SPEAK

The Voice of PEAK

The official newsletter of

Paediatric Endocrinology Association of Karnataka

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The Chairperson Speaks

It gives me great pleasure to introduce our maiden initiative in the state of Karnataka- PEAK (Paediatric and Adolescent Endocrinology Association of Karnataka) and its Voice- SPEAK. Our vision via SPEAK is to create abundant awareness in the field of Paediatric Endocrinology among all medical practitioners, students, nurses and parents at grass root level, by conducting continued medical education meetings, conferences, workshops and postgraduate quizzes. Our mission is

1. Target early detection and treatment of congenital hypothyroidism all over Karnataka at every level.
2. Enroll all children and adolescents with type 1 DM in a registry so that they can avail free check-ups, access to insulin, dietary advice and psychosocial counselling at every taluk and district level in Karnataka.
3. To chalk out a plan to diagnose and manage children/neonates with DSD (Disorders of sex development) using a multidisciplinary approach in Karnataka.
4. School health programme to increase awareness among teachers and caregivers about growth, nutrition and T1 Diabetes in children

Hope to see many more members join hands to fulfill our vision and mission. SPEAK shall reflect all the activities conducted by us to achieve our aim.

Happy learning!

Warm regards
Shaila S. Bhattacharyya

The Advisor Speaks

Dear Friends,

It is indeed with great pleasure that I wish to pen this congratulatory message on the formation of PEAK – the Paediatric Endocrinology Association of Karnataka – with many enthusiastic Paediatric Endocrinologists of our State. It is also heartwarming to note that what we began as a stepping stone with a small group of Paediatric endocrinologists in Bengaluru has now grown into a full-fledged Association. I am delighted that the number of qualified Paediatricians in this vibrant field of endocrinology has increased several folds in the last decade. They continue to kindle the interest of others in this area and I am confident that we shall soon have many others joining our family.

I am glad to note that the Executive Committee of PEAK has already planned extensive activities to create awareness regarding Paediatric endocrine conditions, use of growth charts, prevention of obesity among the public, schools, general medical practitioners and Paediatricians. The Committee has volunteered to organize several screening programmes in the State and also actively initiated the idea of formulating clinical guidelines in endocrinology for the use of Paediatricians. To top it all, PEAK has been invited to undertake the coveted responsibility of hosting the 8th Biennial Meeting of ISPAE (Indian Society of Paediatric and Adolescent Endocrinology) in 2023. Thus, as the name suggests, the motto of PEAK is to scale the summit in all its future endeavours.

Over the years, I have gladly observed the steady growth of Paediatric Endocrinology in the State and the country and as a result, the welcome news is that we are able to serve thousands of deserving children who have immensely benefited from the right diagnosis and optimal treatment.

I sincerely wish PEAK succeeds in achieving all its laudable goals, grow in stature and reach its pinnacle! May the blessings of the Lord Almighty be showered on PEAK and all its members!

Sincerely yours,

P. Raghupathy.

THE TEAM OF PEAK

Dr. Shaila S. Bhattacharyya
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Advisor

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Dr. Shaila Pachapure

Dr. Diksha Shirodkar

HELLO FROM THE EDITORIAL BOARD

Dear All

It gives us great pleasure in announcing the arrival of our maiden newsletter- **SPEAK**, which will be the voice of **PEAK,** our first venture as a state chapter of Paediatric and Adolescent Endocrinology.

This newsletter shall highlight all the efforts put in by the PEAK members in sensitizing the Paediatricians, students, clinicians and parents of the children with Paediatric Endocrine disorders.

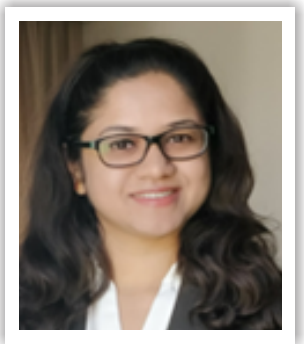
Our cover page shall surprise you by the efforts put in by our little wonders (our patients). Going through this newsletter shall pleasantly walk you through interesting case reports, multiple events and programs conducted, drug reviews and critical review of an article.

We wish to see more members come along in our journey of creating massive awareness in Paediatric Endocrinology and contributions from the members in the upcoming issues

Wishing you all a memorable experience.

Thank you!

