference, −4.50 kg [for absolute change] and −5.01 percentage points [for relative change]). After discontinuation, a greater increase in the BMI SDS was observed with liraglutide (estimated difference, 0.15; 95% CI, 0.07 to 0.23). More participants in the liraglutide group had gastrointestinal adverse events (81 of 125 [64.8%] vs. 46 of 126 [36.5%]) and adverse events that led to discontinuation of the trial treatment (13 [10.4%] vs. 0). Few participants in either group had serious adverse events (3 [2.4%] vs. 5 [4.0%]). One suicide, which occurred in the liraglutide group, was assessed by the investigator as unlikely to be related to the trial treatment. The authors concluded that in obese adolescents, the use of liraglutide (3.0 mg) plus lifestyle therapy led to a significantly greater reduction in the BMI SDS than placebo plus lifestyle therapy.

Critical Appraisal: The study sought to evaluate the efficacy and safety of subcutaneous liraglutide as an adjunct to lifestyle therapy for weight management in obese adolescents. The double blind randomized control trial design was appropriately chosen, and other aspects including the protocol, follow-up and statistical analysis seems satisfactory. They have

reported the strengths and limitations clearly. This was a multinational study, and hence done in a diverse population. The difference in change in BMI SDS was 7.64% which is significant weight loss, but the high frequency of adverse events on liraglutide was one major reason for discontinuation of the drug.

Can Liraglutide be used in our setting? Before answering this, we need to understand a few things clearly. If at all liraglutide is being considered, patient selection is important. The criterion chosen by the authors was BMI adult equivalent of 30 or more as per IOTF. However, the definition of obesity in Asians is different. Lifestyle modification and other drugs including metformin must have been tried to decrease the obesity. It is important to choose a committed patient. It is a costly therapy and adherence to therapy is very important. The cost-benefit ratio has to be analysed, as the improvement in BMI is not dramatic. In some patients, even a little improvement in BMI can help in boosting morale and improving motivation. There is only one previous study regarding liraglutide use in the pediatric population in the Indian setting; we need more RCT evidence from our country before deciding about its use. Hence, liraglutide can be used as an experimental adjunct in our setting.

3. **Basal serum luteinising hormone cut-off, and its utility and cost-effectiveness for aiding the diagnosis of the onset of puberty in girls with early stages of breast development.** Wankanit S, Mahachoklertwattana P, Pattanaprateep O, Poomthavorn P. Basal serum luteinizing hormone cut-off, and its utility and cost-effectiveness for aiding the diagnosis of the onset of puberty in girls with early stages of breast development. Clinical Endocrinology. 2020 Jan;92(1):46-54.

About the Study: The objective was to determine basal and gonadotrophin-releasing hormone analog (GnRHa)-stimulated peak luteinising hormone (LH) cut-offs to diagnose onset of early or normal puberty in girls with Tanner stage II and III of breast development. The authors did a retrospective study of 601 girls with thelarche before 8 years of age who underwent GnRHa test. Patients were categorized as having central precocious puberty (CPP) and premature thelarche. Each group was divided into two subgroups; Tanner II and III. Cost-effectiveness analysis was performed. The results showed that in comparison **with basal LH cut-off of 0.3 IU/L, a basal LH cut-off of 0.2 IU/L had comparable specificity** (Tanner II: 98.0% vs. 94.8%, Tanner III: 98.8% vs. 93.8%), but greater sensitivity (Tanner II: 28.3% vs. 41.7%, Tanner III: 45.2% vs. 59.3%). **Specificity of basal LH cut-off of 0.2 IU/L was not inferior to that of the traditionally used peak LH of 5 IU/L**. Using basal LH cut-off of 0.2 IU/L followed by GnRHa test in girls with negative basal LH was **more cost-saving** when compared with using the cut-off of 0.3 IU/L. Moreover, using basal LH cut-off of 0.2 IU/L followed by GnRHa test provided a cost reduction when compared with performing GnRHa test in all patients. With these results the authors concluded that basal serum LH cut-off of 0.2 IU/L could be a simple and cost-saving tool for initial diagnosis of onset of early or normal puberty in girls with Tanner II and III before proceeding to GnRH testing.

