CAPE NEWS

Newsletter of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) *www.ispae.org.in*

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Contents

From the Editor's Desk

Dear members,
Greetings from the CAPE NEWS team!
I hope you enjoyed reading the last issue of CAPE NEWS. The positive feedback from the readers is the primary motivation for an editorial team. We would be happy to have more constructive inputs and suggestions to improve our CAPE NEWS.
In this issue of the CAPE NEWS, we have compiled a summary of recent guidelines on the use of GnRH analogues in children. The Pedendoscan enlists relevant publications in the field of Pediatric Endocrinology over last few months. Further, we have an exciting Mini-review on Vaccination in children with T1DM apart from the usual features of Case Reports and Photo quiz. A long list of events/activities showcases enormous work by the society members.
The team is very thankful to members who contributed to this issue and request all members to share more academic material.

With warm regards,
Rakesh Kumar and team CAPE NEWS

Message from the ISPAE Office Bearers

Dear Friends,

Greetings from the Executive Council for 2019-2020!

We are happy to share several pieces of good news. Our esteemed member Ganesh Jevalikar has been selected from India as Associate Editor of the GPED Newsletter. Three students - Sapna Nayak, Koushik Urla and Lokesh Sharma - have been selected to attend the APPES Fellows' School to be held in Manila in November 2019. We invited proposals for popularizing the Congenital Hypothyroidism Newborn Screening program among the lay public, funded by GPED. The EC shortlisted 3 of the 5 proposals submitted, and the final decision would be taken shortly. For ISPAE-PET in November 2019, 36 candidates have been selected. Six eminent international faculty have kindly agreed to be part of ISPAE-PET. The conveners, Drs Sudha Rao and Sarah Mathai are in the process of finalizing cases and the scientific program. Dr Dey has a report on ISPAE 2019.

Applications for the ISPAE Observership Award have been invited, last date **31st August 2019.** The expression of interest to hold the biennial meeting ISPAE 2021 has been circulated, and we look forward to hearing from members about an exciting venue.

We warmly welcome fourteen new members to the ISPAE family!

We are always open to suggestions from all our members to further the cause of ISPAE in providing care to our patients and training to our fellows.

With regards
Preeti Dabadghao, Ahila Ayyavoo and Leena Priyambada

ISPAE Observership Awards 2019

ISPAE invites applications for the ISPAE Observership Award 2019.
The applicants should contact a pediatric endocrine center of their choice, anywhere in India. Documentation of acceptance by the Center/ Mentor/ Institute concerned should be submitted along with the application.
The Observership should occur in the financial Year 2019-20, for a 1-3 month period and should be completed no later than 31st March 2020.
Two awards, consisting of Rs 25,000/- each, will be given after the candidate successfully completes his/her tenure and submits a report.
For details of criteria please refer to www.ispae.org.in

Applicants should send in their applications for the award by 31st August 2019, to leenapriyambada@gmail.com and ahila.ayyavoo@gmail.com

Hearty Welcome to New ISPAE Members

Name	Place
Gayatri Sabinkar	DM Endocrinology, Narayana Medical College and Hospital, Nellore.
Manjusha K	Senior Resident, Pediatrics, Government Medical College, Kozhikode.
Divya Ajith	Senior Resident, Pediatrics, SAT Hospital, Government Medical College, Trivandrum
Simran Syal	Clinical Fellow, Pediatric Endocrinology, Bai Jerbai Wadia Hospital for Children, Mumbai
Harshada Dilip Tatiya	Fellow, Pediatric Endocrinology, Bai Jerbai Wadia Hospital, Mumbai
Prachi Karia	Fellow, Pediatric Endocrinology, Bai Jerbai Wadia Hospital, Mumbai
Vinod Kumar Bokadia	DNB Endocrinology, Sir Ganga Ram Hospital, New Delhi
Buddharaju P Varma	DM Endocrinology, SVIMS, Tirupati
Yesha Sunil Patel	Fellow, Pediatric Endocrinology, Bharti Vidyapeeth Medical College, Pune
Anusha ND	DM Enodcrinology, SVIMS, Tirupati
Mohan Kumar Medithi	Pediatrician, Elluru
Saniya Gupta	DM Pediatric Endocrinology, PGIMER, Chandigarh
Keshram Meena	In-charge Pediatric Endocrinology, VMMC and Safdarjang Hospital, New Delhi
Aayush Gupta	Fellow, Pediatric Endocrinology, Manipal Hospital, Bengaluru

FDA approves Liraglutide for Children above 10 years with Type 2 Diabetes

On 17 June 2019, FDA approved one more drug, after metformin in 2000, for use in children above 10 years of age with type 2 diabetes. Based on this approval, ADA recommendation 13.63 (page S156-157, 2019 Standards of Care) has been revised.

UPDATE: "13.63 - If glycemic targets are no longer met with metformin ± basal insulin, liraglutide therapy should be considered in children 10 years or older, if no history or family history of medullary thyroid carcinoma or MEN2. A"

Revision: The first sentence of the fifth paragraph of the "Management" sub-section of Type 2 Diabetes, within "Section 13. Children and Adolescents" has been edited to acknowledge the recent approval of liraglutide for use in patients ≥10 years of age

UPDATE: "Current pharmacologic treatment options for youth-onset type 2 diabetes are limited to three approved drugs — insulin, metformin, and liraglutide (2; Victoza PI)."

This FDA approval was based mainly on the ELLIPSE trial, results of which were published in NEJM (Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al. Liraglutide in children and adolescents with type 2 diabetes. N Engl J Med. 2019 Aug 15;381(7):637-646. doi: 10.1056/NEJMoa1903822.

An Indian website for children and families living with diabetes (www.type1diabetes.co.in)

The Division of Pediatric Endocrinology, Department of Pediatrics, AIIMS, Delhi, has developed a bilingual website for patients with type 1 diabetes (T1D) and their families. The aim was to provide a simple educational resource on T1D for families and children, in Hindi as well as English, which can help them in taking better care of themselves. The website has sections on diagnosis, treatment and complications of diabetes, diet, psychological issues, and FAQs. Each section is divided into several sub-sections, and each page has many icons, on clicking which further details can be seen. The section on "Diet" guides the reader on choosing appropriate foods and simple tips for families that will enable them in making gradual changes in their dietary patterns. The section on "Psychological Aspects" provides useful management tips for the common issues seen in various age groups, from toddlers to adolescents; as well as their siblings and parents. The "Share your story" section invites families with T1D to share their journey, achievements of the child in any field, drawings etc. on the site. An important feature of the website is that it is mobile-friendly, and therefore is easily accessible by families. It has taken more than a year and a lot of effort to get this website ready. It was made possible by an ongoing project funded by the Department of Health Research, Government of India. The link to the site is www.type1diabetes.co.in. We are also planning to develop an app based on this content.

Constructive inputs from the ISPAE members for improvement of the content are welcome at vandanajain2005@hotmail.com.

Vandana Jain, Professor, Division of Pediatric Endocrinology, AIIMS, New Delhi

Excerpts from recent Guidelines

Compiled by Nikhil N Lohiya, Research and Clinical Fellow (Ped Endo) at Hirabai Cowasji Jehangir Medical Research Institute & Jehangir Hospital, Pune.

Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium

Bangalore Krishna K, Fuqua JS, Rogol AD, Klein KO, Popovic J, Houk CP, Charmandari E, Lee PA. Horm Res Paediatr. 2019 Jul 18:1-16.

This update, written by authors designated by multiple Pediatric Endocrinology Societies from around the globe, concisely addresses issues related to changes in GnRHa usage in children and adolescents over the last decade. It is not a consensus statement and hence has not been endorsed by any of the Societies that designated participating authors.

A. Diagnosis, Assessment, Natural History, and Racial Differences.

- Differences in the normal range in puberty of different racial group is not known.
- Early thelarche is not always caused by activation of the HPG axis.
- Though the age of thelarche has declined over past 5 decades, the age of menarche has reduced only minimally.
- Adopted children have 10-20 fold higher chances of central precocious puberty (CPP).
- LH is the best biochemical parameter to diagnose CPP.
- LH >0.2 IU/L is considered pubertal (by ICMA). However, values below this are not necessarily prepubertal; the overlap of levels in pubertal and prepubertal children warrants a GnRH stimulation test.
- Random E2 levels may not verify pubertal activation; E2 done 18-24 hours post GnRH administration improves the sensitivity of the stimulation test.
- Ultrasound examination is not diagnostic of CPP. However, uterus size > 3.5 cm and ovarian volume > 2 ml are consistent with puberty.
- MRI brain to exclude intracranial pathology is advised in all boys with CPP, and in girls who are ≤ 6y.