Vijaya Sarathi H.A.
Editor



Diksha Shirodkar
Co-editor

A WARM WELCOME TO OUR NEW MEMBERS

- **Dr Kavitha Bhat**
  Senior Consultant - Paediatric Endocrinologist,
  Aster CMI Bengaluru

- **Dr. Swathi Padmanabha**
  Fellow in Paediatric Endocrinology,
  IGICH, Bengaluru

- **Dr. Namratha Upadhyay**
  Consultant - Paediatric Endocrinologist,
  Aster CMI, Bengaluru

- **Dr. Joewin Monteiro**
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- **Dr. Thrupthi**
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- **Dr. Rekha Bathala**
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- **Dr Abhishek Patil**
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- **Dr. Payal Kubsad**
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- **Dr Koushik Urala**
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  Department of Paediatrics,
  Kasturba Medical College, Manipal

- **Dr. Avani Hegde**
  Consultant Paediatric and
  Adolescent Endocrinologist,
  Ovum hospital Bengaluru

INAUGURAL CEREMONY OF PEAK

The Paediatric Endocrinology Association of Karnataka (PEAK), being the very first State Branch of ISPAE, was officially launched on March 6th, 2022 with grandeur at the Taj, MG Road, Bengaluru. This was aptly preceded by an academic activity, viz., a Clinical Workshop, organized by Medtronics on the use of Insulin pumps in children, attended by fellows in Paediatric Endocrinology, practising Paediatric Endocrinologists, senior Paediatricians and postgraduate students in Paediatrics from across the state.

The Inaugural function began with an invocation song seeking the blessings of Lord Ganesha. The Secretary, Dr.Vani welcomed the gathering. Chairperson Dr. Shaila Bhattacharyya spoke about the vision and mission of PEAK to encourage and promote teaching, training and research in the field of Paediatric and Adolescent Endocrinology, by conducting CMEs and conferences across the state amongst the Paediatricians, Physicians, General practitioners, Postgraduates and Parents. She also requested everyone to join hands in the care of the children with diabetes not only in their growth, immunization but also financially to provide easy access to insulin, regular check-ups and psychosocial counselling. The Chief Guest of the function, Dr. Ramesh S. Kaulgud, Joint Director, National Vector Borne Disease Control Programme, Directorate of Health and Family Welfare Services, Government of Karnataka, delivered the Inaugural Address and assured complete support from his team in all the projects by PEAK. Our guest of honour, the pioneer in the field of Paediatric Endocrinology in India, Dr. Raghupathy Palany, spoke about the beginning of Paediatric Endocrinology in India, the difficulties and challenges faced since that time contrasting with the welcome changes now and how the current generation of young Paediatric Endocrinologists evolved over time and the active interest evinced by these Paediatricians to specialize and devote themselves to serve children in need of specialist care and attention in this important field. Our Chief guest and Guest of Honour, were felicitated by office bearers, executive committee members of PEAK and Senior Pediatricians . This was followed by the Installation ceremony.

Installation of office bearers was done by our Chief Guest Dr. Ramesh S. Kaulgud and Installation of executive committee of PEAK was done by Dr. Raghupathy Palany, Advisor of PEAK

The e-newsletter which will be the voice of PEAK- hence named as SPEAK was launched by Dr. Vijaya Sarathi and Dr. Diksha Shirodkar. They enumerated the details regarding their plans for the newsletter to be published in future.

The day was concluded by the vote of thanks by the Joint Secretary and Treasurer, Dr. Pavithra Nagaraj. All the participants of the workshop were gifted a plant signifying the concept of a new life filled with dreams and desires for growth.

ACTIVITIES BY PEAK MEMBERS

The CME programs under the flagship of PEAK

1. Paediatric Endocrinology CME at Bagalkot

Our first CME under the president Dr. Shaila Bhattacharyya was conducted on 13.3.2022 at S. Nijalingappa Medical College and Hangal Shree Kumareshwar Hospital. The program was attended by 80 participants from in and around Bagalkot including the paediatricians, general practitioners and post graduates. Dr Shaila Bhattacharyya spoke on plotting of growth charts which was a very interactive session with hands on training on growth charts. This was followed by a case presentation on short stature by a post graduate. Dr Pavithra Nagaraj spoke on approach to short stature which also was an interactive session with practical points on how to check the anthropometric measurements and the usual mistakes encountered along with an overview on the growth hormone therapy. Dr. Shaila Pachapure- spoke on the much-needed topic for the audience “Management of Type 1 Diabetes” with enormous education on the types of insulin, storage, complications etc. Dr. Shaila Bhattacharyya was felicitated by the IAP Bagalkot branch for her contribution in the field of Paediatric and Adolescent Endocrinology in Karnataka.

