APRIL 2021
Volume 25, Issue 1

ISPAE

CAPENEWS

Newsletter of The Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)

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Theme: GROWTH AND ITS DISORDERS

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Message from ISPAE Office Bearers

Dear Fellow ISPAE Members

Greetings from ISPAE executive Council 2021-22!

At the outset we congratulate the newly appointed CAPE NEWS team led by Dr Hemchand Prasad. We are confident that the new team will do a wonderful job with newer ideas and inputs.

We are happy to announce that the 7th ISPAE Biennial meeting 2021 is being held at Pune by the team led by Dr Vaman Khadilkar, Dr Supriya Gupte and Dr Rahul Jahagirdar. ISPAE-PET will also be organized at Pune with Dr Sarah Mathai & Dr Ahila Ayyavoo as the Convenors.

The newly elected ISPAE team has started working since the first week of Jan 2021 and have taken up some important and challenging jobs at hand including the start of ISPAE's official Journal, overhaul of ISPAE Website including online ISPAE membership formalities, advocacy for nationwide newborn screening for congenital hypothyroidism, ISPAE-ACES program targeted specifically to post-graduates in Pediatrics, Pediatric Endocrine Fellows, and practicing general pediatricians (report included in this issue of CAPE NEWS). Hopefully, we will be able to successfully run these programs with active support of all ISPAE members.

We encourage all ISPAE members to conduct more and more academic and other patient welfare activities under the banner of ISPAE, motivate young Pediatricians to take up ISPAE membership and provide advocacy for universal newborn screening in their region and States.

We appeal all ISPAE members to kindly provide suggestions and inputs on existing activities of ISPAE and any other activities which could be initiated for welfare of ISPAE members and children with Pediatric Endocrine disorders.

Best wishes
Shaila Bhattacharyya
Ganesh Jevalikar
Rakesh Kumar

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From the Editor's Desk

Dear ISPAE members,

Greetings from the Editorial Board of CAPE News.

It gives us immense pleasure to connect with ISPAE members through the new look, theme based, CAPE News as I pen this message on behalf of our dynamic team: Dr Anju Virmani (advisor), Dr Aashima Dabas, Dr Diksha Shirodkar, Dr Ravindra Kumar, Dr Nikhil Lohiya and Dr Pragya Mangla. We look forward to carrying the good work done by the previous team led by Dr Rakesh Kumar. Our editorial team has compiled this newsletter with contributions from many members of our Society. We thank all members who contributed.

We plan to have a theme for each issue: the theme of the current issue is "Growth and its Disorders". It carries an interesting review on pediatrician friendly growth charts, an extensive Pedendoscan, a summary of recent GHRS guidelines, and mini-reviews of GH therapy for idiopathic short stature and chronic kidney disease.

We have added: a Patient Corner, a History section, a Drug Corner and a Biochemistry Corner to CAPE News, which we hope members will find useful and interesting. Information on the ISPAE website and upcoming ISPAE meetings is also available. There is a fun crossword for trainee members to solve - we will acknowledge correct submissions in the next issue.

The theme of the next issue is "Obesity". Contributions and feedback/ suggestions for improvement are awaited at editor.capenews@gmail.com.

Regards,

Dr Hemchand K Prasad
Editor, CAPE News 2021-22

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Mini Review- Pediatrician Friendly Growth Charts and Extended Growth Charts

Dr Vaman Khadilkar[1], Dr Madhura Karguppikar[2]
[1]Consultant Pediatric Endocrinologist, Jehangir Hospital, Pune; [2] Fellow Pediatric Endocrinology, Jehangir Hospital, Pune

Growth charts are a time-tested tool used by health care workers, pediatricians and parents to track growth in infants, children and adolescents. Apart from reassuring normal growth, they aid in early diagnosis and intervention in a number of disorders before they become florid. The IAP 2015 growth charts are the most recently updated references on nutritionally well-off children in India.[1] Over the years, growth charts have evolved to conform to the changing trends of growth. [2,3,4] The most recent refinement has been to introduce Pediatrician Friendly IAP Growth Charts for 0-18 years, and Extended Growth Charts for Indian children. [5,6]

The Pediatrician Friendly growth charts have incorporated a quick BMI screening tool and an MPH percentile lookup tool to make it easier for a busy pediatrician to plot the growth parameters while avoiding cumbersome calculations. The quick BMI screening tool is based on weight for height which eliminates the need to calculate BMI and can help to deduce if a child is overweight, obese, normal or underweight. The tool can be used in children beyond 8 years of age; while it does not provide the exact BMI in numbers, it gives a fair estimate of the child's nutritional status and guides further evaluation. It is important to note that since it is a screening tool, all those who are graded as abnormal, need to be confirmed by calculating BMI and plotting on the IAP BMI charts. Since overweight and obesity are a growing problem in India and are associated with various risks like metabolic syndrome, increased risk of coronary heart disease, and stroke, it is important to detect and treat early.

Mid parental height assessment is necessary to understand the child's genetic potential and to check if the child is currently growing within the genetic potential. The MPH percentile lookup tool is a simplified way to eliminate the calculation of MPH: the user can deduce the MPH percentile by joining the father's height to the mother's height (both in cm) and reading the MPH percentile on the middle line for that specific gender. These charts are aimed at helping and encouraging the pediatrician to plot growth on a regular basis without having to do calculations.

Most growth charts depict the standard 7 percentiles (3rd, 10th, 25th, 50th, 75th, 90th, and 97th) for height and weight. While these are sufficient for the majority of health workers to assess growth, even lower centiles and specific height z-score cut-offs are desirable to help endocrinologists to rapidly assess the degree of shortness. This is of particular importance since the degree of shortness guides further evaluation and intervention. Also, initiating and monitoring of any growth enhancing therapy, e.g. growth hormone (GH) therapy in specific indications is necessary for the endocrinologist. Thus, small for gestational age (SGA) children below −2.5 z- score for height and idiopathic short stature below −2.25 z-score qualify for GH therapy, −3 z-score line indicates severe short stature and requires evaluation of the GH-IGF 1 axis, as per recent GHRS [Growth Hormone Research Society] guidelines. Extended growth charts provide extended height percentile lines (10 lines). Additional height z-scores lines are -3 z-score, -2.5 z score and -2.25 z-score. The charts also depict the standard (7 lines) weight charts, and quick BMI assessment tools.

Thus, the pediatrician friendly growth charts and extended growth charts add more value to the existing growth charts: aimed for use by pediatricians and endocrinologists respectively. We would recommend the reader to refer to the IAP website and the paper published in JPEM for a detailed discussion of these charts.

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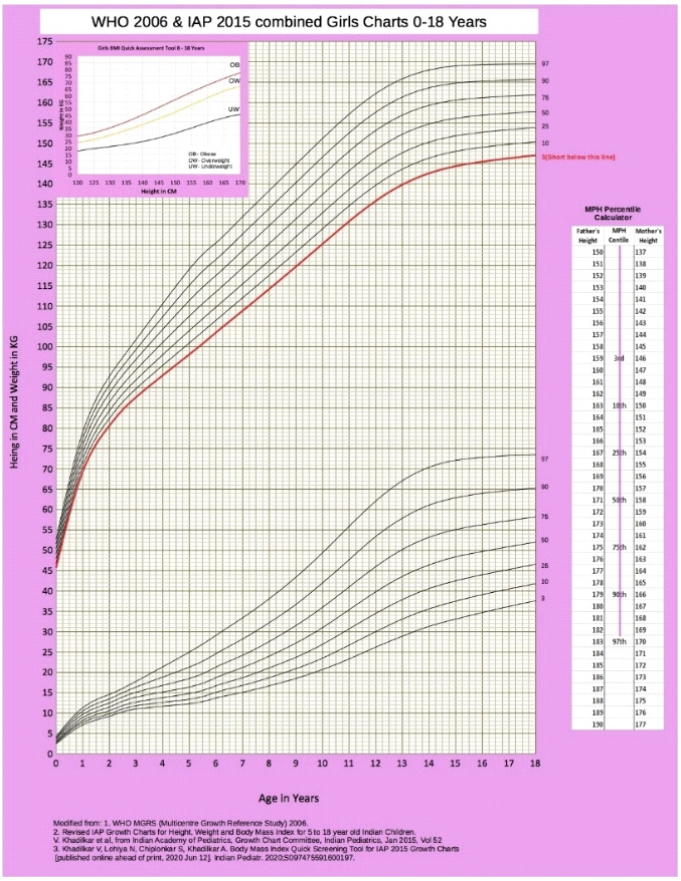

Figure 1: Pediatrician friendly IAP Growth Charts for 0-18 years for Girls (Permission obtained from IAP to reprint for academic purposes)

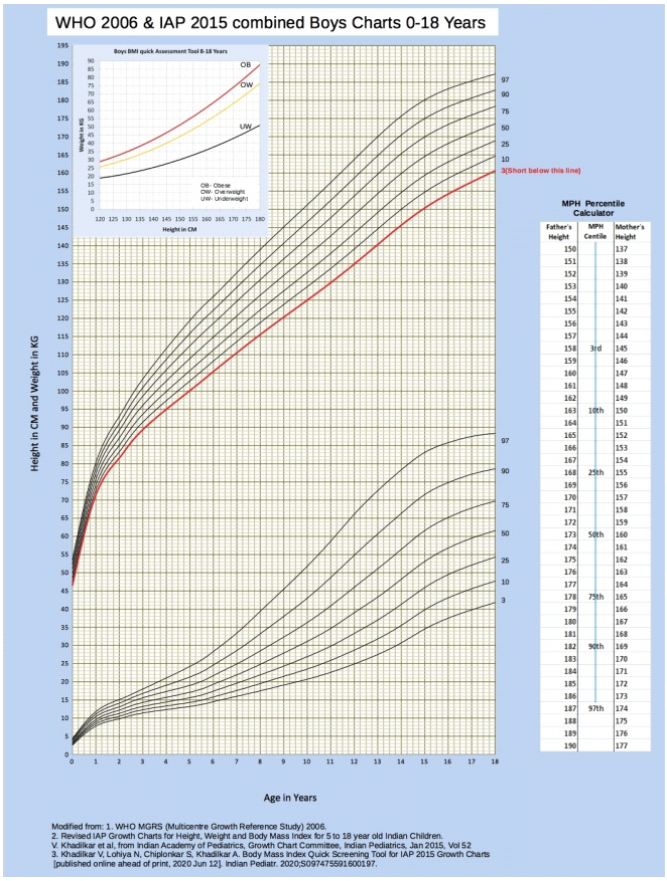

Figure 2: Pediatrician friendly IAP Growth Charts for 0-18 years for Boys (Permission obtained from IAP to reprint for academic purposes)

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Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective

Excerpts from Recent Guidelines

Compiled by : ***Dr Ravindra Kumar***
I/C Pediatric & Adolescent Endocrinology, Hindu Rao Hospital, Delhi.

Recommendations

A. Auxology

1. Children with any of the following characteristics should be considered for evaluation of pathology:
a) short stature with a height SDS below –2.
b) Height that clearly deviates from the familial background.
c) A significant decrease in height SDS (i.e., a deflection of at least 0.3 SDS/year that is not explained by the normal channelling in infancy to adjust linear growth to target height trajectory.
d) The prepubertal growth dip or pubertal delay.
2. Diagnosis of growth hormone (GH) deficiency (GHD) does not require a height cut-off, particularly in the context of very young children with hypoglycaemia and/or midline defects/ pathologies, or recently developed GHD.
3. A short child who has a short parent (Familial Short Stature) may have an underlying genetic cause requiring evaluation.
4. Interpretation of a child's height and height velocity based upon his/her pubertal status reduces misclassification of children with delayed puberty as having GHD.
5. The use of sitting height/height ratio is believed to be more reliable and reproducible, and is preferred over upper/lower segment ratio when available.
6. Patients should be assessed for dimorphisms that may provide clues to the underlying diagnosis, such as a SHOX deficiency (mesomelia and Madelung deformity) or constitutive activation of FGFR3 (macrocephaly and lumbar hyperlordosis).
7. Advanced bone age in a family with dominantly inherited short stature may suggest a mutation in the gene encoding aggrecan [ACAN].