The following table summarises various cut-offs of stimulated LH for diagnosis of CPP with different assays as per different authors.

Stimulated LH (IU/L)	Sensitivity	Specificity	Formulation	Method	Study by
Pubertal: >9.2 @ 30 min Prepubertal: <4.9 @ 30 min	NA	NA	Leuprolide (20 mcg/kg)	ICMA	Houk et al
>5 @ 2h	78	100		ICMA	Sathasivam et al
Adding estradiol >50 pg/ml at 24h	100	100			
>5.5 @ 3h	93	100	Leuprolide (500mcg)	ECLIA	Carretto et al
>6 @ 60 min	89	91	Triptorelin (0.1mg)	ICMA	Poomthvaron et al
>8 @ 3h	76	100	Triptorelin ($0.1mg/m^2$)	ECLIA	Freiree et al
Adding estradiol >80 pg/ml @ 24h	94	100			

B. Available GnRHa and Current Therapeutic Regimens

- GnRHa treatment is the standard of care for treatment of CPP.
- Injections - monthly, 3 monthly, 6 monthly; and subcutaneous implants – annual - are available.
- Weight-based dosing is no longer recommended for the depot forms of leuprolide acetate.
- HPG axis suppression happens within days with histrelin implants, within weeks with high dose leuprolide depot, and in 3 months with low dose leuprolide depot.
- The extent of suppression required for clinical efficacy (decrease in growth velocity, decrease in ratio of bone age to chronological age, increase in predicted adult height (PAH), halt in progression of puberty) remains unclear.
- Clinicians should discuss all of the available options with patients and families, including the expected duration of the therapy, the frequency of administration, and potential short-term and long-term side effects.

Available GnRHa preparations (may vary in different countries)

GnRHa preparation		Dosing
Leuprolide acetate	1 month depot	3.75 mg
		7.5 mg
		11.25 mg
		15 mg
	3 month depot	11.25 mg
		30 mg
Triptorelin pamoate (ambonate)	1 month depot	3.75 mg
		11.25 mg
	6 month depot	22.5 mg
Histrelin acetate	12-month implant	50 mg (65 mcg/day)

C. Considerations for GnRHa therapy in children with CPP: to treat or not to treat?

- Physical changes of puberty between ages 7 and 8y in girls may be temporary, and commonly followed by slow progression of development within the normal range for puberty. with attainment of normal adult height.
- The following factors should be considered to determine the effect of GnRHa treatment -
    - Girls younger than 7y and boys younger than 9y showing progressive CPP, or who with advanced pubertal development (e.g., sexual maturation rating [SMR]; i.e. Tanner stage 3 breast or genital development) with rapid linear growth apparent at their first visit, merit GnRHa treatment. A brisk tempo of pubertal progression increases the risk of adult short stature.
    - For girls older than 7y with SMR 2 breast development, an observation period of 4–6 months is suggested to assess the tempo of pubertal progression, before offering treatment. Height outcomes are much less clear for girls with pubertal onset at age 7y or older. The increase in adult height (AH) over PAH at the onset of therapy varied in one comprehensive review summarizing 29 studies, from 2 to 10 cm, suggesting that some, but not all, patients benefit from therapy starting at this age. Another meta-analysis of 6 studies involving 332 girls treated between ages 7-10y, reported no increase in AH. In fact, most girls with CPP who were not treated with GnRHa do reach a normal AH, although some were shorter than their midparental height range.
    - There have been concerns about psychological morbidity due to CPP with early menses, but adverse behavioral profiles occurring with early maturation may not be as common as earlier described. Families should be informed that when puberty starts close to age 8y or later, menarche usually does not occur for another 2.5–3y, so onset before age 10y is unlikely. Preparation of an early-maturing girl for the onset of menses by a calm and reassuring parent is key to lessening psychological distress. Suppression of menses can still be an option if menarche occurs early and is stressful for the child.
- The following are suggestions for an informed discussion of possible GnRHa treatment for an early-maturing girl (onset at age 7–9y):
    - If the height is above average, with a skeletal age that is not markedly advanced, the AH will probably be normal and may not significantly improve with treatment.
    - Adverse psychosocial stress may not occur from early puberty but if it does, GnRHa treatment may not alleviate such stress.
    - Puberty may progress slowly so that menses may not occur as early as feared. Observation for 4–6 months will help to decide whether a child’s puberty is progressing rapidly.

    - Treatment is expensive, and in addition there is the stress associated with having a condition requiring a pharmacologic intervention, clinic visits, and periodic injections or implant insertion/removal, among other factors.
    - Several studies have failed to find any benefit in terms of height in girls treated after age 8y, and some girls may even lose height as a result of treatment.
- Among males, a similar rationale could be applied in consideration of treatment among those who have a borderline early pubertal onset.

D. Monitoring GnRHa Treatment

- Short-term clinical assessment should occur every 3–6 months to evaluate for stabilization of physical changes.
- Height velocity generally slows to pre-pubertal rates within months of onset of therapy.
- Pubic hair development may stabilize or regress, but is not an accurate indicator of HPG axis suppression as adrenarche could have occurred.
- Skeletal age advancement may decrease after 6 months of therapy, with concomitant gradual increase in the PAH, assuming a reasonable growth rate.
- The HPG axis can be evaluated by measuring unstimulated or stimulated (following GnRH or GnRHa administration) serum LH, sex steroids, or urinary gonadotropin concentrations.
- Indicators of treatment failure – which include clinical pubertal progression, lack of growth deceleration, and continued excessive bone age advancement - should prompt reassessment.
- Treatment failure may be confirmed on clinical grounds alone or verified by GnRHa stimulated LH concentrations minimally > 4 IU/L.
- Adherence to and timing of GnRHa administration should be assessed when treatment fails, with confirmation that the precocity is CPP rather than a GnRH independent cause.
- If there is need to increase the dose of GnRHa, decreasing the dosing interval is an option.
- Discontinuation of therapy: No single clinical variable can determine the best age to discontinue GnRHa. The decision to discontinue treatment should be individualized, and it is appropriate to inquire about the parents' and the patient's perceptions of readiness to stop, since it can be anticipated that pubertal maturation will resume within months.
- Menses may occur from several months to more than 2y after stopping GnRHa treatment.
- It is reasonable to discontinue therapy at a time when puberty would progress concurrently with that of the child's peers.

- Treatment beyond a bone age of 12.5y in girls and 14y in boys may at best result in a minimal increase in height.
- The timing of GnRHa treatment discontinuation is based on patient readiness for resumption of puberty, recent growth rates and shifts in height prediction rather than on bone age alone.

E. GnRHa Adverse Effects

- Allergic or local reactions to GnRHa preparations occur rarely and have been inadequately documented.
- Withdrawal bleeding due to falling estrogen concentrations may occur after the initiation of GnRHa treatment in girls having a significant endometrial lining. Occurrence beyond 2 months of treatment suggests that gonadotropin suppression has not been achieved or another etiology exists.
- Hot flashes are occasionally seen in the initial phases of GnRHa treatment in girls with CPP.
- Convulsions have been reported, though data in the literature is limited, consisting of sporadic case reports.
- A prolonged QT interval associated with GnRHa has not been reported in women or children. For pediatric cases, a screening ECG is recommended only if the individual is receiving other medications known to cause a prolonged QT interval, has a history of congenital heart disease, arrhythmia, or long QT syndrome, has a family history of long QT syndrome or sudden cardiac death, or has symptoms suggestive of long QT syndrome, including syncope.
- Slipped capital femoral epiphysis has been reported in a small number of patients, occurring during GnRHa treatment or after cessation of GnRHa therapy. Prompt evaluation and management are indicated.
- Pituitary apoplexy is a rare complication reported in men with prostate cancer treated with GnRHa for androgen deprivation; it develops within hours of the GnRHa administration. There have been no reported cases of pituitary apoplexy in children or adolescents.

F. Long-Term Outcomes

- **General Health and Wellness**- While studies indicate that early normal puberty is associated with more frequent risk-taking behaviors and functional symptoms in older adolescents, there is insufficient data to determine whether those with CPP, with or without GnRHa therapy, show such behaviors. GnRHa therapy for early puberty may have adverse metabolic profiles, as reported among girls with early normal puberty. Girls with early normal puberty, assumed to be related to a longer

chronic estrogen exposure, have an increased risk of breast cancer and unverified increased risks of obesity, type 2 diabetes mellitus, cardiovascular disease, and other malignancies. The impact of the addition of GnRHa therapy on these risks is unknown.