Critical Appraisal: The study answered the research question well - methodology was clearly defined; the assays used are commonly available; and statistical analysis was appropriate. The cut-off of basal LH of 0.2 IU.L gives a good sensitivity with a reasonable specificity (95%), can distinguish premature thelarche from CPP; with a higher cost benefit ratio. However, the study was retrospective, and there was no control group of Tanner stage 1, which could have given us a clearer picture.

Can it be applied in our setting? The traditional basal LH cut-off of 0.3 IU/L has been challenged by many researchers and reviewed in a few articles. The GnRHa stimulation test used in the above study is commonly used in India. The favorable cost-benefit ratio can be important in resource limited settings like ours. The results can be applied in our setting but perhaps after we have some evidence from our country. The clinician should of course remember to consider the complete clinical picture including history, examination, growth skeletal maturity and lab assay.

Events/Activities organised by ISPAE members

Neonatal Endocrinology CME, Dr Hemchand K Prasad, Mehta Hospital, Chennai.

A CME on Neonatal Endocrinology, held on 9.2.2020, was organized by Dr Hemchand K Prasad from Mehta Hospital, Chennai at MCC School Auditorium, Chennai. The program was attended by 250 pediatricians from Tamil Nadu. Prof Olaf Hiort from Germany gave the oration on "DSD – the way forward". Dr Sudha Rao and Dr Anurag Bajpai were the national faculty. Topics of interest covered were: Osteopenia of prematurity, CAH screening, growth charts, congenital hypothyroidism, DSD, micropenis and calcium disorders. The program was appreciated by one and all. A reckoner in neonatal endocrinology was provided to all delegates.

Type 1 diabetes Parents' Awareness Meeting, Dr Hemchand K Prasad and Dr Thangavelu S, Mehta Children's Hospital, Chennai.

A Parents' Awareness Meeting was held on 1.2.2020 at Rail Museum, Chennai, for families with T1D. Ms Sheryl Salis, an eminent dietician from Mumbai spoke on carbohydrate counting. Parents shared their experiences with carbohydrate counting. Children with good glycemic control and well-maintained logbooks were rewarded. This was followed by a visit to the Rail Museum and lunch. The program was attended by 40 T1D families and appreciated by everyone.

Inauguration of Type 1 Diabetes Foundation of India, Dr Santhosh Olety, Bengaluru

Type 1 diabetes (T1D) Foundation of India was inaugurated on 01/03/2020 at Bengaluru - a great initiative started by T1Ds for the overall well-being of T1Ds. There was an impressive show of leadership from T1Ds from a wide spectrum of professions - lawyers, doctors, businesspersons, social activists, people from HR and IT backgrounds, etc. - from every corner of the country. The event was graced by the Honorable Deputy Chief Minister of Karnataka Dr Ashwath Narayan, and Member of Parliament Mr Tejasvi Surya. The Foundation has taken 3 important demands of T1Ds to be proposed to Parliament: tax exemption on insulin, awareness program from the Government, and inclusion of T1D under the Disability Act. We look forward to great things happening in the coming years and wish them all the strength they need.

Pediatric Diabetes for Postgraduates (PDP) – 2nd edition; Sirisha Kusuma Boddu, Rainbow Children's Hospital, Hyderabad

Pediatric **D**iabetes for **P**ostgraduates program was conceived with the intention of training young pediatric trainees, practicing pediatricians and physicians caring for children with diabetes. A year after our first program, we conducted the second edition on 7th March 2020, at Niloufer Children's Hospital, Hyderabad, with the support of Dr Ravi Kumar, Head, Department of Pediatrics. The faculty were Drs Sirisha Kusuma Boddu, Kishore Baske, Rahul Reddy and Ravi Kumar. It was attended by 30 MD Pediatrics trainees, and a few Assistant Professors of the Pediatrics Department. The session was sponsored by Sanofi India. The 4 hour program included interactive lectures on the basics of insulin therapy, and diabetic ketoacidosis, followed by hands-on workstations covering the topics of insulin, glucagon, blood glucose checking, blood and urine ketones checking, monitoring plan, dietary advice, hypoglycemia treatment, initiating insulin therapy, adjusting doses, adjusting for activity and sick days etc. The program was well received by all attendees (Photograph on next page).