B. Testing for GHD

1. The diagnosis of GHD remains a clinical one, where one synthesizes auxologic, anatomic, and laboratory data to arrive at a diagnosis.
2. It should not be made based solely on laboratory testing.

C. IGF-1/ IGFBP-3

1. IGF-1 measurement should be undertaken using an assay with reliable reference data, with ranges based on age, gender, and pubertal status.
2. Under the age of 3 years, the normal range of IGF-1 values may overlap in children with and without GHD, hence a low IGF-I in young children is difficult to interpret.
3. An IGF-1 level > 0 SDS at any age makes GHD unlikely.
4. IGF binding protein 3 (IGFBP-3) is considered a more reliable biomarker than IGF-1 in children < 3 years of age.
5. A low IGFBP-3 in combination with low IGF-1, while raising the likelihood of GHD, may also be found in long-standing malnutrition and GH insensitivity, including genetic defects in GHR, STAT5B, and IGF ALS.
6. A low IGF-1 associated with normal or elevated IGFBP-3 may be a sign of an IGF-1 genetic defect.

D. Imaging in the Evaluation of GHD

1. An MRI of the hypothalamus and pituitary gland should be performed in all patients diagnosed with GHD, to detect anatomical defects of the hypothalamic-pituitary region, brain tumors, or other CNS disorders.
2. For the initial evaluation in newborns with midline defects, microphallus, and hypoglycemia, cranial MRIs with a focus on the pituitary and hypothalamus are especially useful.
3. If large sellar masses or certain pituitary defects (such as a hypoplastic pituitary gland, hypoplastic or absent stalk, or ectopic posterior pituitary) are present, formal GH provocation testing may be unnecessary when there are other clinical features indicating GHD.
4. Findings on MRI that are most supportive of a diagnosis of GHD include absence of the anterior pituitary gland (empty sella), ectopic posterior pituitary gland, and hypoplasia of the pituitary stalk and/or pituitary gland.
5. The finding of a small pituitary gland by itself is not sufficient to make the diagnosis of GHD, but it may indicate the need for a more extensive evaluation of pituitary function.

E. Clinical Settings for GH Stimulation Tests

GH stimulation test is not necessary

1. In neonates with a high pretest probability of GHD, a random GH level < 7 ng/ml in the first week of life supports the diagnosis of GHD.
2. In infants with a combination of a history of hypoglycemia, hyperbilirubinemia, poor growth, midline defects , microphallus, low IGF-1 and IGFBP-3, multiple pituitary hormone deficiencies, such as TSH and ACTH deficiency, and/or an abnormal cranial MRI.
3. When an alternative diagnosis for short stature is evident e.g. Turner syndrome, Noonan syndrome, Prader-Willi syndrome (PWS), aggrecan deficiency, SHOX deficiency, chronic renal insufficiency, Silver-Russell syndrome (SRS), or in children born small for gestational age (SGA) with unexplained persistent short stature.

Performance and Interpretation of GH Stimulation Tests

1. GH stimulation tests should be performed in the fasting state after adequate replacement of other hormone deficiencies (hypothyroidism and hypogonadism).
2. Failure to respond to 2 provocative stimuli is needed to diagnose GHD.
3. However if there is a high index of suspicion, a single test may suffice to diagnose GHD.
4. A sufficient GH response in one test rules out GHD in most cases.
5. Severe GHD is often defined as a peak GH level < 3 ng/mL on provocative testing in combination with a high prior likelihood of severe GHD based on clinical, laboratory, and imaging information.
6. GH assays, with the advent of monoclonal antibody testing and newer standards, produce GH measurements that are approximately 40% lower than those obtained using older immunoassay-based testing.
7. Hence threshold be revised to 7 ng/mL, depending on the assay.

Sex Steroid Hormone Priming

No clear consensus exists for the use of GH priming outside of adolescence when there is delayed puberty.

F. Genetic Testing for the Evaluation of Short Stature

Should be utilized in the diagnostic assessment of

1. Familial forms of isolated GHD
2. Specific syndromic forms of multiple pituitary hormone deficiencies.
3. Severe short stature (<–3 SDS for the population or > 3 SD lower than mid-parental target height),
4. Body disproportion and/or skeletal dysplasia,

5. SGA who did not present adequate catch-up growth.
   - Whole exome sequencing should be focused on children with the most severe short stature and those with syndromic features.
   - If genetic tests reveal no abnormality, a methylation analysis may be ordered (especially for SGA children).

G. Treatment with rhGH

1. The dose of recombinant human GH (rhGH) should be individualized according to GH responsiveness aiming for the lowest effective dose.
2. The starting dose of rhGH in GHD varies can be 25 µg/kg/day.
3. Patients with more severe GHD, should be initially treated with lower doses of rhGH i.e. 17–35 µg/kg/day may suffice for catch-up growth and attainment of a normal adult height.
4. In infants and adolescents, patients with obesity and those with PWS, rhGH dosing may be based on body surface area rather than weight.
5. The appropriateness of the rhGH dose should be assessed based on height velocity and change in height SDS every 6–12 months.
6. Measurement of IGF-1 levels should be considered annually but may be done more frequently (e.g., after a dose adjustment) or to monitor compliance.
7. When using IGF-1 levels to adjust dose, in general, be close to 0 SDS in GHD. In non-GHD conditions, such as ISS, IGF-1 levels of approximately +1 SDS or higher are usual.
8. Low levels of IGF-1 may indicate poor adherence, inadequate storage, or the presence of another condition affecting GH response.
9. High IGF-1 levels may reflect some degree of IGF-1 insensitivity, especially if associated with a poor growth response.

Suboptimal Response to rhGH

An inadequate response after initiation of rhGH therapy in patients with GHD is often defined as

1. Height velocity < 2 cm/year,
2. Height velocity SDS < 0
3. Height SDS < 0.3/year during the first 6–12 months of therapy.

1. When a suboptimal growth response for pubertal status is noted, a review of adherence and injection techniques is indicated.
2. IGF-I levels can help identify adherence, GH or IGF-1 resistance conditions.
3. Re-evaluation of other etiologies of growth faltering should be performed even after a diagnosis of GHD or other conditions, as the onset of scoliosis and chronic illnesses (in particular, celiac disease and inflammatory bowel disease), hypothyroidism, inadequate nutrition, medications that impair growth, and challenges in the psychosocial environment may inhibit the response to GH.
4. In rare cases of whole GH1 deletions, the presence of neutralizing anti-GH antibodies should be assessed.
5. If none of the above conditions is present, and IGF-1 levels are below the target range, the rhGH dose can be increased to determine whether height velocity and the IGF-I level increases.
6. rhGH should be discontinued if suboptimal response persists.

Alternative Treatments for Suboptimal Response to rhGH

1. May include nutritional and other interventions.
2. If due to genetic forms of GH insensitivity, may respond to rhIGF-1.
3. Aromatase inhibitors in pubertal boys could be considered, but this remains controversial and off-label.
4. Adding a GnRH analogue to rhGH therapy may be considered for children with GHD or SGA and/or SRS patients if height SDS is low at pubertal onset.

H. Safety of rhGH in Children

1. Side effects caused by rhGH therapy are uncommon; there is paucity of data linking the rhGH dose to treatment-related adverse events.
2. Some genetic conditions, such as Turner syndrome, are associated with an increased risk for adverse events.

I. Recent Developments

1. **New Diagnostic Tests**
   i. Macimorelin, a ghrelin agonist that provokes GH release from the pituitary was recently approved as a diagnostic test for GHD in adults in USA and Europe.
   ii. There are no published data regarding the use of this agent in children.
   iii. The use of GH secretagogues as diagnostic tests in children may fail to identify children with hypothalamic dysfunction.
   iv. GHRP2 is an intravenous GH secretagogue used in Japan with the advantage of stimulating ACTH release and the potential ability to assess the hypothalamic-pituitary-adrenal and GH axes simultaneously.
2. **New Growth-Promoting Agents**

i. Long-Acting GH

a) Available for commercial use in China and Korea.
b) These drugs can be administered weekly or even less frequently, which may improve adherence.
c) They are currently being studied in pediatric and adult populations.

ii. Oral Ghrelin Analogues

a) May have potential in children with hypothalamic GHD or milder degrees of pituitary dysfunction.
b) May also be effective in non-GHD children with low BMI, such as SGA, ISS, SRS, and Noonan syndrome given their orexigenic effects.

iii. C-Natriuretic Peptide Analogues (CNP)

a) CNP is expressed in the growth plate and is an important regulator of chondrocyte proliferation and differentiation.
b) CNP analogues may be theoretically useful in hypochondroplasia, CNP deficiency, heterozygous NPR2 mutations, other skeletal dysplasias, and ISS.

Reference:

Paulo F. Collett-Solberg, Geoffrey Amble Philippe F. Backeljauw, Martin Bidlingmaier, Beverly MK Biller, Margaret CS Boguszewski et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. Horm Res Paediatr. 2019; 92(1):1-14

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Growth in Chronic Kidney Disease – Mini-Review

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Introduction

Chronic kidney disease (CKD) is a major health problem worldwide, with increasing incidence and prevalence that is threatening to bring on the onset of a real epidemic[1]. Indeed, pediatric CKD, while sharing the basic pathophysiologic mechanisms with the same disease in adults, presents with certain clinical features that are specific and peculiar to the pediatric age, such as the impact on growth. Approximately 40% children with end stage renal disease (ESRD) have a final height below the 3rd percentile comparing with that of healthy age matched and sex matched controls. It not only affects the psychosocial development of a child but also has significant effects in adult life[2].

Pathophysiology[3,4]:

The etiology of growth failure in CKD is multifactorial and includes malnutrition, mineral and bone disorder, metabolic acidosis, loss of electrolytes and disturbances of somatotropic and gonadotropic hormone axes.

a) SOMATOTROPIC AXIS: Growth hormone (GH) is important in regulating somatic growth, muscle and bone metabolism. CKD is a state of GH insensitivity, characterized by deficiency of functional insulin – like growth factor 1. Increase in IGF binding capacity leads to decreased bioactive IGF, despite normal total IGF levels. 2. Elevated levels of immunoreactive low molecular weight fragments of IGFBP3, especially the 29kDa fragment, which has reduced affinity for IGF peptides, results in impaired delivery of IGF to target sites. 3. Reduced density of GH receptors (GHR) in target organs. This paucity of GHR is reflected by decreased serum levels of GH binding protein that is a product of proteolytic cleavage of the GHR. 4. Defect in the post-receptor GH activated janus kinase/ signal transducer and activator of the transcription signaling pathway.

b) GONADOTROPIC AXIS: Decreased renal clearance of gonadotropins leading to elevated gonadotropin levels and reduced pituitary secretion of bioactive luteinizing hormone and increase in sex hormone binding globulins can occur in adolescents with CKD. These physiological abnormalities contribute to pubertal growth impairment in adolescence.

c) NUTRITION: Nutrition is important in all phases of human growth, particularly so during infancy, because the rate of growth is highest and least dependent on GH /IGF system. Although the mechanisms for cachexia are complex, contributory factors include: anorexia; nausea and vomiting (uremic toxicity, metabolic acidosis, imbalance of regulatory proteins of energy intake such as Leptin, Adiponectin, Resistin and Ghrelin – all levels are increased with declining renal function, resulting in poor growth and cachexia); increased basal metabolic rate; loss of lean body mass and decline in serum proteins.

d) METABOLIC ACIDOSIS: Reduces GH secretion and serum IGF 1 levels, induces resistance to anabolic actions of GH, suppresses albumin synthesis, increases calcium efflux from bone and enhances protein degradation.

e) CKD-MINERAL AND BONE DISORDER (CKD-MBD): Both high-turnover bone disease and low-turnover bone disease, adversely affect growth. Secondary hyperparathyroidism seen in high-turnover states modifies genes involved in endochondral bone formation and alters architecture of the growth plate. Osteoblast activity and bone mineralization are decreased in low-turnover bone disease, which translates into decreased bone formation and impaired growth.