- **Reproductive Function and Fertility-** There is no substantiated evidence that GnRHa treatment for CPP impairs reproductive function or reduces fertility. In most girls, gonadal function is restored promptly after cessation of therapy, with subsequent menarche and regular ovulatory menstrual cycles. Limited data exist on reproductive function in males treated for CPP but they include normal serum testosterone and gonadotropin levels, and semen analysis. Data on paternity rates and fertility are not available.
- **Polycystic Ovary Syndrome-** There is no clear evidence that girls with treated or untreated CPP are more likely to develop polycystic ovary syndrome (PCOS) than their age-matched peers. Reports are conflicting.
- **Psychological Outcome-** Some early studies suggested that psychological and social problems occur among girls with CPP, citing anxiety about breast development and other physical differences from peers. Subsequent reports have not substantiated such findings. There is no basis for expecting a different incidence of psychological problems among those who had CPP with or without therapy than in the general population, although more research is needed.
- **Impact on Weight-** GnRHa treatment does not appear to influence the long-term progression of these children toward obesity during adolescence or adulthood.
- **Bone Mineral Density-** While children treated with GnRHa have a diminished bone accrual during treatment, it is likely that BMD is within the normal range after cessation of therapy by late adolescent ages.

G. Use of GnRHa in the Management of Transgender Adolescents

- Therapy should only be initiated after the individual has begun clinical puberty (breast or genital SMR 2 and testicular volume $\geq$ 4 mL).
- In transgender boys, GnRHa may be continued until subsequent testosterone therapy has resulted in serum concentrations within the adult reference range.
- In contrast, adult dose estrogens frequently do not suppress testosterone production in transgender girls, so GnRHa therapy may be continued if the testes remain in situ.
- Initial treatment of young transgender adolescents with GnRHa is commonly recommended to prevent development of undesired secondary sex characteristics.
- Additional changes include a decrease in height SDS and BMD, along with alterations in body composition, consisting of increased body fat and decreased lean body mass.

- The impact on BMD is of concern, since lumbar spine Z-scores at age 22y were found to be lower than those observed prior to treatment, suggesting a possible permanent decrement in BMD. Thus, it is unclear how long GnRHa can safely be administered.
- GnRHa therapy prevents maturation of primary oocytes and spermatogonia and may preclude gamete maturation. Currently there are no proven methods to preserve fertility in early pubertal transgender adolescents.
- Care for each adolescent must be individualized, with awareness of gender fluidity and ethical guidelines.

H. Use of GnRHa in Other Conditions

- **GH Deficiency:** In GHD children, addition of GnRHa may be considered in 2 situations:
    1. Children treated for malignancy with resultant GHD and CPP. In this group of patients, GnRHa and GH therapy increases the PAH and the AH.
    2. Children with GHD who have not experienced catch-up growth at the onset of puberty, since insufficient height at pubertal onset will result in short AH. The addition of a GnRHa to GH at the onset of puberty and treatment for at least 2 years resulted in gains of AH ranging from 6 to 9 cm (~1–1.5 SD).

  These situations do not include the usual patients diagnosed with isolated GHD who are treated in a timely manner with GH. Use of GnRHa or aromatase inhibitors in such children remains controversial and is not standard of care.

- **Non-GH-Deficient Short Stature-**
    - GnRHa therapy alone has shown improvement of up to 0.6SD in height as compared to controls in a recent trial.
    - Some studies have shown that combined GH and GnRHa treatment for 3 or more years may result in a greater increase in AH, particularly in adopted girls.
    - In addition to height gain, the cost-benefit of such invasive treatments should also be considered, and further larger, long-term, and adequately powered clinical trials, focusing on efficacy, safety, and clinical significance, are needed to fully evaluate the combination of GH and GnRHa in short adolescents.
    - Meanwhile, these approaches should be considered as **experimental**.

- **Small for Gestational Age-** Although the data is limited, it is appropriate to consider the potential advantages and disadvantages of treatment with GH and GnRHa in this population.

- **Fertility Preservation-**
  - GnRHa treatment has been administered just before and during chemotherapy to minimize the risk of premature ovarian insufficiency by reducing exposure to cytotoxic agents and protecting the developmental process of primordial follicles.
  - Systematic reviews and meta-analyses show a higher recovery rate of cyclic ovarian function after chemotherapy in patients treated with GnRHa before and during chemotherapy than untreated groups.
  - However, the results were mixed, depending on the type of tumor.
  - There are no long-term randomized, controlled studies. Thus, the efficacy of fertility preservation by GnRHa in adults is still controversial.

- **Autism, Problematic Behavior, and Developmental Problems-**
  - GnRHa treatment cannot be recommended for autism, as there is no validated evidence of efficacy.
  - Although GnRHa have been used to treat patients with developmental problems (i.e., males who masturbate in public and females unable to care for themselves during menstruation), preventing pubertal progression can be seen at best as a temporary measure.

Mini-Review

Vaccination in Childhood Diabetes Mellitus

Aashima Dabas[1] and Bhanu Kiran Bhakhri[2]

[1]Assistant Professor, Department of Paediatrics, Maulana Azad Medical College, New Delhi. [2]Associate Professor & Head, Department of Pediatric Medicine, Super Speciality Pediatric Hospital and PG Teaching Institute, Noida, UP.

Diabetes mellitus, both type 1 and 2, is being increasingly recognized as a significant health burden among non-communicable diseases in childhood. Affected children carry high risks of morbidity and mortality, with acute and long-term complications of the disease. Hyperglycemia predisposes to developing skin and mucocutaneous infections. Children in a developing country like ours face additional risks of hospitalization and death due to infections like diarrhea, pneumonia and measles. Therefore it is imperative that children with diabetes get immunized against all vaccine preventable diseases (VPDs). The Universal Immunization Program (UIP) under the Government of India advocates and provides for immunization against tuberculosis, diphtheria, tetanus, pertussis, hepatitis B, hemophilus influenza, measles, rubella, polio and, in select districts, Japanese encephalitis. Newer vaccines that are being added to the program include rotavirus and pneumococcal[1]. Therefore, all children with diabetes should be protected with these vaccines.

Though type 1 diabetes (T1D) results from an immune dysregulation in the body, these children per se are not immune-deficient. The risk factors which predispose them to develop infections include hyperglycemia, frequent hospitalizations and poor local hygiene at local injection sites. A large Dutch cohort of adult patients - 705 with T1D and 6712 with Type 2 diabetes (T2D) - was evaluated and compared with non-diabetic controls over a 12-month period. There was a higher risk of lower respiratory tract infections, urinary tract infections and skin and mucous membrane infections among patients with T1D than controls[2].

Few studies have evaluated the seroprotection status of children with T1D with respect to risk for developing VPDs. An initial study from Finland had reported significantly lower mumps antibody titers in children with T1D within 2.5y of their MMR (measles, mumps, rubella) immunization, as compared to non-diabetic children[3]. A recent study compared antibodies against diphtheria, tetanus, pertussis, measles, mumps, rubella and hepatitis B in 90 T1D children (under 15 years of age) with controls. Measles titers showed a difference in seroprotection in only 62% of the children with diabetes, vs. 84% of the controls. Similarly, rubella titers differed in both groups. The rest of the vaccine titers were comparable[4].

Apart from the UIP, there are a few vaccines which are available separately on individual-case basis like varicella, hepatitis A, influenza and pneumococcal. A recent systematic review of 15 studies evaluated the immunogenicity, safety and efficacy of seasonal influenza vaccination in patients with type 1, type 2 and other forms of diabetes for all ages. Seasonal influenza vaccine demonstrated comparable immunogenicity in diabetic and non-diabetic groups, with adequate seroconversion (>40%) and seroprotection (>70%) one month after vaccination[5]. Influenza vaccination is also recommended for elderly diabetics (> 65y, as they are a high-risk group) during epidemics, to reduce the risk of hospitalization and mortality[6,7]. A higher risk of invasive streptococcal respiratory infections has been reported in adults with T2D[8], suggesting the need for providing protection with pneumococcal vaccine. A single dose of pneumococcal polysaccharide vaccine (PPSV) would provide protection against 23 serotypes of bacteria; a single dose of pneumococcal conjugate vaccine (PCV) would induce a more robust immunological response but against fewer antigens. In these high-risk children, it is recommended to immunize with PCV 13/10, followed by PPSV 23 after 8 weeks[7]. Therefore, as per the recommendations of the Indian Academy of Pediatrics, children with diabetes should be offered immunization against hepatitis A, pneumococcal, varicella, influenza and rotavirus (if not administered under regional schedule)[7].

Routine vaccination was postulated to cause an increased risk of developing T1D later. In a large population-based, case-control study of 252 children with T1D matched with 768 controls, the authors did not find any increased risk for developing T1D with DPT, varicella, MMR, hepatitis B or hemophilus influenza (OR 0.28 to 1.36; P >0.05 for different vaccines), indicating vaccine safety[9].