ACTIVITIES BY PEAK MEMBERS

The CME programs under the flagship of PEAK

2. Paediatric Endocrinology CME at Davangere

PEAK conducted a 4 hour long continued medical education program at Bapuji child health hospital and J.J.M, Medical college, Davangere district, Karnataka on 07.04.2022. The team members included Dr. Shaila Bhattacharyya (President- ISPAE AND PEAK, chairperson), Dr. Pavithra Nagaraj (Joint secretary cum treasurer-PEAK) and Dr. Diksha Shirodkar (Executive member-PEAK) .The welcome speech was given by Dr. Muganagowda Patil the Head of department of Pediatrics. The inaugural ceremony was conducted in the presence of all esteemed dignitaries by watering a plant. The topics discussed were approach to congenital adrenal hyperplasia, approach to precocious puberty and management of Diabetic ketoacidosis. There was a panel discussion which was moderated by Dr. Nagamani Agarwal, a senior pediatrician, on common pediatric endocrine queries by practicing pediatricians. The CME was a huge success with over 50 delegates attending it.

ACTIVITIES BY PEAK MEMBERS

The CME programs under the flagship of PEAK

3. Paediatric Endocrinology CME at Tumkur

With over 40 participants including the general practitioners, paediatricians and post graduates from 3 medical colleges and also from both private and government set up from in and around Tumkur, this Paediatric Endocrinology CME at the Urban resort, Tumkur on 17.04.2022 was a success. The program started with a postgraduate presenting a case on short stature which was followed by a talk on growth charts and approach to short stature by Dr. Pavithra Nagaraj. Dr. Mounica Reddy spoke on Ambulatory management of T1 Diabetes Mellitus. Dr. Pavithra and Dr. Mounica- later conducted a panel discussion on obesity and congenital hypothyroidism.

ACTIVITIES BY PEAK MEMBERS

The CME programs under the flagship of PEAK

4. Prader Willi Syndrome (PWS): multidisciplinary clinic at Aster Medicity, Bengaluru

Conducted by Dr Kavitha Bhat (Senior Consultant Paediatric Endocrinologist) & Dr Namratha Upadhya (Specialist Paediatric Endocrinologist)

All consolidated specialist appointments were conducted on a single day for multidisciplinary screening of children with PWS. 13 children with PWS (9months-16yrs) and their families participated in the event including 2 virtual consultations. Pre-clinic problem list was created for each child followed by comprehensive evaluation by paediatric endocrinologists, pulmonologist, orthopaedician, ophthalmologist, dentist, nutritionist, psychologist, physiotherapist, and psychiatrist. Patients were given a handout with anticipatory guidance in PWS and tips to tackle common problems. All specialist inputs were collated, and a composite plan made for each child. The event was acknowledged by the Indian Prader Willi syndrome association on their social media handle and followed up by a virtual facebook live session on 27/5/22, by a multidisciplinary team to answer common queries in PWS.

ACTIVITIES BY PEAK MEMBERS

The CME programs under the flagship of PEAK

5. Paediatric Endocrinology CME at Mangalore

"The Harmony of Hormones", a Paediatric Endocrinology CME was conducted in association with PEAK and IAP Dakshina Kannada group on 12.06.2022 at Moti Mahal convention hall, Mangalore, Dakshina Kannada. It received an overwhelming response by more than 75 participants (including paediatricians affiliated to medical colleges, postgraduates and private practitioners). The program started with a talk by Dr Diksha Shirodkar on Congenital Hypothyroidism- A paediatrician's perspective and covered all the aspects of Congenital hypothyroidism right from how and whom to screen and how to manage. The second talk was on plotting of growth charts and approach to short stature given by the president of PEAK, Dr Shaila Bhattacharyya. This included Hands-on practical exercise on plotting growth charts. This was followed by an inaugural function wherein the office bearers of IAP DK, Ex-President Dr Santhosh Soans and PEAK president Dr Shaila Bhattacharyya lit the lamp. The post-tea session included a talk on Overview of DSD and Approach to CAH delivered by Dr Koushik Urala, Paediatric Endocrinologist from Kasturba medical college (Manipal university), Udupi. It was an interactive session and vote of thanks was given by IAP DK president Dr Shreekrishna GN.