Clinical assessment and evaluation of a child with CKD and growth faltering

The clinical approach to a short child with CKD is summarized in figure-1. Children with clinically defined CKD (GFR <75 ml/min per 1.73 m2 body surface area) should have meticulous history taken and growth assessed using standard calibrated instruments. Age of onset of renal disease (severe in early onset), type of renal disorder (severe in renal dysplasia and obstructive uropathy) and optimization of dialysis regimen should be enquired into. Records should be assessed to see if: acidosis is corrected, Vitamin D levels and parathormone levels are in recommended range and hemoglobin is maintained.

Assessment includes: Length (children < 2 years), Height (children more than 2 years), Weight (in all children) and Head circumference (children < 3 years). Growth velocity should be calculated in all children. Appropriate growth chart should be used to assess growth: WHO 2006 standards (< 5 years), IAP 2015 charts (>5 years) and Indian Growth velocity charts. The frequency of assessment includes: 0.5-2 monthly, 1-2 monthly and 1-6 monthly in children <1 years, 1-3 years and >3 years, respectively. The target height should be calculated and genetic height potential assessed. Sexual maturity should be assessed by Tanner's staging. Children with CKD who have height <3rd percentile or growth velocity < 25th percentile should be evaluated further.

Assessment of growth potential is done by bone age recording. Baseline investigations include complete blood count (hemoglobin, hematocrit), urea, creatinine, electrolytes, metabolic acidosis, serum albumin, protein, calcium, phosphorous, vitamin D, parathormone. A thyroid profile should be done in every child with growth faltering and CKD.

Approach to management

Therapy is aimed at correcting linear and somatic growth.

Step 1: To adequately correct potentially treatable causes of growth failure for a period of 3 (infants) to 6 (children and adolescent) months and reassess height & height velocity.

1. **Correction of malnutrition –** Adequate intake of calories (80% average energy requirement) and proteins (ensure Reference nutrient intake of 2SD above average), replacement of water soluble vitamins. Feeding may be optimized by nasogastric feeding or gastrostomy, where required.
2. **Correction of anemia –** Target hemoglobin levels should be maintained by intravenous iron therapy or erythropoietin administration.
3. **Correction of metabolic acidosis -** 88% of children with CKD and growth retardation are acidemic. Serum bicarbonate should be maintained >22 mmol/l. This is done by oral bicarbonate or lactate based dialysis solutions.
4. **CKD – MBD -** Vitamin D and calcium should be adequately replaced with the aim of keeping PTH in the upper range of normal in children with stage 1–3 CKD, and less than 3 times upper limit of normal in stage 4–5 CKD. Optimal levels of calcium and parathormone is maintained by using and titrating the dose of calcitriol (activated vitamin D3) and alfacalcidol. Serum phosphorous should be maintained <1.5 times upper limit of normal for optimal growth. Serum phosphate levels can be controlled by dietary restriction, modification of dialysis prescriptions, and use of phosphate binders.
5. **Other measures** – children with tubular disorders should have adequate sodium supplementation and free water. Water soluble vitamins like vitamin C, folate and Vitamin B12 should be replaced where necessary. Intensification of dialysis, use of biocompatible peritoneal dialysis should be performed with increased protein administration for growth optimization. Renal transplantation can also lead to growth catch up and improved final height in children with CKD.

Step 2: Growth hormone (GH) therapy in children with CKD leads to catch up growth by increasing IGF-1 level and direct action on the growth plate**.** Persistent growth failure (height <3rd percentile and height velocity <25th percentile beyond a period of 3 months (infants) and 6 months (children and adolescents), despite adequate management of treatable causes, mandates GH supplementation. The key aspects of GH therapy are summarized in table-1. GH is administered as a once a day sub-cutaneous injection. The site of injection should be changed frequently to avoid local complications. Both reference and biosimilars can be used. GH therapy does not lead to deterioration of renal function or compromised safety in transplanted children. Growth velocity > 75th percentile is indicative of catch up. If growth velocity is < 2 cm/year (indicating poor response), one should consider: poor compliance, appropriateness of dose for weight and uncorrected metabolic factors. The anticipated increment in height is 7.2 cm for 2-5 years of GH therapy, with an average increase of +1.0 to +1.4 SD in the prepubertal years. A favourable response is expected in those with: severe stunting, severe bone age delay, longer duration of GH, lesser duration on conservative therapy, severe CKD and early GH therapy.

Table-1. Growth hormone therapy in children with CKD

Indication for GH therapy	Height < 3rd percentile and Growth velocity < 25th percentile with CKD ⩾ stage 3 and no catch up despite conservative measures
Baseline assessment	IGF-1, thyroid profile, fundus assessment
Contraindications	Elevated parathormone levels > 500 pg/mL (increased risk of slipped capital epiphyses), severe diabetic retinopathy, active malignancy and acute critical illness
Dose	0.045 – 0.05 mg/kg/day once a day subcutaneously
Side effects	Slipped capital femoral epiphyses, avascular necrosis, impaired glucose tolerance, benign intracranial hypertension
Monitoring therapy	Growth parameters (height, weight, BMI and growth velocity) Repeat fundus assessment (if headache and vomiting) Measurement of blood sugar and thyroid profile
End point for therapy	Height > 3rd percentile for the population or acceptable for the target height

Special situations

Infancy: GH therapy is safe in infants beyond 6 months. The advantages of early initiation include: lowered dose, improved final height, early transplantation and improved psychological benefit.

Adolescents: GH therapy can be useful in adolescents with unfused epiphyses. Adolescents with severe delayed puberty (no breast budding beyond 15 years or no testicular enlargement beyond 16 years) can be candidates for a short course of sex hormone replacement.

Conclusion

Growth assessment is a pivotal aspect of care of children with CKD. Children with growth faltering should have rectification of correctable factors. GH is a useful and feasible option or growth augmentation in children with CKD who fail to catch up despite conservative measures. GH therapy leads to growth catch up and improved final height in children with CKD.

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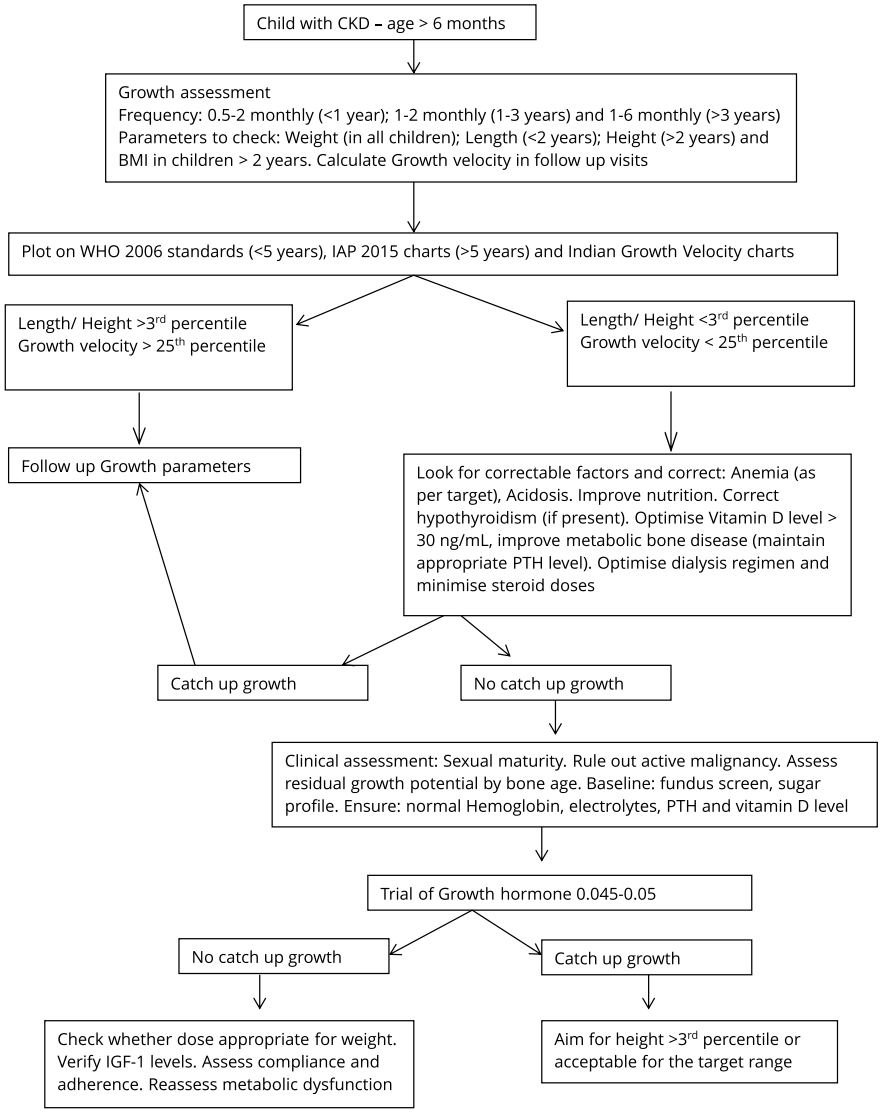
Figure 1. Approach to growth faltering in CKD



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ROLE OF RECOMBINANT GROWTH HORMONE IN IDIOPATHIC SHORT STATURE

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Growth assessment is of pivotal importance in pediatric practice. A common complaint in a pediatric clinic is short stature. Idiopathic short stature (ISS) is a condition in which the height is lower than gender- and age-matched normal children by two standard deviations (SD), excluding short stature induced by growth hormone deficiency (GHD), small-for-gestation (SGA), systemic disease, other endocrine disorders, nutritional diseases, chromosomal abnormalities, skeletal dysplasia, and psychological and emotional abuse. The diagnosis of ISS is described in Table-1. ISS encompasses a heterogenous group of disorders including skeletal and cartilage disorders, genetic defects related and unrelated to the GH pathway, and normal variant short stature where children have appropriate stature for their skeletal maturity or parents' heights. It has generally been seen that in ISS, adult height is less than the target height. The incidence of ISS in the USA is 23/1000 (1). The incidence of ISS in India is not known.

US FDA approved the use of recombinant human GH (rhGH) therapy for children with ISS in 2003. A consensus guideline described the use of GH therapy in ISS in 2008 (2). ISS is an emerging indication for GH therapy in a developing country like ours.

GH therapy can be considered in children more than 5 years when height is below -2.25 SD for the population as described in the new extended growth charts for Indian children (3). The rationale of GH therapy includes: improvement of short term growth, improvement of final height, and reduction of psychological distress. The pros and cons of GH therapy should be discussed at length prior to taking a decision to initiate therapy or not (Table-1). Children with ISS are essentially healthy, so any intervention should be individualised on a case-to-case basis after explaining the safety, burden and anticipated auxological benefit to the family. Supraphysiologic dosages of rhGH, administered over several years, are needed to successfully overcome 'endogenous GH resistance.' It should be kept in mind that despite encouraging mean response data, a substantial proportion of children exhibit only minimal increases in adult height following years of costly and invasive treatment. A final height increment of 4-7.5 cm is described with 4-7 years of GH therapy in children with ISS (2). Also, it remains unproven whether rhGH-mediated height increases translate into clinically meaningful improvements in the long-term psychological well-being of the child.