To conclude, children with diabetes should be provided protection against all preventable communicable diseases to decrease VPDs associated morbidity and mortality. The children should follow the National immunization schedule as per UIP, and additional vaccines can be offered as appropriate, in this high-risk group.

Key messages:

- Diabetic children should receive the vaccines as per UIP at the scheduled times.
- Diabetic children may specifically be offered vaccination for hepatitis A, pneumococcal, varicella, influenza and rotavirus.
- Vaccination may be postponed if the child is acutely sick, e.g. hospitalized for diabetic ketoacidosis, but must be resumed at the earliest.

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Case Report 1

Refractory hypoglycemia in an infant with Isolated Severe Primary Hypothyroidism

Shreya Sharma, Sudha Rao Chandrashekhar, Division of Pediatric Endocrinology, BJ Wadia Hospital for Children, Mumbai.

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Introduction

Isolated hypothyroidism as a primary cause of hypoglycemia is not a well-known phenomenon. The following case illustrates how isolated severe primary hypothyroidism can lead to symptomatic refractory hypoglycemia as part of myxoedema crisis complex.

Case Description

A 6 month-old female infant, born of a nonconsanguineous marriage, was hospitalised with gross abdominal distension and history of chronic constipation. There was failure to thrive with weight 3.3 kg (SDS -6), length 51 cm (SDS -6.97), and head circumference (36 cm, SDS -5.13).

She was born at term, birth weight 2 kg, by caesarean section in view of oligohydramnios. Postnatally, she developed exaggerated unconjugated hyperbilirubinemia, which required phototherapy for 4 days. Global developmental delay was evident as infant had not achieved head control or social smile.

The infant was initially hospitalised in a surgical unit in view of gaseous abdominal distension, to rule out intestinal obstruction. Barium enema showed a nonobstructive pattern, but sluggish intestinal transit. During her hospital stay, she became lethargic. On examination, she had mottled skin, cool extremities, and hypotension. Capillary blood glucose was 32 mg/dl, so she was administered 15 ml of 10% dextrose, and transferred to the pediatric intensive care unit for stabilization. Hypotension persisted, with marked hypothermia and relatively bradycardia, which was treated with fluid boluses, dopamine infusion, empirical intravenous hydrocortisone (50 mg/m^2/day), glucose infusion (up to 12.5 mg/kg/min), and active warming. Chest X-ray showed globular heart with increased hilar markings. There was no clinical or laboratory evidence of sepsis. An electrocardiogram showed low voltage complexes with normal rhythm. Cardiac contractility was poor with low ejection fraction and thin rim of pericardial effusion.

Clinically, the baby was noticed to have coarse facies, pallor, umbilical hernia, open posterior fontanelle, hypotonia, with delayed relaxation of deep tendon reflexes. There was

no organomegaly or corneal clouding. An urgent thyroid profile showed severe primary hypothyroidism (free T3 0.49 pg/ml, free T4 0.03 ng/dl, thyroid stimulating hormone: >100 µIU/ml). Ultrasonogram of thyroid showed athyreosis. She was promptly started on oral thyroxine replacement at dose of 10 µg/kg/day, with ongoing glucocorticoid cover.

She also had severe macrocytic anemia (hemoglobin 6.4 g/dl, mean corpuscular volume 96 fl) for which she received a blood transfusion, and subsequently oral iron, folate and vitamin B_{12} supplements. Total leucocyte and platelet counts were normal.
Meanwhile, evaluation for persistent hypoglycemia continued. Critical sample sent at a blood glucose of 23 mg/dl showed a non-acidotic, non-ketotic picture, with normal serum electrolytes, ammonia (90 mmol/L) and lactate (1.8 mmol/L). Serum cortisol was 29 µg/dl and serum insulin 0.5 µIU/ml - appropriate hormonal responses to hypoglycemia. Urine for reducing substance was negative and tandem mass spectrometry did not suggest any inborn error of metabolism.

She required continuous milk infusion with added uncooked corn starch powder and sucrose for hypoglycemia management for a period of approximately 72 hours, amounting to maximum total carbohydrate loading of 84 g/day. Formal 2-D echo repeated 3 days after start of thyroxine replacement showed improved ejection fraction (64%). Free T4 level repeated two weeks later was normal (0.94 ng/dl). The child is now 2 years old and has shown significant catch up in growth and development.

DISCUSSION

Literature clearly highlights the importance of hypothyroidism as a precipitating factor for hypoglycemia (1). Hypothyroidism is considered a cause of unexplained hypoglycemia in patients with diabetes mellitus, after exclusion of other known causes. Rare case reports have described hypoglycemia secondary to primary hypothyroidism previously (2). Severe hypothyroidism is linked with low growth hormone and cortisol responses to insulin-induced hypoglycemia, which impair counter-regulatory responses. Here, the pituitary dysfunction is a consequence of primary hypothyroidism rather than a cause of thyroid dysfunction. However, cortisol response to hypoglycemia was adequate in our patient. Hypothyroid patients may also have a reduced adreno-medullary response to stress (3). The processes of gluconeogenesis and glycogenolysis are also impaired in hypothyroidism, both in skeletal muscle and in adipose tissue. Other abnormalities in hypothyroidism include a reduction in glucagon secretion, reduced effect of glucagon on hepatocytes, and slowing of insulin clearance (1). Contributory factors also include the effect of hypothyroidism on the gastrointestinal system by slowing gastric emptying and decreasing intestinal absorption of glucose as well as portal venous flow.
The refractory hypoglycemia in our patient was a part of the constellation of myxoedema crisis. The decreased sympathetic drive was evident in her, in the form of hypothermia and bradycardia in the face of hypotension.

The thyroid axis must not be neglected in the evaluation of persistent hypoglycemia as isolated severe hypothyroidism may cause/precipitate hypoglycemia in the absence of other pituitary or adrenal hormone deficiencies.

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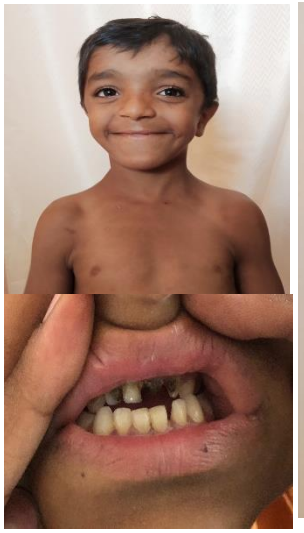
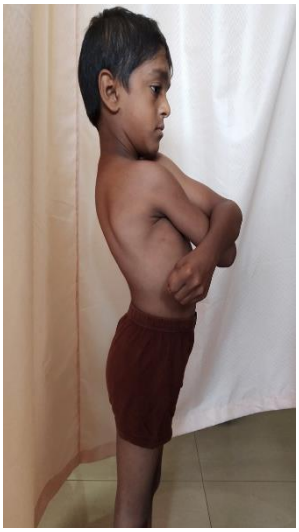
Photo Quiz 1

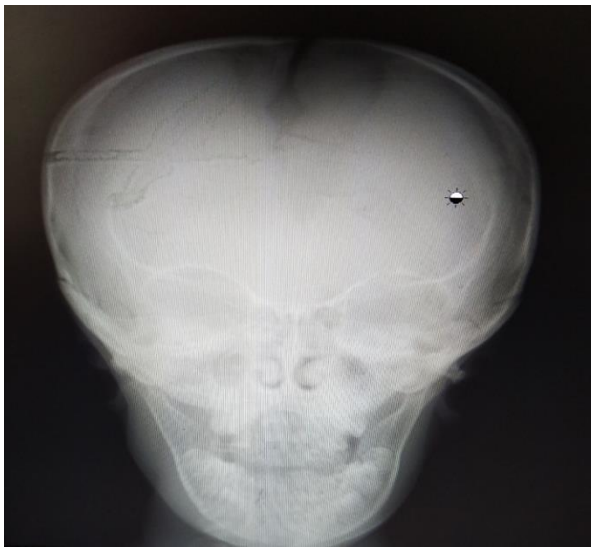
Sowjanya GT, Shruti Appaji, Akanksha Parikh, Raghupathy P, Department of Pediatric Endocrinology, Indira Gandhi Institute of Child Health, Bengaluru.

A 10y 3mo old boy, born to a non-consanguineous couple, was brought with the complaints of short stature noticed since 7y of age. He had mild motor delay with normal intelligence, and no significant past and family history. Clinical examination revealed brachycephaly, wide open anterior fontanelle (AF), depressed nasal bridge, hypertelorism and persistent primary dentition. A striking feature was the presence of narrow shoulders with the ability to voluntarily bring them together. He also had pectus excavatum, lumbar lordosis and a waddling gait. His clinical and radiological pictures are shown below.





What is the diagnosis?