World Obesity Day Celebration (4th March 2020), Dr. Priti Phatale & Dr Hemant Phatale, Samrat Endocrine Institute, Aurangabad

The World Diabetes Day program was organized in collaboration with Aurangabad Academy of Pediatrics (AAP), Indian Medical Association (IMA, Aurangabad), and Women Doctors Wing (IMA). The objective was of creating awareness regarding the rising trends of obesity & its consequences at family, school & society level with the theme 'Together we can create a healthier future'. As a part of the program, a catchy slogan competition, rally with school children, interactive sessions for school children, awareness campaign through different media and poster exhibition were organised. Children who coined good slogans for obesity awareness were rewarded.

State-of-affairs: T1D among children and adolescents in Karnataka State

Dr Santhosh Olety, Bengaluru

Digital survey to estimate number of children less than 18 yrs of age with type 1 diabetes in Karnataka

A simple questionnaire was designed on survey monkey (a cloud-based software) and circulated to endocrinologists and diabetologists practicing in Karnataka. The survey period was over 6 weeks beginning 20th February 2020. Repeated reminders sent to personal contacts, emails and WhatsApp groups of diabetologists, endocrinologists and pediatricians, resulted in a total of 70 responses. Where no response was received from a few centers providing diabetes care, data was collected through the CDiC program registry. Here is some of the data gathered.

Total number of children <18y with T1D = 5039 (4562 survey data + 477 CDiC data)

- Boys = 2012, Girls = 1684, Gender information not available = 1343
- Percentage of children getting access to free supplies of insulin through any Charity such as CDiC, LFC or other philanthropic organization - About 40 centers were providing such support, ranging from 1% to 100% of registered children. (Mean 41%)
- Number of deaths due to T1D in last 1 year (Jan to Dec 2019) = 18 (0.36 %)

Limitations of the survey:

1. Duplication of numbers as children could be registered in several centers.
2. Many children would be missed if not registered and cared for by an endocrine / diabetes specialist.
3. Some of the centers quoted numbers as approximate.
4. Not everybody caring for diabetes would have participated in the survey.
5. Not all deaths related to T1D would have been included.

There has been a rapid advancement of information technology in the area of clinical and population health data management since 2000. Widespread adoption of electronic health records (EHRs) and expansion of patient registries present opportunities to improve patient care, population health and advance translational research. A Diabetes Registry provides care givers, patients and administrators an opportunity to facilitate delivery of health care, implement evidence-based medicine to assist development of cost effective strategies for management of T1D, overcome fragmented care and measure health outcomes of management. We desperately need a national level Registry for childhood diabetes. All of us are aware of the usefulness of having our own national registry. It needs a collective effort from all of us, which can be facilitated through our ISPAE.

Publications by ISPAE members

Dr J Dhivyalakshmi

1. Varadharaju N, Jeevarathnam D, Rajan M, Nagarajan VP, James S. A case of treatment induced neuropathy in an adolescent with type 1 diabetes. Ann Pediatr Endocrinol Metab. 2019; 24(3): 203-206.
2. Premkumar S, Ramanan PV, Lakshmi JD. Rural Childhood Obesity - an emerging health concern. Indian J Endocr Metab 2019:23:289-92
3. Premkumar S, Ramanan PV, Dhivyalakshmi J, Gayathri T. Comparison of Nutrition Status as Assessed by Revised IAP 2015 Growth Charts and CDC 2000 Growth Charts in Lower Socioeconomic Class School Children. Indian J Pediatr (2019) 86:1136-1138.

Dr. Pragya Mangla

1. Mangla P, Gupta S, Chopra A, Bhatia V, Vishwakarma R, Asthana P. Influence of Socio-Economic and Cultural Factors on Type 1 Diabetes Management: Report from a Tertiary Care Multidisciplinary Diabetes Management Center in India. Indian J Pediatr. 2020 Feb 21. doi: 10.1007/s12098-020-03227

Dr Neha Agarwal

1. Agarwal N, Dave C, Patel R, Shukla R, Kapoor R, Bajpai A. Factors associated with cerebral edema at admission in Indian children with diabetic ketoacidosis. Indian Pediatr. 2020 Apr 15;57(4):310-313.
2. Brandt A, Agarwal N, Giri D, Yung Z, Didi M, Senniappan S. Hyperinsulinism hyperammonaemia (HI/HA) syndrome due to GLUD1 mutation: phenotypic variations ranging from late presentation to spontaneous resolution. J Pediatr Endocrinol Metab. 2020 Mar 25. pii: /j/jpem.ahead-of-print/jpem-2019-0416/jpem-2019-0416.xml. doi: 10.1515/jpem-2019-0416.