ACTIVITIES BY PEAK MEMBERS

The CME programs under the flagship of PEAK

6. Paediatric Endocrinology CME at Raichur

The CME program at Raichur along with IAP Raichur conducted on 3/7/2022 had an overwhelming response with an attendance of over 50 participants including the post graduates. The CME started with Dr. Shaila Pachapure talking about the ambulatory management of type 1 diabetes followed by Dr. Pavithra Nagaraj discussing on the most commonly encountered paediatric endocrine cases in the OPD with hands-on session on growth charts along with approach to short stature. This was followed by a panel discussion on thyroid disorders in children moderated by Dr. Pavithra Nagaraj and the panellists were Dr. Amarnath Kulkarni, Dr. Chaithra, and Dr. Shaila Pachapure. Dr. Amarnath Kulkarni concluded the session by talking on the most awaited topic of interest- approach to hypoglycaemia in children.

ACTIVITIES BY PEAK MEMBERS

The CME programs under the flagship of PEAK

7. "Wishes fulfilled" at Karnataka Institute of Endocrinology and Research under the able guidance of Dr. Santhosh Olety and team

With the help of an NGO 'Make a Wish Foundation India' and under the able guidance of Dr. Santhosh Olety and his team, around 120 children with Type 1 diabetes were granted their wishes from February 2022 over 4 months. Wishes included cycles, TV, laptop, remote control cars, a family visit to a wildlife sanctuary, dresses, make-up sets, cricket kit, mobile phones, badminton sets, etc. Dr. Santhosh thanked all the kids and their families for their co-operation and enthusiasm. He was also grateful to Mr. Arun and Mr. Bosco (Make a wish team) for supporting and arranging the grants. Dr Indumathi , Director, Directorate of Health and Family Welfare services, Dr. Ravi (Director of KIER), the nutrition department and all the supporting staff were responsible for making this noble event possible.

THE PATIENT SPEAKS - AN INTERESTING CASE REPORT

Isolated Congenital Central Hypothyroidism Caused by a Novel TSHB gene Mutation

Ankita Srivastava, Fellow in Paediatric Endocrinology
Kavitha Bhat, Senior Consultant Paediatric Endocrinologist
Aster CMI hospital, Bengaluru

BACKGROUND:

Isolated congenital central hypothyroidism is rare (incidence 1 in 65000).[1] It is associated with either subnormal or inappropriately normal TSH levels and therefore evades diagnosis in newborn screening programs for congenital hypothyroidism (CH). The four human glycoprotein hormones chorionic gonadotropin, luteinizing hormone, follicle stimulating hormone, and thyroid stimulating hormone (TSH) are dimers consisting of alpha and beta subunits. The alpha subunits are identical; however, beta chains are unique and confer biological specificity. TSHB gene encodes beta subunit of thyroid stimulating hormone. Homozygous mutations in this gene result in severe, isolated, central congenital hypothyroidism (ICCH).[2]

CASE PRESENTATION:

A 22 months old boy presented to our unit with global developmental delay and abnormal thyroid function test. The patient was born to non-consanguineous parents following an uneventful, full-term pregnancy. His past medical history revealed that he was evaluated for poor weight gain at 1 month of age and was started on L-thyroxine (T4) treatment which was discontinued at 7 months of age. On physical examination, the patient exhibited a normal general condition with dry skin and hair, open anterior fontanelle with unchanged lung and heart auscultation. The patient's weight was 0.67 standard deviations and his length was –1.6 standard deviations of the age-appropriate value. Clinical phenotype, auxological parameters, and laboratory findings are shown in Table 1.

Laboratory tests confirmed the diagnosis of central hypothyroidism (TSH=0.02 mIU/L; Reference value (RV) =0.5–4.50 mIU/L and free

T4=0.29 ng/dL; RV=0.7-2 ng/dL). The patient also had a low total T3 level (10 ng/dl; RV=90-240 ng/dL).