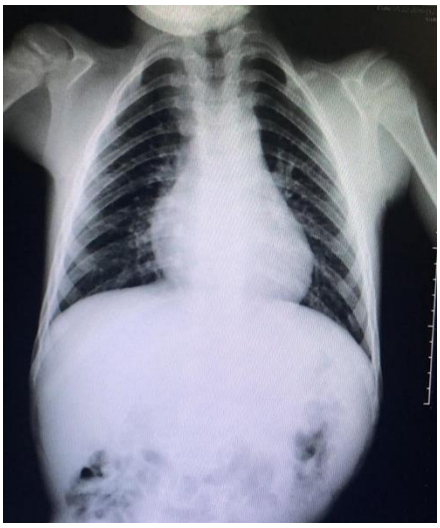
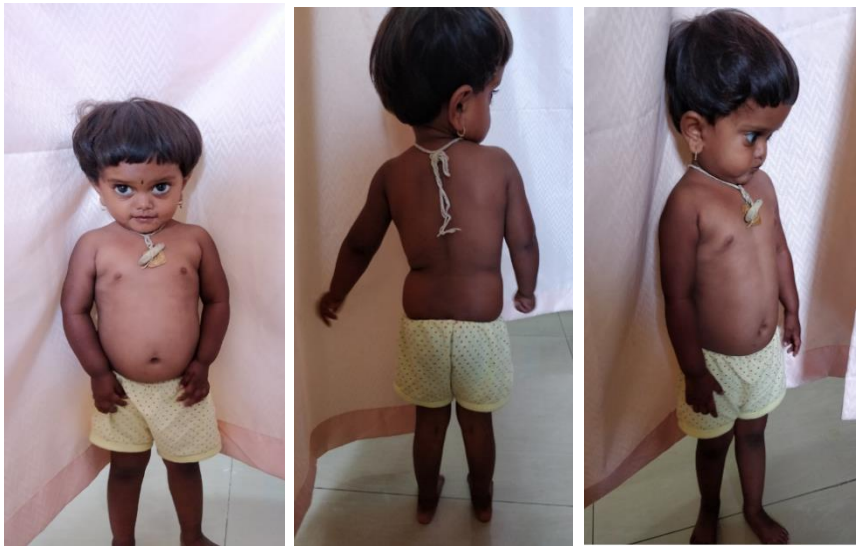


Photo Quiz 2

Sowjanya GT, Proteek Sen, Akanksha Parikh, Raghupathy P, Department of Pediatric Endocrinology, Indira Gandhi Institute of Child Health, Bengaluru.

A 3y 4mo old girl, 3rd born to a consanguineous couple, presented with history of not gaining height and weight since age 6 months. She had an uneventful birth history with a birth weight of 2.75 kg. There was no history of seizures, vomiting, visual disturbances, poor feeding, polyuria, polydipsia, constipation or any history suggestive of systemic illness. She was developmentally appropriate for age. No other family member was similarly affected. Her anthropometric parameters were as follows: height 66 cm (<3rd centile, -7.97 SDS), weight 6 kg (<3rd centile), head circumference 44 cm (<3rd centile), upper:lower segment ratio 1.2. Her clinical pictures are shown below.



What is the diagnosis?

Pedendoscan

Compiled by: Nikhil N Lohiya, Research and Clinical Fellow (Ped Endo), Hirabai Cowasji Jehangir Medical Research Institute & Jehangir Hospital, Pune.

Liraglutide in children and adolescents with type 2 diabetes. N Engl J Med 2019 Apr 28. Doi: 10.1056/NEJMoa1903822.

Metformin is the regulatory-approved treatment of choice for most youth with type 2 diabetes (T2D) early in the disease, but early loss of glycemic control has been observed with metformin monotherapy. Whether liraglutide added to metformin (with or without basal insulin treatment) is safe and effective in youth with T2D is unknown. In this study, patients age 10-17y were randomly assigned, in a 1:1 ratio, to receive subcutaneous liraglutide (up to 1.8 mg per day) or placebo, for a 26-week double-blind period, followed by a 26-week open-label extension period. Inclusion criteria were a body-mass index greater than the 85th percentile and a glycated hemoglobin level of 7-11% if the patients were being treated with diet and exercise alone, or 6.5-11% if they were being treated with metformin (with or without insulin). All the patients received metformin during the trial. The primary end point was the change from baseline in the glycated hemoglobin level after 26 weeks. Secondary end points included the change in fasting plasma glucose (FPG) level. Safety was assessed throughout the course of the trial. Of 135 patients who underwent randomization, 134 received at least one dose of liraglutide (66 patients) or placebo (68 patients). Demographic characteristics were similar in the two groups (mean age 14.6y). At 26 weeks, mean A1c had decreased by 0.64% with liraglutide and increased by 0.42% with placebo, i.e. estimated treatment difference of −1.06% ($P<0.001$); the difference increased to −1.30% by 52 weeks. The FPG decreased at both time points in the liraglutide group but increased in the placebo group. The number of patients who reported adverse events (AE) was similar in the two groups -56 [84.8%] with liraglutide and 55 [80.9%] with placebo, but the overall rates of AE and gastrointestinal AE were higher with liraglutide. In children and adolescents with T2D, liraglutide, at a dose of up to 1.8 mg/day, added to metformin, with or without basal insulin, was efficacious in improving glycemic control over 52 weeks, with increased frequency of gastrointestinal AE. (Funded by Novo Nordisk; Ellipse ClinicalTrials.gov number, NCT01541215opens in new tab.)

Effects of Estrogen Therapies on Outcomes in Turner Syndrome: Assessment of Induction of Puberty and Adult Estrogen Use. J Clin Endocrinol Metab. 2019 Jul 1;104(7):2820-2826. doi: 10.1210/jc.2018-02137. Turner syndrome (TS) is often associated with delayed puberty. To induce puberty, estrogen is administered in incremental doses at an age determined by age of presentation. After puberty, various types of maintenance estrogen replacement therapy (ERT) are used.

The objective of this study was to seek associations between age of induction of puberty and type of ERT on adult health outcomes. Health surveillance data included blood profiles, bone density, and blood pressure from 6679 clinic visits of 799 women with TS, at the Adult TS clinic at University College London Hospital. Authors assessed interactions between these data and age at first estrogen exposure; and also according to ERT subgroups [combined oral contraceptive pill (OCP), oral estrogen (OE), and transdermal estradiol (TE)], controlling for age, body mass index, and height. Estrogen start age was negatively correlated with adult bone density (spine: r = -0.20 and hip: r = -0.022; $P \leq 0.001$). OCP users had higher BP and an adverse lipid profile compared with other ERT subgroups. TE was associated with elevated liver enzymes and hemoglobin A1c compared with OE ($P \leq 0.01$). They concluded an earlier age of induction of puberty may be beneficial for adult bone density; that the use of OCP for ERT should be limited, given the high prevalence of hypertension in TS; and that OE may be a benefit for steatohepatitis.

Improved General and Height-Specific Quality of Life in Children With Short Stature After 1 Year on Growth Hormone. J Clin Endocrinol Metab. 2019 Jun 1;104(6):2103-2111. doi: 10.1210/jc.2018-02523.

Short stature in children and adolescents may lead to social and emotional stress, with negative effects on quality of life (QoL). GH treatment may improve QoL through height normalization. The objective in this study was to evaluate general and height-specific QoL after 1 year of GH treatment. It was a prospective, single-center, observational cohort study of children ≥ 4y of age starting GH from 2012 to 2015. Patients with serious diseases, syndromic short stature, or developmental delay were excluded. At treatment initiation and 1 year later, patients and their parents completed the general PedsQL 4.0 and height-specific Quality of Life in Short Stature Youth (QoLiSSY) questionnaires. Correlations between self-report and parent-report scores and between height gain and QoL improvements were assessed based on Pearson correlation coefficients. Seventy-four children (42 boys), median age (± SD) 10.2 ± 3.0y (range 4.1-16.6y), were included. The self-report PedsQL indicated significant improvements in emotional ($P = 0.02$) and social ($P = 0.03$) QoL. As assessed by the QoLiSSY, children reported improvement of social QoL (+0.2 SD; $P = 0.04$), and parents reported improvement of children's physical (+0.1 SD; $P < 0.0001$), emotional (+0.3 SD; $P < 0.0001$), and social (+0.3 SD; $P < 0.0001$) QoL. Height SD score (SDS) gains showed moderate positive correlations with QoLISSY self-report score gains ($R = 0.53$, $R2 = 0.28$; $P < 0.001$) and QoLISSY parent-report gains ($R = 0.60$, $R2 = 0.41$; $P < 0.00001$).