Dr Rakesh Kumar

1. Deepanjan Bhattacharya, Rakesh Kumar, Jaivinder Yadav. Pituitary macroadenoma secondary to Hashimoto's thyroiditis: inadvertent diagnosis in a pre-pubertal girl. Tropical Doctor. First Published February 27, 2020 Case Report https://doi.org/10.1177/0049475520907421

Awards and Fellowships

Dr J Dhivyalakshmi has been awarded the **ESPE Clinical Fellowship** for the year 2019. She will complete her Fellowship at Nottingham Children Hospital, Nottingham, UK.

Dr GD Ramchandani (Sr. Physician & Consultant Diabetologist, Ramchandani Diabetes Care & Research Center, Kota, Rajasthan) has been conferred the prestigious Award of AACE "**AACE Outstanding Service Award for the Promotion of Endocrine Health of an Underserved Population**". This award is presented every year to an individual for outstanding contribution to endocrine care, health and services to an underserved population in the United States or abroad via Leadership, Long-term commitment, Vision, Innovation, Impact or Outcomes.

Dr Riddhi Patel, MD Pediatrics, Fellowship Pediatric and Adolescent Endocrinology; Center for Diabetes Endocrinology and Research, Kanpur, was awarded first prize for the oral paper presentation on "Novel Mobile Application provides rapid and accurate assessment of bone age in pediatric practice" under the category of "Best Innovative Research Idea in Child and Adolescent Health (ResNovae)". She was awarded this prestigious award at the 2nd National Conference of Indian Academy of Pediatrics Research In Child Health Society (RESRCHCON 2020) held at Lady Harding Medical College, New Delhi, on 28th February 2020.

ANSWER TO PHOTOQUIZ

Genetic testing confirmed a heterozygous mutation in the *ACVR1* gene on exon 6 (c.617G>A, p.Arg206His) consistent with Fibrodysplasia Ossificans Progressiva (FOP). FOP is a rare, disabling genetic condition characterized by congenital malformations of the great toes and progressive heterotopic ossification (HO) in specific anatomic patterns (1). FOP is the most catastrophic disorder of HO in humans. Flare-ups are episodic; immobility is cumulative.
A common mutation in activin A receptor 1 (ACVR1), a bone morphogenetic protein (BMP) type I receptor, exists in all sporadic and familial cases with a classic presentation of FOP (1). Approximately 97% of individuals with FOP have this recurrent mutation (1). The discovery of the *ACVR1* gene established a critical milestone in understanding FOP, revealing a highly conserved therapeutic target in the BMP signaling pathway, and propelling approaches for developing novel inhibitors of ACVR1-mediated BMP signaling. The current management however is focused on early diagnosis, assiduous avoidance of injury or iatrogenic harm, symptomatic amelioration of painful flare-ups, and optimization of residual function. Steroid prophylaxis is recommended for significant blunt muscle trauma, for dental and surgical procedures, for the symptomatic relief of emergent flare-ups of the limbs, jaw and submandibular area. Singing, swimming and incentive spirometry are encouraged to maintain lung function.

References:
1. Kaplan FS, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Proc Intl Clin Council FOP 1:1-111, 2019]

Information on Upcoming important Conferences

1. 59th ESPE Meeting. ESPE Liverpool will now be held from 7-9 May 2021.
2. The Annual ISPAD Conference ISPAD 2020 Abu Dhabi will be rescheduled to take place in 2022.
3. ISPAD is developing a new virtual meeting program for its 46th Annual Scientific Conference in October 2020. It will be in a different format to the previously planned meetings. More information will follow soon, so do regularly visit 2020.ispad.org to remain informed. ISPAD continue to welcome submissions of scientific abstracts and nominations for ISPAD prizes.
4. 54th Annual Meeting of the JSPE. Postponed (new date to be announced).
5. ISPAE-ISPAD Midterm Meeting: Status to be decided.
6. 11th Biennial Scientific Meeting of APPES. Postponed both Biennial Congress and Fellows School to November 2021.