The safety profile of GH therapy in children with ISS is comparable to GH therapy for other FDA approved indications. They should be monitored for side effects and response to therapy (4,5,6), which can be discontinued when the child reaches a height acceptable for the population (height above -2 SDs) or when height velocity falls below 2 cm/yr, and/or when bone age is >16 yr in boys and >14 yr in girls. Stopping therapy is influenced by patient/ family satisfaction with the result of therapy or ongoing cost-benefit analysis.

Table - 1. Growth Hormone Therapy for ISS (2,7)

Criteria for diagnosis	Auxological criteria for initiation of GH therapy	Dose	Monitoring	Indication to stop GH therapy
Normal birth weight Normal GH response to stimulation test No systemic disease Normal proportions No endocrine disease No chromosomal defect Normal nutrition	Height SD score < -2.25 Age ⩾5 years	45-65 µg/ kg/ day	Clinical: height, weight, BMI, growth velocity, Blood pressure, fundus assessment for benign intracranial hypertension, clinical assessment of scoliosis and slipped capital femoral epiphyses Biochemical assessment: IGF-1 and blood sugar	Height SDS > -2 in the range acceptable for the population or Growth velocity < 2cm/year with bone age more than 14 years in girls and 16 years in boys

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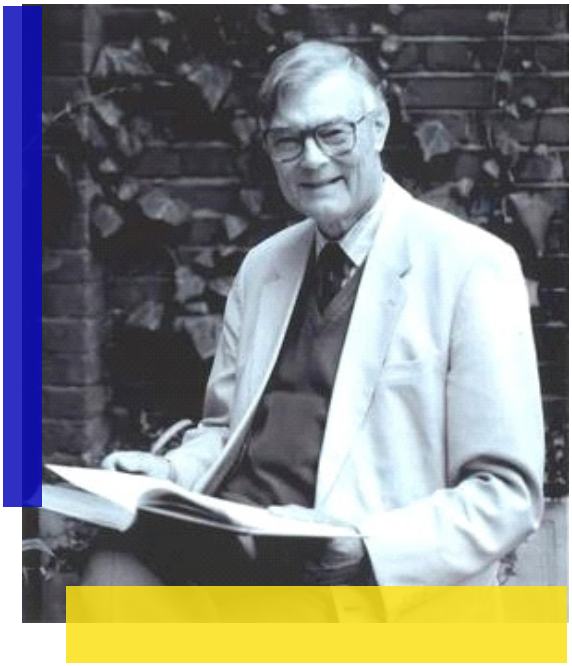
HISTORY CORNER

Dr Nikhil Lohiya, Pediatric Endocrinologist, Silver Lining Pediatric Super-specialty Center for Growth, Development, Behavioral & Endocrinology, Nagpur.

J M Tanner is a world-recognized figure and his contribution to the field of pediatric endocrinology in growth and puberty is known to everyone. He was inarguably the authority in growth disorders during the second half of the 20th century.

Jim Tanner started his medical training at St Mary's Hospital Medical School, London. He was an athlete and got admission through a scholarship for athletes. During World War II, to avoid interruptions in medical studies, the Rockefeller Foundation created scholarships for medical students in London, to finish their studies in the USA. Tanner was selected for this fellowship, and completed his medical training at the University of Pennsylvania, followed by 9 months of internship at the John Hopkins Hospital. In his first study, during his training, he assessed the blood pressure in 53 individuals and found that body structure influences the measurements. From this, he developed an interest in anthropology. He returned to England to obtain a diploma in Psychology Medicine, and was involved in the rehabilitation of soldiers and families who were traumatized post-WWII. He also obtained the Viking Trust Travelling Fellowship to visit different centers in the USA doing longitudinal growth studies, and came back to the UK with a desire to initiate the first British longitudinal growth study.



James Mourilyan Tanner

Image source- https://www.rcpch.ac.uk/paediatrician/professor-james-mourilyan-tanner

In 1949, the Harpenden growth study was initiated by JM Tanner and RH Whitehouse, and continued till 1974, with the team of Tanner and Whitehouse doing some unbelievable work during their association. They were considered parallel to Rolls and Royce in the future. In 1956, Tanner set up the Department of Growth and Development at the Institute of Child Health London, and also started a twice-weekly clinic at Great Ormond Street Hospital, London. This clinic was of immense importance as it trained many clinicians across the globe in the diagnosis and management of children with growth disorders. Tanner also established the Child Growth Foundation, which still functions as one of the leading charities for growth disorders.

Among his many contributions, some of the major publications were: Growth at Adolescence (1955), Education and Physical Growth (1961), The Physique of the Olympic Athlete (1964), Worldwide Variation in Human Growth (with Phyllis B. Eveleth) (1976), Fetus into Man (1978), Human Growth: A Comprehensive Treatise (with Frank Falkner) (1978), and A History of the Study of Human Growth (1981). Specifically in the field of Pediatric Endocrinology, his immense contributions include the Tanner scale or stage, bone age assessment, growth charts for the UK, Height Velocity charts, and Height prediction equations.

His achievements and honors cannot be summed up in this write. Suffice it to say that Tanner's tangential thinking and dedication led to many path-breaking contributions. He inspired thousands of clinicians, and played a vital role in providing a better quality of life to millions of children.

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PATIENT CORNER

Dr Nikhil Lohiya, Pediatric Endocrinologist, Silver Lining Pediatric Super-specialty Center for Growth, Development, Behavioral & Endocrinology, Nagpur.

Charles Straton was a child with short height, born to parents of normal height, who were first cousins. He was born with a birth weight of 4.5 kg and grew well till 6 months of age to 64 cm. After that, he started faltering and was 66.5 cm at 4 years. He was discovered by PT Barnum at the age of 5. Barnum taught him to sing, dance, mime, and impersonate. He became a sensation on his Europe tour of 7 years and was celebrated as an international star. He also noticed having delayed puberty and continued to grow in his twenties, with a final height of 96.5 cm. He married Lavinia Warren, another short girl (presumably GHD). Nicknamed General Tom Thumb, he continued his work and attained further fame on stage, but succumbed at the age of 45 years in 1883. Though there no medical records or investigations to diagnose the cause of his extreme short stature, many believe that given his normal birth length and weight, growth retardation mainly after infancy, normal intelligence and delayed but normal sexual development, he had GHD. Charles is a prime example of how one can convert inability into one's best attribute. Though he remained untreated, his name is registered forever in America's history as a great entertainer.

General Tom Thumb

Image source- *By Unknown author - The Metropolitan Museum of Art, Public Domain, https://commons.wikimedia.org/w/index.php?curid=9521889*

Lionel Messi

(*Image source- https://lifebogger.com/lionel-messi-childhood-story-plus-untold-biography-facts*

At the age of 4 years, Lionel Messi joined the local football club of Rosario. He continued for 6 more years at that club and scored more than 500 goals there. However, at 9 years, he was diagnosed with growth hormone deficiency (GHD). The cost of growth hormone was around 1000$ per month. His father's health insurance could cover only 2 years of his treatment. No club was able to pay for his treatment in Argentina due to the economic collapse. His career was in doubt. As he has some relatives in Catalonia (Spain), they sought the arrangement of a trial with FC Barcelona. At first sight, he impressed all, but it was not common to sign on a non-European player at such a young age during those days. Finally, he was signed on by one of the members of management on a tissue napkin. At the age of 14, Messi reached Barcelona and was inducted in the training with a contract including payment for his therapy. He was 120 cm when diagnosed with GHD and with GH therapy, grew to 165 cm, the average height of an Argentinian. He is one of the prime examples of the contribution of medical science. To be physically capable in football, he needed to have some physical attributes which would have been impossible without GH therapy. He has scored more than 700 goals and contributed to more than 1000 goals (as a scorer or assist). He is always thankful to FC Barcelona for the support he received for his treatment.

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Drug Corner: Vosoritide

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Achondroplasia is a common cause of genetic short stature. The pathophysiology of achondroplasia involves a gain-in-function mutation of the FGFR23 gene, that gives rise to MPAK mediated inhibition of endochondral ossification. The efficacy of drug treatment, including human growth hormone, has been limited. Vosoritide, a long-acting analogue of C-type natriuretic peptide, has been tried in achondroplasia in the last 4-5 years. It was shown to have improved long-bone growth in mice with achodroplasia, by inhibiting FGFR3 mediated MAK signaling pathways [1].

The dose-finding phase 2 human trial [2] showed sustained increase in growth velocity over 42 months with doses of 15mcg/kg and 30mcg/kg. However, severe adverse effects were seen in 11% patients. In the phase 3 trial in children with achondroplasia between ages 5-18 years, a dose of 15mcg/kg given as a single subcutaneous injection showed annual growth increment of 1.57cm over 52 months, compared to placebo [3]. No drop outs due to severe adverse effects were seen in the phase 3 trial. BioMarin Pharmaceutical's vosoritide is under review by the European Medical Agency, and the company has recently applied for FDA approval. While vosoritide has the limitations of being given as injection, another FGFR3 inhibitor drug ASP5878 is being tried in animal models as a potential oral drug for achondroplasia.

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BIOCHEMISTRY CORNER - To Prime or not to prime!!

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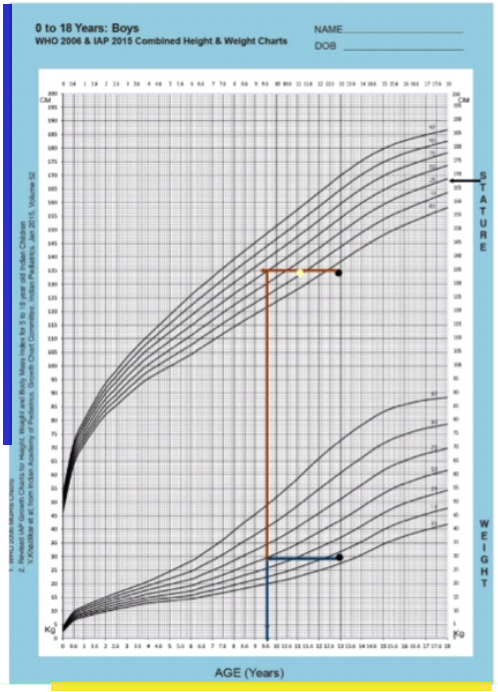
Presentation
This thirteen-year-old boy presented with a complaint of growth failure (height 135 cm and weight 30 kg). His height was just below the third percentile and parental expectations. Screening tests were normal. The treating physician diagnosed GHD based on a low GH after clonidine stimulation (peak GH of 3.2 ng/mL).



Plan
Low GH levels after stimulation suggest GHD; marginal growth failure, in this case, indicates a low pretest probability for the condition. The severity of growth failure in the case is more suggestive of constitutional delay of puberty and growth (CDGP) than GHD. Key aspects to assess in the case include the pubertal status and bone age. An inquiry into the protocol of the GH test, in particular, priming, is also important.

Results:
The child was prepubertal, with a bone age of 11 years. The GH test had been done without priming. A repeat testosterone primed GH test showed a peak value of 15.2 ng/ml, thus excluding GHD. On follow-up, the child grew at a normal rate, achieving parental expectation.

Diagnosis:
CDGP misdiagnosed as GHD.

Rationale:
Estrogen induces GH secretion in both girls and boys. Estrogen deficiency in prepubertal children reduces the GH response to a pharmacological stimulus, causing a false diagnosis of GHD. This can be prevented by sex hormone priming. Sex hormone priming is indicated in prepubertal girls older than ten years (17 beta-estradiol 2 mg for two days) and boys above 11 years (100 mg testosterone 5-7 days prior to the test) and a predicted adult height in the normal range.

Messages
- Consider CDGP in a pre-pubertal boy with mild growth failure and delayed bone age.
- GHD usually presents with a significant delay in bone age (height SDS for bone age below -2) and growth (height SDS below -3).
- Recommend GH stimulation tests only when the pre-analytic probability is very high.
- GH stimulation testing should be done after priming in prepubertal girls above 10 years and boys above 11 years with predicted adult height in the normal range.