Multigene Sequencing Analysis of Children Born Small for Gestational Age With Isolated Short Stature. J Clin Endocrinol Metab. 2019 Jun 1;104(6):2023-2030. doi: 10.1210/jc.2018-01971.

Patients born small for gestational age (SGA) who present with persistent short stature (SS) could have an underlying genetic etiology that will account for prenatal and postnatal growth impairment. The authors applied a unique massive parallel sequencing approach in a

cohort of patients with exclusively nonsyndromic SGA to simultaneously interrogate for clinically substantial genetic variants. The objective was to perform a genetic investigation of children with isolated SS born SGA. Design was Screening by exome (n = 16) or targeted gene panel (n = 39) sequencing, conducted at a tertiary referral center for growth disorders. In 55 selected patients born SGA with persistent SS without an identified cause of SS, they identified heterozygous pathogenic or likely pathogenic genetic variants in 8 (15%), all in genes already associated with growth disorders. Four of the genes are associated with growth plate development, IHH (n = 2), NPR2 (n = 2), SHOX (n = 1), and ACAN (n = 1), and two are involved in the RAS/MAPK pathway, PTPN11 (n = 1) and NF1 (n = 1). Seven patients were SGA only for length; one was SGA for both length and weight; none had clinical findings that allowed for a clinical diagnosis. These genomic approaches identified pathogenic or likely pathogenic genetic variants indicating mild forms of skeletal dysplasia as a cause of growth disorders in this group of patients.

Genetic Polymorphisms Associated with Idiopathic Short Stature and First-Year Response to Growth Hormone Treatment. Horm Res Paediatr. 2019;91(3):164-174. doi: 10.1159/000496989. Epub 2019 Apr 10.

The term idiopathic short stature (ISS) describes short stature of unknown, but likely polygenic, etiology. This study aimed to identify genetic polymorphisms associated with the ISS phenotype, and with growth response to supplemental GH. Using a case-control analysis, authors compared the prevalence of "tall" versus "short" alleles at 52 polymorphic loci (17 in growth-related candidate genes, 35 identified in prior genome-wide association studies of adult height) in 94 children with ISS followed in the Genetics and Neuroendocrinology of Short Stature International Study, versus 143 controls from the Fels Longitudinal Study. Four variants were nominally associated with ISS using a genotypic model, confirmed by a simultaneous confident inference approach: compared with controls, children with ISS had lower odds of "tall" alleles (odds ratio, 95% CI) for GHR (0.52, 0.29-0.96); rs2234693/ESR1 (0.50, 0.25-0.98); rs967417/BMP2 (0.39, 0.17-0.93), and rs4743034/ZNF462 (0.40, 0.18-0.89). Children with ISS also had lower odds of the "tall" allele (A) at the IGFBP3 -202 promoter polymorphism (rs2855744; 0.40, 0.20-0.80) in the simultaneous confident inference analysis. A significant association with 1st-year height SD score increase during GH treatment was observed with rs11205277, located near 4 known genes: MTMR11, SV2A, HIST2H2AA3, and SF3B4; the latter, in which heterozygous mutations occur in Nager acrofacial dysostosis, appears the most relevant gene. In children with ISS, associations with "short" alleles at a number of height-related loci were identified. In addition, a polymorphic variant located near SF3B4 was associated with the GH treatment response. The findings in this small study warrant further investigation.

Biological Significance of Anti-GH Antibodies in Children Treated with rhGH. Horm Res Paediatr. 2019;91(1):17-24. doi: 10.1159/000497409. Epub 2019 Apr 4.

The occurrence of antidrug antibodies is common in children treated with recombinant human growth hormone (rhGH), but the clinical significance is unclear. This laboratory-based retrospective study over 6y, aimed to examine the clinical significance of anti-GH antibodies by analyzing the phenotype of patients who tested positive, in relation to the quantity of anti-GH antibodies. Anti-GH antibodies were measured using a radioprecipitation assay; positive samples underwent a confirmatory assay. Out of a total of 104 samples from 66 patients, positive test results were found in 28 samples from 13 patients. Clinical data were available from all but one. The group with positive test results comprised 6 patients with a normal response to GH provocative tests (group A) and 6 with an insufficient response or with isolated GH deficiency (IGHD) type 1A (group B). Diagnoses in group A were neurosecretory dysfunction, bioinactive GH syndrome and constitutional delay of growth and puberty. Diagnoses in group B were IGHD type 1A, septo-optic dysplasia, and cerebral midline defect with multiple pituitary hormone deficiency. Insufficient growth response to rhGH was absent except in one sibling pair with IGHD type 1A and a patient with cerebral midline defect. These patients had the highest concentrations of anti-GH antibodies. The biological significance of anti-GH antibodies seems to be limited to patients with high concentrations of anti-GH antibodies. For all other patients, we recommend a careful "wait and see" strategy and monitoring antibody titers.

CYP21A2 Gene Pathogenic Variants: A Multicenter Study on Genotype-Phenotype Correlation from a Portuguese Pediatric Cohort. Horm Res Paediatr. 2019;91(1):33-45. doi: 10.1159/000497485. Epub 2019 Mar 19.

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is an autosomal recessive disorder characterized by 3 overlapping phenotypes: salt-wasting (SW), simple virilizing (SV), and non-classic (NC). Authors aimed at conducting a nationwide genotype description of the CAH pediatric patients and to establish their genotype-phenotype correlation. CAH patients were recruited from Portuguese pediatric endocrinology centers and classified as SW, SV, or NC. Genetic analysis was performed by polymerase chain reaction (sequence specific primer, restriction fragment length polymorphism) or direct Sanger sequencing. Genotypes were categorized into 4 groups (0, A, B, and C), according to their predicted enzymatic activity. In each group, the expected phenotype was compared to the observed phenotype to assess the genotype-phenotype correlation. This cohort had 212 unrelated pediatric CAH patients (29% SW, 11% SV, 60% NC). The most common pathogenic variant was p.(Val282Leu; 41.3% of the 424 alleles analyzed). The p.(Val282Leu) variant, together with c.293-13A/C>G, p.(Ile173Asn), p.(Leu308Thr), p.(Gln319*), and large deletions/conversions were responsible for 86.4% of the mutated alleles. Patients' stratification by disease subtype revealed that the most frequent pathogenic variants were c.293-13A/C>G in SW (31.1%), p.(Ile173Asn) in SV (46.9%), and

p.(Val282Leu) in NC (69.5%). The most common genotype was homozygosity for p.(Val282Leu; 33.0%). Moreover, we found 2 novel variants: p.(Ile161Thr) and p.(Trp202Arg), in exons 4 and 5, respectively. The global genotype-phenotype correlation was 92.4%. Group B (associated with the SV form) showed the lowest genotype-phenotype correlation (80%). Author's cohort has one of the largest NC CAH pediatric populations described. Authors emphasize the high frequency of the p.(Val282Leu) variant and the very high genotype-phenotype correlation observed.

Treatment with Growth Hormone in Noonan Syndrome Observed during 25 Years of KIGS: Near Adult Height and Outcome Prediction. Horm Res Paediatr. 2019;91(1):46-55. doi: 10.1159/000498859. Epub 2019 Apr 2.

There is little information how rhGH treatment affects height in NS. This study aims to analyse data from the NS patients in KIGS over 25 years. Of 613 (389 males) NS patients documented, 476 (302 m) were treated for 1 year, 237 (160 m) of whom served to develop a 1st year height velocity (HV) prediction algorithm. 140 (74 m) had reached near adult height (NAH). Factors affecting NAH on rhGH were determined. At the start of rhGH, the NAH groups were (median, m, f) 11.0 and 10.3y, with a height SDS of -3.2 and -3.8 SDS (Prader), respectively. The total gain after 6.3 and 5.6y on rhGH (0.27 and 0.30 mg/kg/week) was 1.2 and 1.3 SDS. Age at the start of rhGH (negative), height at the start of rhGH, rhGH dose, number of rhGH injections/week and birth weight (all positive) explained 36% of the variability of the 1st year HV. Height at the start of rhGH, 1st year growth on rhGH, birth weight, and gender explained 74% of the variability of NAH. Causes for rhGH treatment discontinuation and adverse events were also analyzed. In conclusion rhGH treatment increases NAH in NS. Prediction algorithms may optimize treatment in the future.

Prevalence of dyslipidemia and factors affecting dyslipidemia in young adults with type 1 diabetes: evaluation of statin prescribing. J Pediatr Endocrinol Metab. 2019 Apr 24;32(4):327-334. doi: 10.1515/jpem-2018-0383.