THE PATIENT SPEAKS - AN INTERESTING CASE REPORT

TABLE 1. Clinical phenotype, auxological parameters, and laboratory findings before treatment	
Neonatal TSH-based screening	Not available
Gestational age	Full term
Birth weight [g (SDS)]	3400 (-0.67)
First endocrine clinic visit Clinical complaint	Global developmental delay
Chronological age (months)	22 months
Physical examination	Dry skin, AF open, no goiter, had erupted upper and lower central and lateral incisor teeth
Auxological parameters at diagnosis Body length [cm (SDS)] Weight [kg (SDS)] Head circumference [cm (%)]	 78.3(-1.6) 12.6 (0.67) 46.8 (10-25)
Thyroid ultrasound	Isthumus- 2mm normal Rt lobe 11x3.3x3.2mm Left lobe- 10x4x3.3mm
Radionuclide thyroid scan	No e/o functional thyroid tissue (agenesis of thyroid gland)
Cranial MRI	Pituitary hyperplasia
Thyroid function test at diagnosis TSH (mIU/liter) (RV, 0.5-4.5) FT4 (ng/dl) (RV, 0.7-2)	 0.01 0.29
Cortisol (mcg/dl) (RV, 3-21) Prolactin (ng/ml) (RV, 4.79-23.3)	 7.5 14.17
Age at onset of treatment (months)	22
	Dull normal intellectual functioning

Normal 8 am cortisol and prolactin levels (cortisol=7.5 µg/dL; RV=3-21 µg/dL; prolactin=14.17 ng/mL; RV=4.79-23.3 ng/mL) ruled out multiple pituitary hormone deficiency. Interestingly, sella magnetic resonance imaging revealed a hyperplastic pituitary gland an unexpected finding in patients with ICCH[3]. Moreover, no 99Tc thyroidal uptake was recorded, although ultrasound revealed a normal size thyroid gland. The diagnosis of ICCH of possible genetic origin was made, Levothyroxine therapy was initiated at a dose of 25 mcg/day with subsequent dose adjustments during follow-up.

OUTCOME AND FOLLOW UP:

The patient progressed with complete resolution of signs and symptoms of central hypothyroidism, but with dull normal intellectual functioning. Between the age of 7 months to 4-year child had 6 episodes of febrile seizure, diagnosis was established by normal MRI brain and sleep EEG.

By 7 years of age he had become obese and had developed dyslipidemia and at 9 years of age he had prediabetic HbA1C value in addition to dyslipidemia. During last visit at 9yrs 6 months of age his BMI had reduced from obese to overweight level. Molecular analysis was conducted 7 years later the clinical suspicion, which revealed a homozygous 2 base pair deletion in exon 2 of the TSHB gene (chr1:g.115033467_115033468del; Depth: 55x).The observed variation was in the RING-type zinc finger domain of the TSHB protein. This deletion results in a frameshift and premature truncation of the protein 38 amino acids downstream to codon 37 (p.Ala37LeufsTer38; ENST00000256592.3).

DISCUSSION:

ICCH is a rare variant of congenital hypothyroidism, the majority of cases is associated with mutations in the TSHB gene(OMIM#188540), and the inheritance is autosomal recessive[4]. The TSHB gene, located on the short arm of chromosome 1 (1p13.2), has three exons, two of which encode a 138 amino acid protein[5,6]. Nine different TSHB gene mutations have been reported, all with clinical manifestations[7]. In the present study, a

THE PATIENT SPEAKS - AN INTERESTING CASE REPORT

molecular analysis performed, when the patient was 9 years old, showed a mutation in exon 2 of the TSHB gene, (chr1: g.115033467_115033468del; Depth: 55x)., the variant which has not been reported so far in literature. The same variant was detected in heterozygous state in parents. Molecular analysis is important because it helps to extend genetic counselling to other family members. As described in the literature, newborn screening test shows high levels of TSH in primary congenital hypothyroidism, whereas normal concentrations of TSH and decreased concentrations of free T4 delay the diagnosis in newborns with ICCH. The patient described in the present report was diagnosed at 22 months of age, after exhibiting clinical manifestations of global developmental delay. The delayed diagnosis resulted in impaired cognitive development.

TAKE HOME MESSAGE:

Our case and other ones reported in the literature support the theory that mutation in TSHB may be a common cause of isolated TSH deficiency. Since in most screening programs attention is only paid to high TSH levels and fT4 is not measured, patients with ICCH are usually missed. Therefore, diagnosis and initiation of thyroid hormone substitution may be delayed in these cases, resulting in developmental delay.[8] reduce the diagnostic delay in patients with central hypothyroidism thyroid hormone levels (fT3, fT4) should be analyzed immediately if hypothyroidism is clinically suspected, and when possible, molecular genetic study is indicated. Identification of affected and carriers allows the diagnosis, treatment and adequate genetic counselling.