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Pedendoscan - Growth

Compiled by Dr Pragya Mangla,
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1. Bang P, Woelfle J, Perrot V, Sert C, Polak M. Effectiveness and safety of rhIGF1 therapy in patients with or without Laron syndrome. Eur J Endocrinol. 2021 Feb;184(2):267-276. doi: 10.1530/EJE-20-0325.

Children and adolescents (n = 242) receiving rhIGF1 therapy from 10 European countries, enrolled in 2008–2017 in an ongoing, open-label, observational study were reported on. Of them, the treatment-naïve/ prepubertal (NPP) cohort was divided into subgroups based on reported genetic diagnosis of Laron Syndrome (LS) (n = 21) or non-LS (n = 117). Change in height and weight over 5 years and adverse events (AEs) were assessed. The LS subgroup was significantly younger, had more severe short stature, lower IGF-1 levels, higher GH secretion, and more frequent history of spontaneous hypoglycemia, compared with the non-LS subgroup, at baseline. The LS subgroup had a significantly higher rhIGF1 therapy starting dose compared with the non-LS subgroup (median (Q1; Q3): 40 (40; 40) vs 40 (20; 40) µg/kg BID; P = 0.013), but no significant difference in dose was observed from year 1 to year 5 after dose escalation.

The duration of treatment was not significantly different between those with and without LS. Responders started on a slightly lower starting dose of rhIGF1 compared to patients with LS (P = 0.011) but with no difference observed from year 1 to year 5; they were treated for a similar duration. In NPP patients without LS, responders were significantly younger than poor-responders. Mean height SDS gain was greatest in year 1 and continued to steadily increase in years 2–3 then remained stable in years 3–5. Among NPP patients without LS, poor-responders and responders had similar rhIGF1 doses from baseline to year 5; however, duration of treatment was significantly shorter in poor-responders (median: 3.47 vs 4.59 years; P = 0.028). Overall, 65.3% of patients experienced treatment emergent adverse events (TEAEs), which included headache, chronic middle ear infection, papilledema, hypoglycemia, acromegalic facial changes, edema, gynecomastia, hearing loss, intracranial hypertension, lipohypertrophy at injection sites, myalgia, sleep apnoea, tonsillar hypertrophy and cardiomegaly. There were 3 benign and 1 malignant neoplasm TEAEs.

rhIGF1 therapy promotes linear growth in most NPP children with severe primary IGF deficiency, with or without LS. Hypoglycemia was the most common adverse event noted.

2. Yuan Y et al. Meta-analysis of metabolic changes in children with idiopathic growth hormone deficiency after recombinant human growth hormone replacement therapy. Endocrine. 2021 Jan;71(1):35-46. doi: 10.1007/s12020-020-02435-w.

The authors aimed to assess the effects of rhGH replacement therapy on metabolic changes; they analysed data from 16 clinical trials involving 1319 children (<18 years) with idiopathic growth hormone deficiency (IGHD). Effect-size estimates are expressed as weighted mean difference (WMD) with 95% confidence interval (CI). Overall analyses showed a favorable role of rhGH replacement therapy where total cholesterol was significantly decreased (WMD: −0.20 mmol/l; 95% CI: −0.30 to −0.10; p < 0.001), and high-density lipoprotein was significantly increased (WMD: 0.29 mmol/l; 95% CI: 0.24 to 0.33; p < 0.001), with marginal increase in low-density lipoprotein (WMD: −0.22 mmol/l; 95% CI: −0.47 to 0.22; p = 0.092).

Subsidiary and meta-regression analyses revealed that the length of intervention and the sample size were possible causes of heterogeneity. There was a low probability of publication bias.

Favorable effect of rhGH replacement therapy was seen on lipid metabolism in children with IGHD.

3. Modan-Moses D et al. Prospective longitudinal assessment of linear growth and adult height in female adolescents with anorexia nervosa. J Clin Endocrinol Metab. 2021 Jan 1;106(1):e1-e10. doi: 10.1210/clinem/dgaa510.

A prospective observational study was done in a tertiary university hospital in Israel to assess linear growth and adult height in 225 female adolescents with Anorexia Nervosa (AN). They aimed to characterize growth retardation in these patients, and to assess the effect of weight restoration and factors affecting catch-up growth and adult height (AH). Mean age at admission was 15.4±1.75 years, mean BMI was 15.7±1.8 kg/m2. Pre-morbid height-SDS was not significantly different from that expected in normal adolescents. However, height-SDS at admission, discharge, and at AH, were significantly lower than expected. Furthermore, AH was significantly shorter compared to the mid-parental target height. Stepwise forward linear regression analysis identified age ($r=0.32$, $p=0.002$) and bone age ($r=-0.29$, $p=0.006$) on admission, linear growth during hospitalization ($r=0.47$, $p<0.001$), and change in LH during hospitalization ($r=-0.265$, $p=0.021$) as independent predictors of improvement in height SDS from the time of admission to adult height.

The premorbid height of female adolescent AN patients is normal, but illness leads to linear growth retardation. Weight restoration leads to catch-up growth, but complete catch-up is often not achieved.

4. Luo Y et al. Effects of growth hormone on cognitive, motor, and behavioral development in Prader-Willi syndrome children: a meta-analysis of randomized controlled trials. Endocrine. 2021 Feb;71(2):321-330. doi: 10.1007/s12020-020-02547-3.

Metaanalysis of 10 relevant randomized controlled trials with a total of 302 participants <18 years of age was done to quantitatively evaluate the effects of GH on cognitive, motor function, and behavioral development in children with PWS. The authors observed no significant difference between the GH treatment group and the control group in cognitive performance (general cognition and total IQ) ($p = 0.197$) and on objective assessments of behavioral development ($p = 0.53$). GH treatment was shown to remarkably improve motor development in PWS children compared with the control treatment ($p < 0.001$), with moderate positive treatment effects (Hedges'g [95% CI] = 0.71 [0.38, 1.03]).

GH treatment in PWS markedly improves motor development but has no effect on cognitive and behavioral development.

5. Ke X et al. Clinical characteristics of short-stature patients with an NPR2 mutation and the therapeutic response to rhGH. J Clin Endocrinol Metab. 2021 Jan 23;106(2):431-441. doi: 10.1210/clinem/dgaa842.

Six Chinese patients with short stature, with whole exome sequencing proven heterozygous NPR2 mutation, were reported by the authors, with a literature search for the characteristics of patients with *NPR2* mutation and their therapeutic response to rhGH. Homozygous or compound heterozygous *NPR2* mutations can cause acromesomelic dysplasia, Maroteaux type. They show broad or protruding forehead, low and flat nose bridge, midface dysplasia, abnormal face shape and low ear position, typical disproportionately short stature and skeletal deformities, including apparent mesomelic shortening, broad and shortened metatarsals and phalanges, elbow contraction and extension limitation and excess skin. Conical epiphysis, abnormal physiological curvature of the spine, posterior wedge-shaped vertebral body, and sometimes ilium wingspan

and bilateral acetabular dysplasia are seen on X-ray. Heterozygous *NPR2* mutations result in short stature with nonspecific skeletal deformities, facial anomalies and Miura-type osteochondral dysplasia. Skeletal dysplasia mainly included brachydactyly, shortened metacarpals or metatarsals and clinodactyly, mesomelic limb shortening, muscular hypertrophy, cubitus valgus, and cone-shaped epiphysis. About one-fifth of cases had facial abnormalities, mainly high-arched palate, low nasal bridge, frontal bossing, strabismus and dental malposition. The authors reported some new phenotypic features like trident hand, slightly synophrys, short neck and mild knee valgus, and mild spine scoliosis along with Madelung deformity. rhGH treatment significantly improved the height SDS of patients with *NPR2* heterozygous mutation (median -2.1 vs -2.9, *P*<0.001), especially in girls. The height SDS change was negatively correlated with the initial age of treatment. Height SDS change of patients with NPR2 heterozygous mutation in guanosine cyclase (GC) domain was significantly higher than that of extracellular receptor-binding (ECD) domain (median 1.9 vs 0.6, P=0.019).

ISS patients with skeletal deformities should be tested for NPR2 mutation. rhGH treatment appears to be beneficial for short stature patients with NPR2 heterozygous mutation and needs further study.

6. Peeters S et al. DNA methylation profiling and genomic analysis in 20 children with short stature who were born small-for-gestational age. J Clin Endocrinol Metab. 2020 Dec 1;105(12):dgaa465. doi: 10.1210/clinem/dgaa465.

Twenty SGA children with failure of catch-up growth treated with growth hormone (GH) were selected from the BELGROW database for exome sequencing, SNP array and genome-wide methylation analysis to identify the (epi)genetic cause. The first year response to GH was compared to the response of SGA patients in the KIGS database. database. The authors identified (likely) pathogenic variants in 4 children (from 3 families) using exome sequencing, which included compound heterozygosity for two variants in the *ELAC2* gene, bi-allelic pathogenic variants in *CEP57* and *de novo* missense variant in the *HNRNPH1* gene. They found pathogenic CNV in 2 probands using SNP array. In a child harboring a *NSD1*-containing microduplication, they identified a DNA methylation signature that is opposite to that of Sotos syndrome, while in another child a *de novo* deletion resulted in the 22q11.2 deletion syndrome. They observed multi-locus imprinting disturbances in two children. Five out of 6 children with a genetic diagnosis had an "above average" response to GH.

A more advanced approach with deep genotyping can unravel unexpected (epi)genomic alterations in SGA children with persistent growth failure.

7. Gursoy S et al. Detection of SHOX gene variations in patients with skeletal abnormalities with or without short stature. J Clin Res Pediatr Endocrinol . 2020 Nov 25;12(4):358-365. doi: 10.4274/jcrpe.galenos.2020.2019.0001.

The authors aimed to describe the clinical features and molecular results of SHOX deficiency in a group of 15 Turkish patients from four different families, who had skeletal findings with and without short stature. Three different point mutations (two nonsense, one frameshift) and one whole SHOX gene deletion were detected in these 15 patients. Four of them had Langer mesomelic dysplasia (LMD). The remaining patients had clinical features compatible with Léri-Weill dyschondrosteosis (LWD). Madelung's deformity, cubitus valgus, muscular hypertrophy and short forearm were the most common phenotypic features, along with short stature. Additionally, hearing loss was detected in two patients with LMD.

SHOX deficiency should be especially considered in patients who have disproportionate short stature or forearm anomalies with or without short stature. SHOX gene sequencing should be performed in suspected cases.

8. Coghlan RF et al. Norms for Clinical Use of CXM, a Real-Time Marker of Height Velocity. J Clin Endocrinol Metab. 2021 Jan 1;106(1):e255-e264. doi: 10.1210/clinem/dgaa721.

The goal of this study was to confirm the authors initial observations supporting the utility of a bone growth by-product collagen X biomarker (CXM) as a height velocity (HV) biomarker in a larger number of individuals and establish working reference ranges for future studies. A total of 432 CXM measurements (done from archived blood samples) were plotted by age, and sex-specific reference ranges were calculated. Serial values from 116 participants were plotted against observed HV. Matched plasma, serum, and dried blood spot readings were compared. A correlation of blood CXM with conventional HV was confirmed. The slope and corresponding correlation of the HV/CXM lines of best fit for girls is 3.5 CXM ng/mL per cm/year HV (r =0.82) compared with 3.19 CXM ng/mL per cm/year HV for boys (r = 0.78). CXM levels demarcated the pubertal growth spurt both in girls and boys. CXM levels differed little in matched serum, plasma, and dried blood spot samples.

Scatter plots of CXM vs. age showed a similar pattern to current HV norms, and CXM levels demarcated the pubertal growth spurt both in girls and boys.

9. Gonc EN et al. Genetic IGF1R defects: new cases expand the spectrum of clinical features. J Endocrinol Invest. 2020 Dec;43(12):1739-1748. doi: 10.1007/s40618-020-01264-y.