There is limited information about cardiovascular complications among young adults (YA) with type 1 diabetes mellitus (T1DM) who are transitioning from pediatric to adult care. The authors aimed to study the prevalence and associated factors of dyslipidemia (DLD) and statin treatment in these patients; 129 YA with T1DM aged 15-25y were recruited. In a cross-sectional analysis, the prevalence of DLD (low-density lipoprotein cholesterol [LDL-C] $\geq$ 100 mg/dL, high-density lipoprotein cholesterol [HDL-C] <40 mg/dL [males] or <50 mg/dL [females], total cholesterol [TC] $\geq$200 mg/dL or triglycerides [TG] $\geq$150 mg/dL) was reported. Socioeconomic and clinical characteristics were compared between YA with and without DLD. DLD was found in 64% of YA, predominantly increased LDL-C (34.9%). Higher mean glycated hemoglobin (HbA1c) was associated with DLD ($p < 0.043$). Of all YA who met the criteria for statin therapy, only 42% had one prescribed. The prevalence of DLD is high in YA with T1DM and is associated with poor glycemic control, and use of statin therapy in this high-risk population is low.

Cardiovascular risk factors in children with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2019 Jul 26;32(7):699-705. doi: 10.1515/jpem-2018-0382.

Cardiovascular disease is a major complication among children with type 1 diabetes mellitus (T1DM). This prospective study aimed at examining 175 children with T1DM for the presence of cardiovascular risk factors; with 150 non-diabetic children as normal controls. The diabetic children had significantly higher carotid IMT (cIMT) and aortic IMT (aIMT), higher values for diastolic wall stress (DWS), incremental elastic modulus (IEM), and flow-mediated dilatation (FMD) than the controls. The levels of tumor necrosis factor-α (TNF-α), interleukin-4 (IL4), high-sensitivity C-reactive protein (hs-CRP) and leptin were significantly higher in T1DM patients. In T1DM children, the cIMT and aIMT were correlated with several risk factors, including age, weight, body mass index (BMI), duration of diabetes, waist/hip ratio, as well as levels of total cholesterol, triglycerides and apolipoprotein B (apoB). In addition to common risk factors, cIMT was also associated with systolic blood pressure (BP). Other risk factors, such as height, diastolic BP, low-density lipoprotein (LDL)/high-density lipoprotein (HDL)-cholesterol ratio, apolipoprotein A1 (apoA1) and S-creatinine levels, were not all independent risk factors of cardiovascular disease in T1DM children. T1DM is associated with early impairment of the common carotid and aortic artery structure and function, and the diabetic state may be the main risk factor for arterial wall stiffening and thickening.

The metabolic consequences of overweight in a cohort of children with type 1 diabetes. J Pediatr Endocrinol Metab. 2019 Jul 26;32(7):715-719. doi: 10.1515/jpem-2018-0483.

The objective of this study was to estimate the prevalence of overweight and obesity among a cohort of children with type 1 diabetes mellitus (T1D) and its metabolic consequences. This was a cross-sectional study conducted in the Pediatric Diabetic Clinic at Shaare Zedek Medical Center and Clalit Health Care Services. Background information was taken from the patients' files. Anthropometric measures, blood pressure, waist and hip circumference (WC and HC), hemoglobin A1c (HbA1c) and lipid profile were recorded. The prevalence of metabolic derangements was compared between normal and overweight children. The study included 96 patients with T1D, mean age 14.1 ± 3.7y, mean diabetes duration 3.9 ± 3y, and mean HbA1c level 8.1 ± 1.4% (65 mmol/mol); 37% were overweight; of them 11.5% were obese. In the overweight group, the high-density lipoprotein (HDL) levels were significantly lower and systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were higher compared with normal weight participants. Multivariate analysis showed that BMI and age at study affected SBP and HDL levels, while age at study and HbA1c levels affected DBP. Female patients were significantly overweight compared to males and had higher low-density lipoprotein (LDL) and cholesterol levels. Waist-to-hip ratio, an indicator of central obesity, was abnormally high among overweight males and females. In this cohort of children with T1D, significant number of overweight children, with a higher prevalence

in females. Components of metabolic syndrome were more prevalent among overweight and obese diabetic individuals.

High frequency of non-classical congenital adrenal hyperplasia form among children with persistently elevated levels of 17-hydroxyprogesterone after newborn screening. J Pediatr Endocrinol Metab. 2019 May 27;32(5):499-504. doi: 10.1515/jpem-2018-0398.

Early diagnosis after newborn screening (NBS) for congenital adrenal hyperplasia (CAH) allows proper treatment, reducing mortality rates and preventing development of hyperandrogenic manifestations and incorrect sex assignment at birth. Despite the high NBS sensitivity to detect CAH classical forms, one of the main issues is identifying asymptomatic children with persistently increased 17-hydroxyprogesterone (17-OHP) levels. This study aimed to contribute to understanding the diagnosis of these children. Children with increased serum 17-OHP levels, and without disease-related clinical features during follow-up, underwent the entire CYP21A2 gene sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis (SALSA MLPA P050B CAH). Patients' genotypes were subsequently sorted as compatible with CAH disease, and children were evaluated to determine the clinical status. During the study period, 106,476 newborns underwent CAH NBS. During follow-up, 328 children (0.3%) were identified as having false-positive tests and 295 were discharged after presenting with 17-OHP levels within reference values. After a mean follow-up of 3.4y, 33 remained asymptomatic and with increased 17-OHP, and were subjected to molecular analysis – 17 of them carried mutations: 7 in the heterozygous state, 9 non-classical genotypes and one a classical genotype. The authors conclude that their finding non-classical CAH (NCCAH) so frequently in children with persistently high 17-OHP supports molecular studies in these asymptomatic children, to confirm diagnosis. This is relevant to guide follow-up, allow genetic counseling and avoid over-treating NCCAH.

Evolution of circulating thyroid hormone levels in preterm infants during the first week of life: perinatal influences and impact on neurodevelopment. J Pediatr Endocrinol Metab. 2019 Jun 26;32(6):597-606. doi: 10.1515/jpem-2018-0537.

Transient hypothyroxinemia of prematurity (THOP) has been a topic of debate, with incomplete understanding of pathophysiology, and no consensus on therapeutic approach. This study aimed at gaining insight into the pathogenesis by studying the trends in thyroid hormone (TH) levels during the first week of life. This single-center prospective observational study analyzed the plasma levels of total thyroxine (T4) and free thyroxine (fT4), total triiodothyronine (T3), thyroid-stimulating hormone (TSH) and T4-binding globulin (TBG) in cord blood and at the end of the first week of life in 120 preterm infants (gestational age [GA] <37 weeks). The change over time was calculated (delta, Δ). The impact of perinatal and subsequently postnatal variables on Δ was studied by hierarchical multiple regression. The impact of Δ on the neurodevelopmental outcome at the corrected ages of 9 and 24 months, measured by the Bayley Scales of Infant Development (BSID)-II,

was assessed by logistic regression. ΔfT4 levels were negatively affected by GA and use of dopamine, whereas only GA was associated with low ΔT3 levels. Negative ΔfT4 levels were present in 75% of the extremely low-for-gestational-age infants, whereas 23.5% had a negative ΔT3 level. There was an increased risk for an abnormal mental developmental score (<85) with decreasing ΔT3 at 9 months corrected age, but not at 24 months. A negative evolution in circulating TH levels is principally an immaturity phenomenon, whereas dopamine can further suppress the hypothalamic-pituitary-thyroid axis. There is at least a temporary negative effect of this evolution on the infants' neurodevelopment.

Etiology of primary adrenal insufficiency in children: a 29-year single-center experience. J Pediatr Endocrinol Metab. 2019 Jun 26;32(6):615-622. doi: 10.1515/jpem-2018-0445.

Primary adrenal insufficiency (PAI) in children is a rare condition and potentially lethal. The clinical characteristics are non-specific. It may be manifested as a chronic condition or crisis. The etiologies of PAI in children are different from the adult population. Therefore, diagnostic investigation becomes challenging. A retrospective study was conducted at The First Affiliated Sun Yat Sen University Pediatric Endocrine unit between September 1989 and July 2016. A total of 434 patients (237 males) were identified as having PAI. Congenital adrenal hyperplasia (CAH) was the most frequent etiology (83.4%, n = 362, male: female = 174: 188), of which 351 (97.2%) had 21-hydroxylase deficiency. Non-CAH etiology accounted for 11.3% (n = 49, male:female = 47:2), of which 46 (93.9%) were non-autoimmune. The etiologies of the 49 cases were adrenoleukodystrophy (n = 22), X-linked adrenal hypoplasia congenital (n = 20), autoimmune polyglandular syndrome (n = 3), triple A syndrome (n = 2), steroidogenic factor 1 gene mutation (n = 1) and adrenalectomy (n = 1). No etiology was identified in 23 patients (5.3%, male: female =16:7). Clinical symptoms were in accordance with the cause: genital ambiguity (42.6%), vomiting and diarrhea (35.5%), failure to thrive (26.5%), premature puberty or sexual infantilism and amenorrhea (21.2%), hyperpigmentation (9.7%), adrenal crisis (4.1%), neurological symptoms (3.2%), fatigue (2.5%) and prolonged jaundice (2.1%). The etiology of PAI in children was mostly of congenital forms, with a wide spectrum of clinical characteristics. For etiological diagnosis, chromosomal karyotyping is recommended for patients with female phenotype.