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THE PATIENT SPEAKS - AN INTERESTING CASE REPORT

Diabetic Ketoacidosis And Milky Serum

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We report a case of a 9-year-old developmentally normal school going girl who presented with history of abdominal pain, vomiting, hurried breathing and altered sensorium. Her random blood sugar by glucometer was 418mg/dl with HbA1c of 11.25%. Venous blood gas showed a pH of 7.29, with bicarbonate of 10mEq/L. She was admitted in a peripheral hospital and was started on Diabetes Ketoacidosis ISPAD protocol with intravenous fluids and insulin infusion. Her serum samples showed lipemia. On doing her lipid profile, elevated triglyceride level of 17700mg/dl and total cholesterol of 1420 mg/dl were found. She was referred to our center for further management after 24 hours. There was a history of dyslipidemia in both parents as well as among paternal grandparents.

On examination, her anthropometry showed a weight of 20kg at 3rd centile and height of 127cm between 3rd and 10th centiles on the revised IAP growth charts for 5-18 years. She did not have any cutaneous xanthomas. After hospitalization in the intensive care unit she was continued on intravenous fluids and insulin infusion. Her lipid profile showed an elevated cholesterol of 783mg/dl and triglyceride of 2763mg/dl. Her amylase and lipase levels were normal. With intravenous insulin, there was a decrease in the triglyceride levels from 2763 to 658 mg/dl. After 24 hours, child was switched to subcutaneous insulin. After discharge, the child was followed up and her lipid profile after 1 month was found to be normal with a total cholesterol of 137mg/dl and triglyceride of 62mg/dl. Currently the child is doing well on rapid acting and long acting insulin analogues – lispro and degludec respectively, with no further episodes of DKA or hyperlipidemia. Genetic testing was done as there was a family history of dyslipidemia, however there were no abnormalities found.

DISCUSSION :

Insulin is required for lipoprotein lipase activity which is involved in the metabolism of lipoproteins rich in triglycerides. In DKA, due to insulin deficiency, the triglyceride levels can therefore be elevated. Free fatty acid levels in DKA are elevated due to lipolysis in the absence of insulin. This can also lead to acute pancreatitis in Type 1 DM patients as a rare complication[1]. This child however did not develop pancreatitis. There was a resolution of hyperlipidemia with IV fluids and insulin infusion alone used as part of DKA protocol. A study done by Haddad et al among 50 pediatric DKA patients showed that 40% of them has triglyceride level above 200ng/dl[2]. The highest level of triglyceride in DKA has been reported by Kravetz et al in a 16 year old adolescent male, which was 40,176 mg/dl[3]. He also had pancreatitis. Hypertriglyceridemia required 2 courses of plasmapheresis as the triglyceride levels did not decrease with insulin

THE PATIENT SPEAKS - AN INTERESTING CASE REPORT

therapy. Plasmapheresis has been used for bringing down triglyceride levels above 1000mg/dl. In a systematic review by Click B et al which studied the role of apheresis in hypertriglyceridemia induced pancreatitis, it is stated that plasmapheresis must be instituted in cases of acute severe pancreatitis, if triglyceride levels remain elevated above 1000mg/dl despite IV fluid therapy and in those with signs of end-organ failure[4]. Further trials will be required to assess the efficacy and safety of plasmapheresis in pediatric population with DKA presenting with hyperlipidemia and pancreatitis. Baidwan et al reported a case of a 13 year old adolescent girl with DKA presenting with a triglyceride level of 22,228 mg/dl and mildly elevated amylase and lipase levels, with external features of eruptive xanthomas[5]. She required IV insulin for 7 days along with fenofibrate therapy in contrast to our patient who required shorter duration of IV insulin (i.e, 48 hours) and did not require fibrates to lower her triglyceride levels. Also the severe hypertriglyceridemia did not result in acute pancreatitis in our patient.

CONCLUSION:

Type 1 Diabetes mellitus often presents as Diabetic Ketoacidosis with altered lipid profile. The actual incidence of marked hyperlipidemia among pediatric patients is yet to be explored. Hypertriglyceridemia often responds well with appropriate Intravenous fluid and insulin therapy in children with diabetic ketoacidosis.