The authors aimed to identify the phenotypic variability of IGF1R defects in a cohort of short Turkish children with normal GH secretion. Fifty children (25 girls) with short stature and a basal/stimulated GH over10 ng/ml, having either low birth weight or microcephaly, were enrolled. MLPA and then Sanger sequence analysis were performed to detect IGF1R defects. The auxological and metabolic evaluation were carried out in index cases and their first-degree family members whenever available. A total of seven (14%) IGF1R defects were detected. Two IGF1R deletions and five heterozygous variants (one frameshift, four missense) were identified. Three (likely) pathogenic, one VUS and one likely benign were classified by using ACMG 2015. All children with IGF1R defects had a height < − 2.5SDS, birth weight < − 1.4SDS, and head circumference < − 1.36SDS. IGF-1 ranged from − 2.44 to 2.13 SDS. One child with a 15q terminal deletion had a normal phenotype and intelligence, whereas low IQ was a finding in a case with missense variant. One patient had hypergonadotropic hypogonadism. Two parents who carried IGF1R mutations had diabetes mellitus, hypertension and hyperlipidemia, experienced premature ovarian failure and early menopause.

In patients with IGF1 receptor defects, birth weight, head circumference, intelligence, dysmorphic features, IGF-1 levels and even height are not consistent among patients. The carrier parents and family members also had significant variability in adult height. Metabolic and gonadal complications may appear during adulthood, suggesting that patients should be followed into adulthood to monitor for these late complications.

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Report on ISPAE ACES Program

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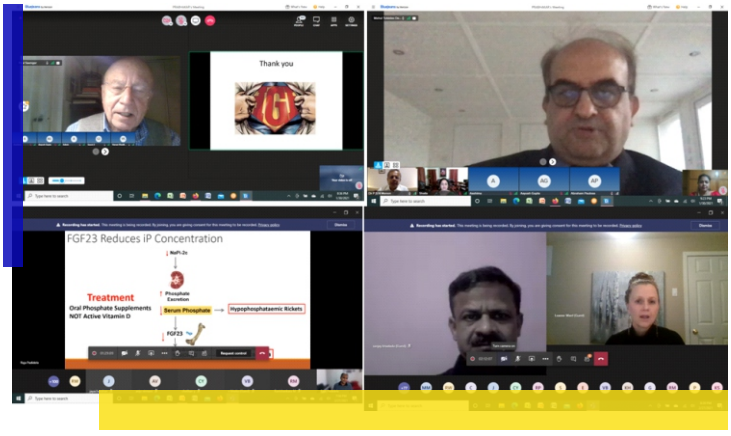
Asst. Prof and Pediatric Endocrinologist, Sri Ramachandra Medical College

Greetings from ISPAE EC 2021-22!
The new executive Council has launched an exclusive teaching program - Academics and Clinical Education Series (ISPAE-ACES) - targeting pediatric endocrine fellows, DM endocrinology trainees, and pediatricians interested in pediatric endocrine disorders. The program is theme-based, with two case presentations followed by two didactic lectures by experts in the field. Call for abstracts for ACES meet case presentation is circulated to all ISPAE members, and the two best abstracts are selected for presentation after a thorough scrutiny by the EC. The program is a virtual one, scheduled to be conducted on last Saturday of every month, with the case presentations and lectures uploaded in the ISPAE YouTube channel.

The first ISPAE-ACES meet, conducted on 30th January 2021, with the theme of "Growth disorders in children", had case presentations by Dr Avani Hegde (IGICH, Bengaluru) on "Small baby with poor growth" and Dr Aayush Gupta (Manipal Hospitals, Bengaluru) on "Case conundrum - craniopharyngioma". The session had expert talks by Dr Paul Saenger (NYU Langone, New York, USA) on "Long-acting growth hormone" and Dr Mehul T Dattani (Great Ormond Street Hospital, London, UK) on "Genetics of hypopituitarism". The meeting was moderated by Dr PSN Menon and Dr Vaman Khadilkar, and attended by around 400 delegates (national and international).

The second ISPAE-ACES meet on 27th February 2021, highlighted the "Rare disease day", with the theme of "Pediatric metabolic bone disorders". Case presentations were by Dr Chethan Y (Seth GS Medical College, Mumbai) on "An unusual case of hypophosphatemic rickets" and Dr Kaushal V Sheth (Yashoda Hospital, Secundarabad) on "A novel COL1A2 missense mutation causing osteogenesis imperfecta type IV". They were followed by state-of-the-art expert talks by Dr Raja Padidela (Royal Manchester Children's Hospital, Manchester, UK) on "Management of hypophosphatemic rickets" and Dr Leanne Ward (University of Ottawa, Canada) on "An update on the management of osteogenesis imperfecta". The meet was moderated by Dr Vijayalakshmi Bhatia and Dr Sanjay Kumar Bhadada. The session was live streamed on the ISPAE YouTube channel and attended by around 200 delegates.

The next ACES meet is scheduled for 27th March 2021 from 7-9 pm, with the theme "Pediatric thyroid disorders". We appeal to all ISPAE members to actively participate and contribute to this highly academic and useful monthly series. Please send in your abstracts on themes selected before the 15th of each month, to ispaeaces@gmail.com. The Fellows who present cases in this program will be given certificates of appreciation by ISPAE. Subscribe to the ISPAE YouTube channel for instant updates towards ACES meets live streaming and video uploads. ***https://www.youtube.com/channel/UC3ez8DJwpJEmAPzMK5m_akg***



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An update from ISPAE Web-Team

Dr Sirisha Kusuma B
Consultant Pediatric Endocrinologist, Rainbow Children's Hospital, Hyderabad

Greetings from the 2021-2022 ISPAE Web-team!

As you all are aware, Dr Karnam Ravikumar had been instrumental in creating the ISPAE website many years ago. Ever since he has been maintaining and updating it single handedly, devoting his valuable time and expertise. Many of you have contributed significantly over time, adding to our collection of excellent patient care resources and pamphlets on wide ranging pediatric endocrine conditions. As our Society continues to grow and expand, we realized that there is a need for more interactive features in our website (e.g., online application for memberships, observerships, an efficient member search which would enable one to search for a pediatric endocrinologist practicing in any city/town, etc.,). To be able to activate these features and renovate our website, the Executive Council decided that it is time to take technical help by outsourcing this task to a website developer. Dr Ravikumar graciously agreed to continue in the role of Advisor by providing constant support in this process. The brand-new website is currently in the process of being made, and in the next few weeks will go live with all the exciting features.

ISPAE has its presence in the social media as well, in the form of a Facebook page and its own YouTube channel. We decided to keep these sites active by regular updates. You will be able to keep in touch with all up-to-date ISPAE related news like upcoming meetings, notifications on ISPAE-ACES series, announcements for awards etc., by following our Facebook page. To make the most of our YouTube channel, we started live streaming of our exciting monthly ACES meets. You can also see highly informative lectures on pediatric diabetes and metabolic syndrome, videos on practical aspects of pediatric diabetes management from "Pediatric Diabetes Update-2020" on the channel. In time, we plan to upload more scientific content, as well as care related videos for patients.

Subscribe to ISPAE YouTube channel now so that you do not miss these excellent educational videos, and **like our *FB page*** to get timely updates on ISPAE activities.

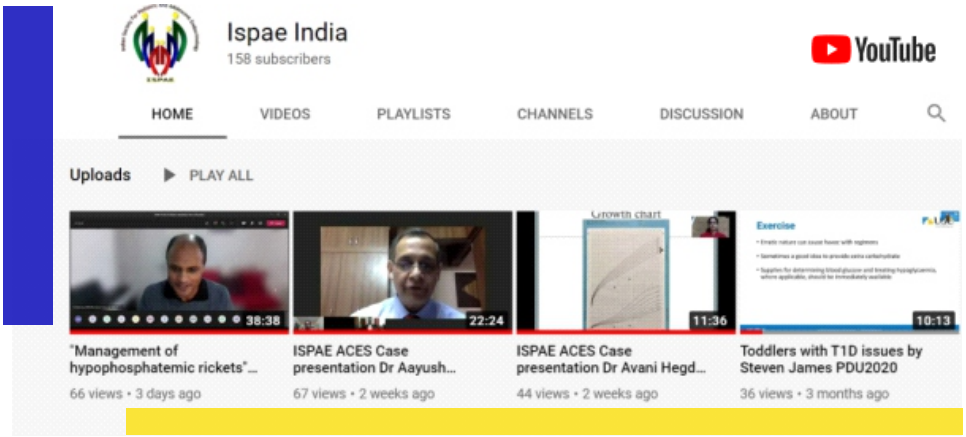
https://www.youtube.com/channel/UC3ez8DJwpJEmAPzMK5m_akg

https://www.facebook.com/ISPAE-Indian-Society-for-Pediatric-and-Adolescent-Endocrinology-474438942957055/

Webmaster: Sirisha Kusuma B

Advisor: Karnam G Ravikumar

Web-team members: Aayush Gupta, Chetan Dave



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Central PEDICON 2021 – Learning Pearls

Compiled by:
Dr Amarnath Kulkarni, Dr Mahesh Maheshwari and Dr Hemchand K Prasad

The faculty included: Dr Suijeewala Amarsena from Sri Lanka, Drs Riaz I, Kumar Angadi, Vaman Khadilkar, Sangeeta Yadav, Abishek Kulkarni, Mahesh Maheshwari, Anju Virmani, Anurag Bajpai, Sudha Rao, Ruchi Parekh, Ganesh Jevalikar, and Amarnath Kulkarni.
Learning pearls:

Thyroid

- T3 is ordered primarily to help diagnose hyperthyroidism and to help monitor treatment of a person with a known thyroid disorder.
- Newborn screening: in sick babies, preterm babies, babies on vasopressors – additional testing is indicated, irrespective of initial screening results.
- Central hypothyroidism: very low T4 and TSH are diagnostic, but sometimes TSH can be elevated marginally, up to 20 mIU/L.
- On follow up of congenital hypothyroidism, TSH may take time to settle. Elevated Free T4 above the normal range in the initial few days is not worrying.
- Do not use adult cut-offs for interpretation of thyroid results in children.
- Children with hemiagenesis may have a marginally high TSH. They require lifelong therapy.
- Hearing screening is universally recommended, especially in children with dyshormonogenesis.

Metabolic syndrome

- Non communicable diseases are emerging as major killers in low and middle income countries also.
- The current pandemic has increased obesity and metabolic syndrome owing to: reduced activity, increased cooking and eating, increased screen time, more stress, and broken routines.
- Height, weight, waist circumference, blood pressure and BMI should be measured annually in children.
- Use the pediatric cut off for SGPT to recognize fatty liver: > 25 IU/L and >22 IU/L in males and females.
- As Asians are a high-risk group for metabolic complications, all overweight and obese children should be screened for dysglycemia.
- Tall and obese children usually have nutritional rather than pathologic obesity.

Challenges in Insulin therapy in Type 1 diabetes

- Basal bolus regimen should be the initial therapy in all children with type 1 diabetes (T1D) - either with syringe, pen or pump.
- Mid-morning snack is not mandatory in children on rapid acting analogs.
- Children should not be on fixed doses: prandial doses are determined by food quantity and quality, and adjusted for: pre-meal BG correction, activity, age, puberty.
- Morning exercise may be beneficial in children with diabetes to prevent nocturnal hypoglycemia.
- Toddlers and children on sick days can consider taking ultra-short-acting insulin after food, but this should be avoided as a routine.
- Emergency use of 30 mcg/kg of glucagon can avoid emergency hospitalization due to severe hypoglycemia.
- Detemir has a dose dependent action, hence it needs to be given as two doses/day.
- FIASP is the shortest acting insulin, and can be given 2-5 minutes prior to food.
- Degludec and Glargine U-300 are ultra-long-acting (36-42 hours) insulins; they can be used in patients over 1 year old with greater flexibility in timing and reduced less complications like hypoglycemia and glucose variability.
- With Continuous Glucose Monitoring (CGM), Time In Range (TIR) is becoming a better indicator of

DKA

- Point of care testing can help in making early diagnosis of DKA.
- Assessment of venous pH, blood ketones and anion gap help in assessing severity and the treatment response.
- There is no advantage of giving insulin bolus in DKA.
- Tubing should be flushed with insulin containing fluid, before starting IV insulin: this is called 'priming'.
- Hypokalemia and cerebral edema are two iatrogenic complications of DKA.
- Early basal insulin can be started in those with breakthrough DKA, 6-12 hours before changing over to subcutaneous (s/c) pre-prandial insulin: this helps to reduce hospital stay.
- Pediatricians should be requested to start hydration and give a s/c shot of 0.2-0.3 units/ kg human regular insulin to any child newly diagnosed with DKA, while referring to a higher center. This will prevent mortality and morbidity due to DKA.
- Consciousness level assessment helps in early diagnosis of cerebral edema in DKA.
- Blood ketone strips are replacing urine ketone strips, as being more accurate, more convenient, and less prone to error. Patients too can use them at home.
- S/c only insulin can be used successfully at peripheral centers where infusion pumps are not available for DKA management.
- Post DKA insulin requirements may be as high as 2-3 units per kg per day for a few days.
- Intensive Insulin therapy (IIT), i.e. s/c insulin every 2-3 hourly is preferred over conventional 6 hourly insulin regimen in the post DKA period.
- Tender loving care and proper diabetes education and counseling, along with the 4 pillars of diabetes - diet, exercise, insulin, and home sugar monitoring - should be stressed from the beginning, so that equal importance is given to all.

Vitamin D

- Lack of skin exposure to sunlight is the main cause of Vitamin D deficiency (VDD) in Indian children; outdoors activities between 11 am -3 pm are recommended to prevent VDD.
- More local data and dose response studies are needed to decide optimal doses of Vitamin D for Indian children.
- Adherence and adequate dietary calcium intake should be ascertained in all children of all age groups initiated on Vitamin D supplementation.
- Oral replacement is preferred over parenteral replacement. Single large doses are best deferred.

Growth Charts

- The recently published growth charts are pediatrician friendly and should be used by pediatricians in Indian children.
- In children less than 5 years of age: weight for height is useful to diagnose failure to thrive early.
- The new pan-Indian waist circumference charts should be used, and 70th percentile can be used to recognize metabolic risk.
- The new Indian Growth Velocity charts are useful to monitor growth velocity: a cut off of 25th percentile can be used to recognize growth faltering early.
- Indian data on sitting height and sub-ischial length is available and should be used to recognize disproportionate stature in Indian children.
- Introduction of MPH and BMI sub-charts in the growth charts have made them user friendly for pediatricians, avoiding separate calculations for BMI and MPH.
- Extended Indian Growth Charts are useful for pediatric endocrinologists, and help monitor as well as reduce extensive investigations.·
- Growth monitoring and anthropometry are invaluable tools in the hands of pediatricians & health care workers.
- New Indian Turner syndrome charts have been introduced.
- Recommended timing for growth monitoring:
    - Under 3 years: Birth, 6 weeks, 10 weeks, 14 weeks, 9 months, 12-16 months: at immunization, and additionally every 6 months. Parameters include weight, length/ height and head circumference.
    - Children from 4-18 years: every 6-12 months: height, weight and BMI. Opportunistic measurements should be done at visits for sickness.

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ISPAE - ACE Series: Growth disorders in children – Learning Pearls

Compiled by *Dr Avani Hegde*
Clinical Fellow in Pediatric and Adolescent Endocrinology, IGICH, Bangalore

Learning pearls from case of "Silver Russell syndrome (SRS)" were:

- SRS is diagnosed clinically, using a combination of characteristic features, and can be confirmed by molecular genetic testing in almost 60% cases.
- Nutrition therapy is of utmost importance.
- SRS is one of the indications for GH therapy; GH stimulation testing is not necessary.

Learning points from "Case conundrum: Craniopharyngioma" were -

- There is a triphasic response of ADH post neurosurgery.
- Steroid replacement should be done prior to initiation of thyroxine replacement.
- Glucocorticoid deficiency can mask diabetes insipidus.
- There should be no active tumor for at least 1 year before starting GH therapy post-surgery.
- Initiation of GH increases the dose of thyroxine replacement.

Professor Paul Saenger gave a talk on long acting GH – details of various preparations and their clinical trials. Phases of each of the trials were discussed in great detail.

Professor Mehul Dattani spoke about his extensive experience with genetics of hypopituitarism. Various genetic defects causing hypopituitarism was discussed with case-based scenarios. The main learning points were:

- A genetic cascade is involved in pituitary development.
- Strategies for gene identification are shifting from candidate gene-based approach to Next Generation Sequencing techniques.
- Detailed pathophysiology involving Hesx1/SOX2/SOX3 was discussed.
- Newer genes such as TCF7C1 (SOD), KCNq1 (CPHD), FOXA2 and RAX have been recently identified in the hypopituitarism cohort.
- Novel phenotype (panhypopituitarism, sensory-neural deafness, skeletal and skin defects) has been described with LHX4 gene mutations.

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ISPAE - ACE Series: Bone disorders in children – Learning Pearls

Compiled by
Dr Chetan DM Endocrinology trainee, GS Seth Medical College and KEM Hospital
Dr Diksha Shirodkar Assistant Professor (Pediatrics) and Pediatric Endocrinologist, Yenepoya Medical College

Pearls for Hypophosphatemic rickets:

1. Active absorption of phosphate occurs via active vitamin D through the NaPi2b cotransporter (gut).
2. Passive absorption of phosphate occurs from the diet.
3. Renal phosphate reabsorption occurs through NaPi2a and NaPi2c.
4. Dietary phosphate deficiency is unlikely, unless in extreme starvation, refeeding syndrome and usage of phosphate binders (formula).
5. The most common cause of hypophosphatemia is renal phosphate wasting.
6. FGF23 binds to FGF receptor and klotho, which down-regulate the co- transporters and cause loss of phosphate and inhibition of 1-alpha hydroxylase, hence decreasing 1,25 di-OH D.
7. All conditions except Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) have high FGF23.
8. XLHR: Clinical features include rickets (varum/valgum), dental abscesses, craniosynostosis and raised intracranial pressure.
9. The standard treatment of XLHR is with oral phosphate and active vitamin D.
10. Considerations during treatment: frequent dosing is required, secondary hyperparathyroidism should be watched for, and active D3 supplementation may be needed (FGF23 increases which inhibits active D).
11. Active D causes hypercalciuria and nephrocalcinosis, hence close titration is needed to allow healing of rickets while preventing nephrocalcinosis.
12. Conventional therapy is successful in healing rickets, but one must never try to normalise phosphate.
13. Frequency of bio-marker monitoring (ALP, PTH, Urinary Ca/creatinine ratio) in infancy is every 3 monthly, in childhood every 4-6 months, in puberty every 3-4 monthly and in adulthood annually.
15. Renal ultrasound for nephrocalcinosis should be done annually.
16. If nephrocalcinosis is present or persisting, with all biomarkers normal, then reduce the phosphate and alphacalcidiol, provided ALP is in normal range.
17. Cinacalcet may be required if PTH is persistently elevated, to prevent autonomous PTH secretion.
18. Do not use serum phosphate as a biochemical marker for monitoring therapy in conventional therapy.
19. Burosumab (monoclonal antibody) is superior to conventional therapy: it binds to FGF23, increases renal cotransporters and increases active D, causing phosphate reabsorption.
20. Biochemical markers for monitoring Burosumab therapy are serum phosphate, ALP, PTH and urine phosphate excretion TmP/GFR.
21. It is important to use age related reference values and collect fasting blood samples.
22. HHRH: mutation in SLC 34A3, so the NaPi2c is decreased, causing increased phosphate excretion, resulting in low serum phosphate, and hence low FGF23, resulting in high active D, causing nephrocalcinosis.
23. Management of HHRH is oral phosphate supplements and ***not*** active D.
24. Renal tubulopathy also needs treatment with oral phosphate without active D.

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ISPAE - ACE Series: Bone disorders in children – Learning Pearls

Pearls for Osteogenesis Imperfecta (OI)

1. Classical features are blue/grey sclera, recurrent fractures, hearing loss and joint laxity.

2. Skeletal assessment, degree of trauma, fracture site/s and characteristics are important in diagnosis of fragile bones.

3. Low trauma fracture is defined when falling occurs from standing height or height less than 3m at no more than walking speed.

4. More than 2 dozen genes (collagen and collagen related) are attributed to OI

5. Agents in children for the management of OI are the following -

a) Agents that affect bone resorption in the same direction (decrease resorption and decrease formation) e.g. Bisphosphonates, RANK L inhibition.

b) Agents that uncouple bone resorption and formation e.g. Sclerostin inhibition.

6. IV bisphosphonates are better than oral because of the following reasons:

a) Decrease in long bone fractures per year

b) Less pain

c) Increase in BMD

d) Facilitation of rod insertion

e) Increase in cortical thickness in the growing child

f) Decrease in vertebral fractures; cause vertebral body reshaping

7. Denosumab is a powerful antiresorptive agent

Advantage: infrequent dosing, subcutaneous;

Be watchful about the Rebound phenomenon i.e. when abruptly stopped, there is increase in serum calcium and bone turnover, decrease in BMD and increase in vertebral fractures.

8. With antiresorptive therapy, bone density is more modifiable than bone geometry (trabecular bone >long bone)

9. Atypical femur fractures include

a) lateral convexity
b) distal to lesser trochanter
c) no/minimal trauma,
d) transverse or short oblique
e) non comminuted
f) through both cortices with/without a medial spike.

These are not common because of use of IV bisphosphonates, but because of the disease process.

10. Anti sclerostin antibody increases the periosteal circumference, BMD and Cortical thickness.

11. A potential strategy could be saltatory sequential therapy - to use romosozumab and denosumab lternatively in the subclinical phase and maintenance phase and to use zolendronic acid during discontinuation.

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Activities by ISPAE members

Compiled by ***Dr Aashima Dabas***
Associate Professor, Department of Pediatrics, Maulana Azad Medical College, New Delhi

Diaversary Celebration by Dr Tushar Godbole, Harmony Health Specialty Clinic, Nashik (online Meeting)

Diavarsary celebration was observed as the anniversary of diagnosis of diabetes of patients who have diabetes duration of more than 10 years and reasonably good sugar control. This is a monthly activity on Zoom platform. Two interviews have been conducted so far, starting from February 2021, where Dr Tushar interviewed the patient, discussed the diabetes journey, struggles, achievements etc. At the end of the interview, other children with diabetes and their parents greeted the celebrity patient.

Clinical Pearls: Childhood diabetes by IAP COCHIN & IAP KERALA (Webinar)

A Zoom webinar, "Pediatric Potpourri", was organized by IAP Kochi on 10 February 2021 from 8-9.30 pm. The topic was "Clinical Pearls in Childhood Diabetes". The audience targeted was practicing pediatricians and pediatric postgraduate students. The session, attended by more than 100 participants, was moderated by Dr Jeeson C Unni (Scientific Chair, IAP Kochi, and Lead Consultant Pediatrics, AsterMedcity, Kochi). The topics covered were:

1) Case scenarios and diagnosis of diabetes in children – Dr Parvathy L (Consultant Paediatric Endocrinologist, AsterMedcity, Kochi)
2) Ambulatory management of Type 1 diabetes in children – Dr Hemchand Prasad (Consultant Paediatric Endocrinologist, MehtaHospital, Chennai)
3) Nutritional management of Type 1 diabetes in children – Ms Sheryl Salis (Founder Director, Nurture Health Solutions, Mumbai)
4) PG Quiz – for pediatric postgraduates followed by a discussion.