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THE DRUG SPEAKS

Liraglutide in Pediatric Obesity

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BACKGROUND:

Hidden behind the curtains of COVID-19, there has been another ongoing pandemic – Obesity. Worryingly, the increase has been more in children than in adults. The prevalence of obesity among 5- to 19-year-old Indian children across different studies has ranged between 3.6 and 11.7%.[1] As per World Obesity Federation; India is expected to have over 27 million children with obesity by 2030.[2]

Obese children are at higher risk of co-morbidities like pre-diabetes and diabetes, dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome (PCOS), obstructive sleep apnea (OSA) and psychosocial issues. Stepwise approach to obesity treatment includes (1) Lifestyle intervention (LSI) with dietary modification, physical activity and behavioral therapy which is the mainstay; (2) pharmacotherapy; and (3) bariatric surgery.[3] It is crucial to focus on the family as a single unit to follow lifestyle approach. LSI alone is generally associated with moderate weight loss; however weight is gradually regained in a subset of population, in whom pharmacotherapy may be indicated.

Glucagon-like peptide-1 (GLP-1) receptor agonists have shown promising results in various large-scale trials in adults (SCALE and STEP) in anti-obesity treatment. GLP-1 receptors are present in the hypothalamus, intestines and pancreas. Most important mechanism for the weight-reducing properties is activation of neural pathways causing reduction in appetite-regulating regions in the hypothalamus causing reduction in appetite and food intake and thereby promoting weight loss.[4,5] Liraglutide is the first and so far the only class of GLP-1 receptor agonist which has received FDA approval for use in children aged 12–17 years with obesity (weight >60 kg and BMI of >30 kg/m2 in accordance with international standards 10/≥95th percentile) in 2020. Clinical trials are ongoing on use of Semaglutide in pediatric obesity.obesity.

REVIEW OF LITERATURE:

Structurally, Liraglutide is a polypeptide which is 97% homologous to human GLP-1 with a fatty acid side chain attached through a linker molecule.[6] Semaglutide is similar to Liraglutide, though with minor changes in the GLP-1 moiety with an additional fatty acid side chain and it is 94% homologous to human GLP-1.[6] This modification gives Semaglutide a longer half-life allowing once weekly dosing versus once daily administration of Liraglutide.[7]

The safety and efficacy of subcutaneous Liraglutide 3.0 mg as an adjunct to lifestyle therapy for weight management in adolescents with obesity were evaluated in a randomized, double-blind, placebo-controlled, phase 3 trial between 2016 to 2019.[8] The trial had a 12-week run-in period, a 56-week treatment period, and a 26-week follow-up period without treatment. They enrolled individuals aged 12 to <18 years with obesity and a poor response to lifestyle alone. A total of 125 participants were assigned to the Liraglutide group and 126 to the placebo group.

Liraglutide was found to superior to placebo on comparing the change from baseline in the BMI standard deviation score at week 56 with an estimated difference –0.22. A reduction in BMI of 5% was observed in 43.3% participants in the Liraglutide group vs 18.5% of participants in the placebo; reduction in BMI of 10% was observed in 33% and 9% of

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participants respectively. The trial observed a greater reduction with Liraglutide compared to placebo for BMI [estimated difference, –4.64 percentage points], for body weight [estimated difference, –4.5 kg for absolute change and –5.01% for relative change]. On discontinuation of treatment, a greater increase in the BMI standard deviation score was observed with Liraglutide vs placebo.[8]

Gastro-intestinal adverse events were reported in more participants in the Liraglutide group (64.8% vs. 36.5%) and adverse events that led to discontinuation of the trial treatment (10.4% vs. 0%). Serious adverse events were reported in only a few participants in either group (2.4% vs. 4%). During the 26-week follow-up period, additional serious adverse events occurred in 1 participant [Liraglutide (1 event)] vs 4 participants [placebo (5 events)]. No clinically relevant differences with respect to results on mental health questionnaires were observed. Events related to psychiatric disorders occurred in Liraglutide (10.4%) vs placebo (14.3%). More episodes of hypoglycaemia were reported with Liraglutide vs placebo (26 vs. 18); none was considered as severe according to the ADA/ISPAD classifications. There were no apparent differences between both groups in growth or pubertal development.[8]

Currently, a double-blind placebo-controlled phase 3 trial is ongoing to evaluate the efficacy and safety of Liraglutide 3.0 mg on weight management in children with obesity aged 6–12 years (Clinicaltrials.gov ID:NCT04775082). Also, there is a phase 2 trial evaluating the efficacy of the use of Liraglutide in adolescents (12–20 years) with obesity after sleeve gastrectomy (Clinicaltrials.gov ID: NCT04883346) and a double-blind placebo controlled phase 3 trial evaluating the efficacy and safety of subcutaneous Semaglutide 2.4 mg once weekly in the management of adolescents (12-17 years) with overweight and obesity (Clinicaltrials.gov ID: NCT04102189).