The program was well appreciated and has had nearly 400 views till now in YouTube.

CME in Basic Pediatric Endocrinology and 3rd Dr Thangavelu S Oration by Dr Hemchand K Prasad (Webinar)

An online webinar was organized by the Dept of Pediatric Endocrinology, Mehta Hospital on 20-21 Feb 2021. The topics covered were neonatal endocrinology, endocrine issues in SGA babies, obesity, diabetes, bone and mineral metabolism, growth and thyroid function tests. There were panel discussions on pubertal disorders and neonatal endocrine issues, and debates on optimal Vitamin D levels, and the utility of WHO standards in Indian children less than 5 years. A book on Practical Assessment of Growth and Growth Disorders was released. A case presentation competition was held: 31 cases were submitted, and the top cases awarded prizes. The 3rd Dr Thangavelu S oration was delivered by Prof Ragnar Hanas on "Diabetes in the toddler - challenges and strategies for optimisation of optimization of control". The program was attended by 700 delegates.

Pediatric Endocrine Update, 2021, Ahmedabad by Dr Shalmi Mehta and Dr Ruchi Shah (Webinar-dIAP platform)

A Pediatric Endocrine Update was held under the auspices of Academy of Pediatrics, Ahmedabad and Gujarat, as a virtual meeting on 28 Feb, 2021. Faculty for the event, moderated by Dr Shalmi Mehta, were Drs Vaman Khadilkar, Sudha Rao, Anju Virmani, Ahila Ayyavoo, Ganesh Jevalikar and Ruchi Shah, who delivered talks on short stature, DSD, Type 1 diabetes, Hypoglycemia in children, Congenital hypothyroidism and Pediatric Endocrinology in COVID. The program received a positive feedback from the delegates.

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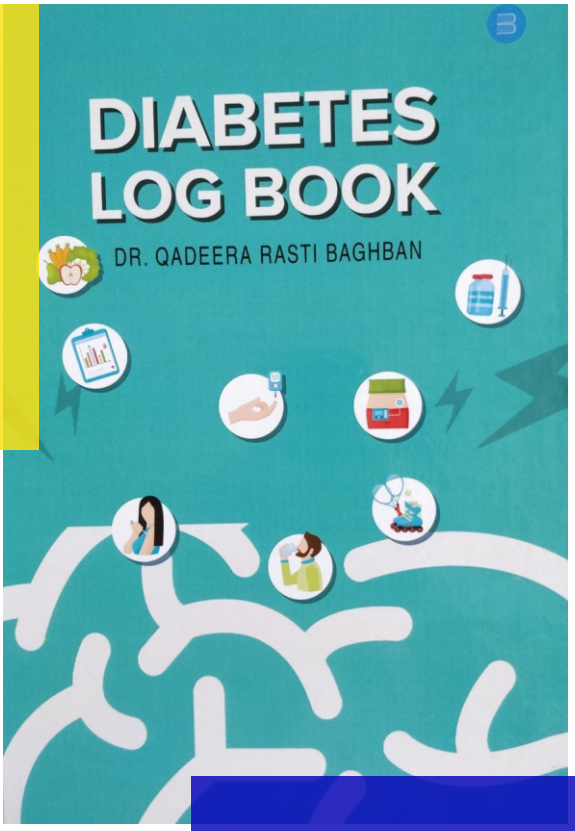
Activities by ISPAE members

Neonatal Hypoglycemia by Dr S Ramkumar, Paedendo Clinic, Apollo Children's Hospital & Institute of Child Health, Madras Medical College
(Webinar)

A webinar was conducted on Neonatal Hypoglycemia under the banner of Paedendo Clinic along with Apollo Children's Hospital and Institute of Child Health, Madras Medical College, on 7 February 2021. There were 13 Speakers from India and abroad, from Pediatrics, Endocrinology, Neonatology, Genetics and Nuclear medicine. The topics included, approach, management, genetics, nuclear imaging, and long term follow of congenital hyperinsulinemic hypoglycemia. Almost 200 members participated from India and abroad.

Diabetes Log Book by Dr Qadeera Rasti Baghban from Bangalore

A diabetes log book was created by Dr Rasti to address the monitoring and documentation issues in children with Type 1 diabetes (T1D). Management of T1D is mainly by periodic monitoring of blood sugars, carbohydrate counting, and exercise. This handbook serves to document each of these in a proper format, which might help in avoiding diabetes related complications, and also help physicians in regularly tracking the health of the affected children.



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WELCOME TO NEW MEMBERS

Chirantap Markand Oza — HCJMRI, Jehangir Hospital, Pune

Madhura Karguppikar — HCJMRI, Jehangir Hospital, Pune

Arti Yadav — PGIMER, Chandigarh

Bharat Sharma — Allahabad

NEWS ON MOVING

ISPAE Member	Previous Place of Work	New Place of Work
Dr Pragya Mangla	Dept. of Pediatrics, School of Medical Sciences and Research and Sharda Hospital, Greater Noida	Dept. of Endocrinology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi

ISPAE OBSERVERSHIP AWARDS

The ISPAE Observership Awards for the year 2021-22 have been awarded to:

ISPAE Member	**Affiliation**	**Host Institute for Observership**
Dr Seema Rai	Assistant Professor, Dept of Pediatrics, GGS Medical College Faridkot, Punjab	Division of Pediatric Endocrinology, Advanced Pediatrics Centre, PGIMER, Chandigarh
Dr Nithya T	Senior Resident, Dept of Pediatrics, Jubilee Mission Medical College, Thrissur, Kerala	Endocrinology Department, Aster Medcity Hospital, Kochi.

Congratulations and best wishes to the winners!

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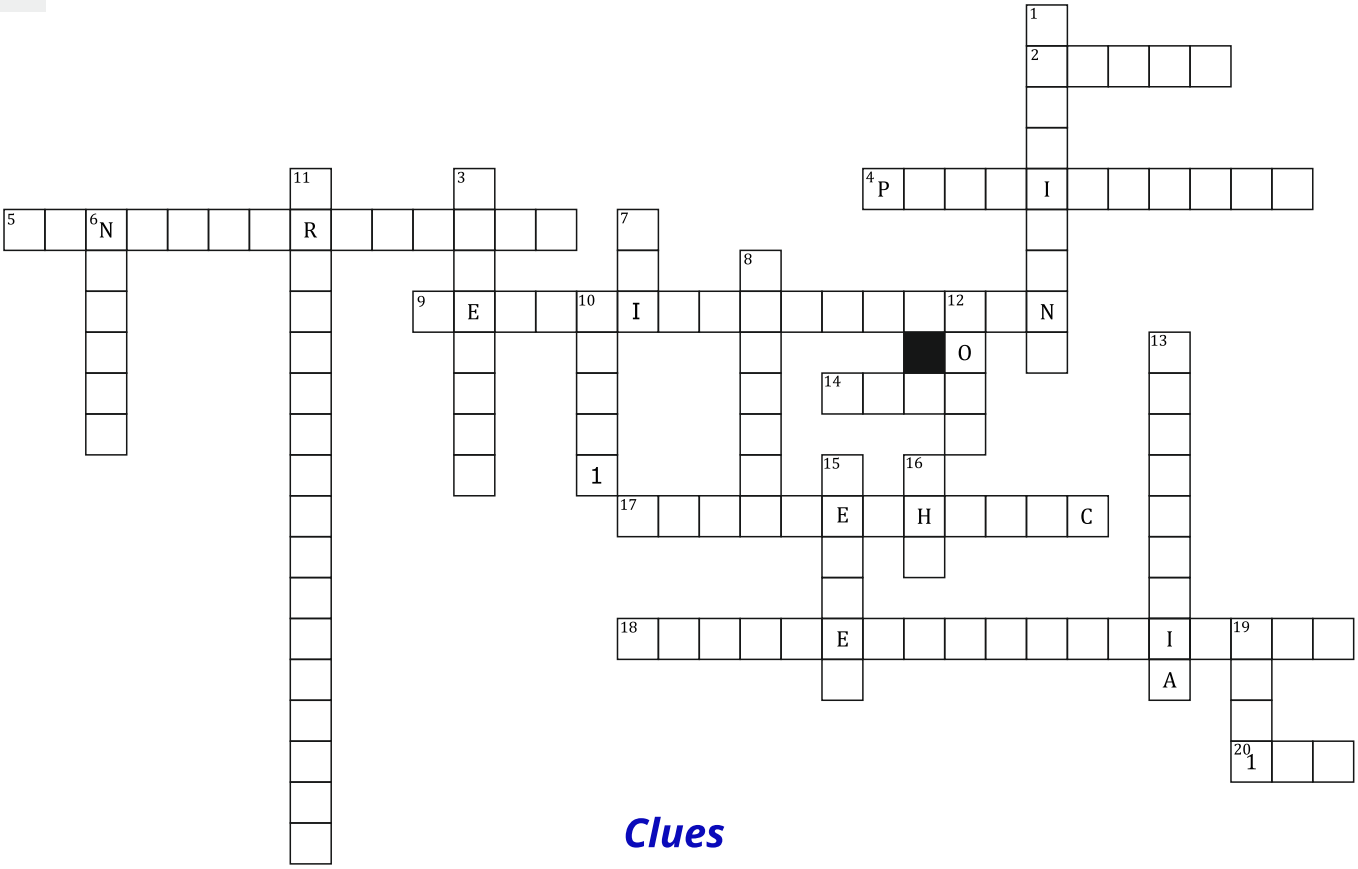
CRACK THIS CROSSWORD QUIZ ON GROWTH. *Wishing you good luck.*

Dr Diksha Shirodkar, Assistant Professor (Pediatrics), Pediatric Endocrinologist,
Yenepoya Medical College & Hospital, Yenepoya University, Mangalore, Karnataka



Clues

Across

2. IGF1 is produced by this organ
4. GH antagonist
5. Acquired hypothyroidism, short stature, precocious puberty and delayed bone age.
9. The scoring criteria for Silver Russell syndrome
14. One of the pseudo autosomal regions - absence of which causes short stature
17. A rare syndrome of failure to thrive in infants with hypothalamic tumors
18. What 'H' denotes in SHORT Syndrome
20. The total number of amino acids in GH

Answer in the next issue of CAPE News!

Please send your responses to **editor.capenews@gmail.com by 15th May.** Members who submit correct responses will be acknowledged and rewarded!

Down

1. A drug used for GH stimulation testing
3. Deformity seen in Leri Weill Dyschondrosteosis.
6. Syndrome caused mostly due to PTPN 11 mutation
7. First name of the famous Pediatric Endocrinologist after whom Laron syndrome is named
8. The most common hormone responsible for hyperphagia in Prader Willi syndrome
10. Mutation of this gene is associated with septo-optic dysplasia
11. What are adamantinomatous and papillary histological types of ?
12. The mutant gene responsible for X linked-classic pituitary stalk interruption, cysts and craniopharyngeal canal
13. Shortening of the middle segments of the limb eg. Radius, ulna
15. Bird headed dwarfism
16. The gene attributed to GH deficiency which results in anti-GH antibodies post administration of rhGH
19. Treatment of Growth hormone Insensitivity

ISPAE 2021

PUNE

IAP Pune Branch

7th Biennial Meeting of

The Indian Society for Pediatric & Adolescent Endocrinology

SAVE THE DATE

12th – 14th November 2021

ISPAE PET Fellows School

9th – 12th November 2021

Dr. Sarah Mathai
PET Convener

Dr. Ahila Ayyavoo
PET Co-Convener

Dr. Vaman Khadilkar
Organizing Chairperson

Dr. Supriya Gupte
Organizing Secretary

Dr. Rahul Jahagirdar
Organizing Joint Secretary

Details will follow soon..