SUMMARY:

The current data suggests that GLP-1 receptor agonists are safe and effective in reducing weight and in improving cardiometabolic profile in children with obesity who are poor responders to LSI. Liraglutide 3.0 mg as an adjunct to lifestyle therapy led to a greater reduction in the BMI than placebo in the trial. However, this treatment may not be suitable for all patients considering the higher frequency of gastrointestinal adverse events observed with Liraglutide. More large population based pediatric trials are needed in the near future to fulfil the knowledge gaps.

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CRITICAL REVIEW

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Chaudhary S, Walia R, Bhansali A, Dayal D, Sachdeva N, Singh T, Bhadada SK. FSH-stimulated Inhibin B (FSH-iB): A Novel Marker for the Accurate Prediction of Pubertal Outcome in Delayed Puberty. J Clin Endocrinol Metab. 2021 Aug 18;106(9):e3495-e3505.

STUDY ABSTRACT SUMMARIZATION:

This is a prospective investigational study by Chaudary S et al. to analyse the role of follicle stimulating hormone (FSH)-stimulated inhibin B (iB) for prediction of onset of puberty. A total of 62 subjects were enrolled into two cohorts, namely 'Explorative cohort (n=42)' and 'Validation cohort (n=19)'. The exploratory cohort was further divided into group 1 (healthy children with spontaneous puberty [SP], n=26) and group 2 (patients with hypogonadotropic hypogonadism [HH], n=16). The validation cohort included children who presented with complaints of delayed puberty. Participants were subjected to FSH-stimulation test and gonadotropin releasing hormone analog (GnRHa)-stimulation test. Cut-offs derived from the exploratory cohort for basal and FSH-stimulated iB (FSH-iB) were applied on the validation cohort. Basal LH, GnRHa-stimulated LH, basal iB, and FSH-iB were compared with clinical outcomes on a prospective follow-up (till 18 years or onset of puberty). There was a statistically significant increment in FSH-iB in both male (188.8 pg/mL; P = 0.002) and female (1065 pg/mL; P = 0.023) subjects of group 1 (SP) but not in group 2 (HH). FSH-iB at a cut-off of 116.14 pg/mL in males and 116.50 pg/mL in females had 100% sensitivity and specificity for predicting entry into puberty. On application of these cut-offs on the validation cohort, FSH-iB had 100% positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy for prediction of pubertal onset. Hence, the authors concluded that iB was FSH-stimulable in both male and female subjects. FSH-iB can be considered a novel and promising investigation for prediction of onset of puberty in adolescents with delayed puberty. However, future studies are required for further validation.

STUDY REVIEW:

CDGP and HH have similar clinical presentation at adolescence. Currently available diagnostic investigations for the differential diagnosis of delayed puberty include basal LH, GnRH-stimulated LH, testosterone response to hCG, and basal inhibin B. These tests are helpful; however, none is fully reliable.

For the first time Shakun et al explored the possibility of stimulability of iB by exogenous FSH, and provided a cut-off value for FSH-iB which could predict the onset of puberty with 100% specificity, sensitivity, PPV, NPV and diagnostic accuracy. The other aforementioned tests which are employed here, could not demonstrate such a potential in predicting the onset of puberty, and their diagnostic accuracy ranged from 55-82%. FSH-iB levels were able to perform accurately even in cases of subjects with typical phenotypic associations of HH and managed to enter puberty, showcasing its diagnostic acumen and utility in clinical grey zones. The authors utilized the concept of 'priming of gonads' which is believed to occur in normal individuals during minipuberty and prepubertal period, causing increased sensitivity of Sertoli cells to FSH and also development of stimulable levels of hormone pool. Simple protocol, short duration, easy availability of FSH, comparatively low cost, not requiring hospitalization, high accuracy are the factors which make FSH-iB levels a game changing step in evaluation of delayed pubertal disorders.

LIMITATIONS:

Small number of subjects in validation group is a significant limiting factor, and hence, the need for further studies validating the same in large cohorts. Secondly, the tests were validated against entry into puberty and not the completion of puberty. As both partial HH and constitutional delay in growth and puberty (CDGP) may demonstrate entry into the puberty, the ability of the novel test to differentiate the two conditions needs further evaluation.

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Upcoming Events

- August 2022: CME in Gadag under the flagship of Harmony of hormones
- September 2, 2022: Bangalore Pedicon workshop
- October 14, 2022: Paediatric Endocrinology workshop in South Pedicon

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