Events/Activities organised by ISPAE members

GET TOGETHER OF CHILDREN WITH DIABETES AT GOVERNMENT MEDICAL COLLEGE, KOZHIKODE. Dr M Vijayakumar

A get together of children with diabetes was conducted on 16th June, 2019 at the Auditorium, Government Medical College, Kozhikode, Kerala, as a joint venture of Students' Union (Imprints), IAP Kozhikode, and ISPAE. The Hospital Superintendent, Dr Sreekumar, inaugurated the function. Glucometer strips supply for 2 months were distributed to 56 children. A refrigerator was donated to a poor girl who could not store her vials properly. Dr Ajith Kumar VT, Dr Mohandas Nair and Dr M Vijayakumar felicitated the function, and Dr Nihas Naha, IAP Secretary, gave the vote of thanks.

WORLD THYROID DAY CELEBRATION-DEPARTMENT OF PEDIATRICS AND IAP MEERUT BRANCH. Dr Vijay Jaiswal

World Thyroid Day was celebrated on 25th May Saturday by the Department of Pediatrics, LLRM Medical College, and IAP Meerut. About 30 resident doctors and pediatricians from the city attended the talk on '**Universal Congenital Hypothyroid Screening –onus on all'**. There was good discussion among the participants, who appreciated the meeting. It was emphasized that at LLRM Medical College all inborn babies are being provided thyroid screening, with administrative help. Media persons were also involved for dissemination of this important message to the community.

...तो थायरॉइड बिगाड़ देगा अक्ल और शक्ल

मेडिकल कॉलेज में फ्री में हो रही थायरॉइड स्क्रीनिंग, कराएं बच्चों की जांच, दिमाग से मंद हो सकता है बच्चा

वर्ल्ड थायरॉइड डे

जासं, मेरठ : थायरॉइड बीमारी अक्ल और शक्ल दोनों बिगाड़ सकती है। पश्चिमी उप्र में बड़ी संख्या में इसके मरीज हैं। मेडिकल कॉलेज के बाल रोग विभाग ने बच्चों में थायरॉइड जांच की नई मुहिम शुरू की है। अब तक करीब एक हजार बच्चों की स्क्रीनिंग की जा चुकी है। बाल रोग विभागाध्यक्ष डा. विजय जायसवाल का कहना है कि जन्म के दो से पांच दिन के अंदर ब्लड ग्रुप की तरह बच्चे की थायरॉइड जांच होनी चाहिए। 14 दिनों में दवा शुरू कर दी गई तो अपंगता का खतरा हमेशा के लिए खत्म हो जाता है। टीएसएच लेवल 20 से ज्यादा होने पर थायरॉइड की पूरी जांच होनी चाहिए। चिकित्सकों के मुताबिक रोजाना एक गोली थायराक्सिन खिलाने से बीमारी दूर हो जाती है।

महत्वपूर्ण बातें

- भारत में औसत 1000 में से एक बच्चे में बीमारी मिलती है।
- बच्चे का तीन साल तक ब्रेन का विकास होता है, ऐसे में जांच जरूरी।
- थायराक्सिन की गोली हार्मोंस की कमी को दूर करती है।
- मेरठ समेत पश्चिमी उप्र में सिर्फ दस फीसद लोग ही अपने बच्चों का टेस्ट कराते हैं

ये हैं लक्षण

- थायरॉइड की कमी से नई कोशिकाएं नहीं बनती तो बच्चा बूढ़ा लगने लगता है।
- देर से बोलना, देर से चलना व पेट फूलना खास लक्षण हैं।
- नसिका हार्निया, दांतों में टेढ़ापन व हड्डियों में विकार नजर आता है।
- थायरॉइड ब्रेन में न्यूरान्स बनने में मदद करते हैं, जो दिमाग को वयस्क नहीं होने देते।
- सिर बड़ा होने के साथ ही आंखें भी धंस जाती हैं।

मेडिकल कॉलेज सभी नवजात की थायरॉइड स्क्रीनिंग कर रहा है। अब तक करीब एक हजार बच्चों की जांच की जा चुकी है। सही समय पर जांच करते हुए तीन साल तक सटीक इलाज किया जाए तो बच्चा आजीवन विकलांगता के खतरे से मुक्त हो जाएगा। सभी मां-बाप अपने बच्चे की जन्म के पांच दिन के अंदर जांच कराएं, अन्यथा बाद में कुछ नहीं हो सकता।

डा. विजय जायसवाल, विभागाध्यक्ष, बाल रोग विभाग मेडिकल कॉलेज

3rd ANNUAL PEDIATRIC AND ADOLESCENT ENDOCRINOLOGY CONFERENCE BY THE GRS SOCIETY, DELHI. Dr IPS Kochar

The 3rd Annual Pediatric and Adolescent Endocrinology conference by the GRS Society, conducted in Indraprastha Apollo Hospital on 8-9th June under the guidance of Dr IPS Kochar, had prominent faculty from all over India and abroad. Day 1 focused on hands-on insulin pump station, clinical case scenarios, pediatric and neonatal endocrine emergencies. On Day 2, the latest on growth, diabetes, obesity, bones, adrenals and thyroid was covered. It was attended by over 100 delegates from all over India, and well received by faculty and delegates alike. With such positive support and feedback, the GRS society intends to incorporate the same in all future endeavours.

MEGA CAMP FOR TYPE 1 DIABETES MELLITUS CHILDREN- JUVENILE DIABETES FOUNDATION, RAJKOT. Dr Zalak Upadhyay

The Juvenile Diabetes Foundation, Rajkot (JDF) was started in February 2004, by Mr Apul Doshi, whose child has Type 1 Diabetes (T1D). Now more than 1200 patients with T1D are enrolled with this Foundation, which holds camps for children with T1D 3-4 times a year and a picnic once a year. The 59th mega camp was organised on 13-14th July 2019, in which children were provided free strips, free blood tests, eye check-up and endocrinology consultation. As Rajkot does not have a Pediatric Endocrinologist, Dr Upadhyay attended this for the first time. The approximately 600 children who attended the camp were examined and counselled. As education program followed by lunch was arranged for both days. Mr Jaydev Unadkat, our Indian cricketer, was invited to give them an inspirational talk and the kids were more than happy to listen to him. Overall, it was a good exposure to serve the needy, and the efforts put by JDF round the year for all the patients is praiseworthy.

PEDENDO UPDATE, VIJAYAWADA. Dr Sirisha Kusuma Boddu, Rainbow Hospital, Hyderabad; Dr Ramprasad P, IAP Krishna Distrauct, Andhra Pradesh

On 14th July, Rainbow Children's Hospital, Hyderabad, in association with Indian Academy of Pediatrics, Krishna District branch, Andhra Pradesh, organized a one day CME, "PEDENDO UPDATE" at Vijayawada, AP, with Dr Leenatha Jakkidi, Dr Leena Priyambada, Dr Kavitha Bhatt, Dr Kavitha Sakamuri, Dr Karthik Nalluri, and Dr Vijayasarathi as the faculty. The program was attended by about 70 practicing pediatricians and pediatric postgraduate students. Common endocrine conditions faced by pediatricians, including recommendations for nutritional rickets prevention, newer perspectives in Type 1 Diabetes management, approach to persistent hypoglycemia, how to plot growth charts and identify abnormalities, when to worry in case of early or late puberty, approach to ambiguous genitalia and congenital hypothyroidism screening and management were discussed. Interesting cases were presented between lectures, by postgraduate students. The entire session was very interactive, with productive discussions. Pfizer (Vaccine division) provided financial support, and Andhra Pradesh Medical Council awarded 2 CME credit hours for the delegates.

GROWTH UPDATE- GROWTH CHART APPLICATION PROMOTION & WORKSHOP-DILSUKHNAGAR PEDIATRIC FORUM. Dr Amarnath Kulkarni & Dr Sunkoj Bhaskar

A growth Update and Workshop was organised at Hotel Sitara, Grand LB Nagar, Hyderabad on 29th June 2019. The topics covered were diagnosis of all Endocrine & Growth disorders based on only growth charts, growth velocity and bone age; downloading of the IAP growth chart application by all pediatricians and pediatric post graduates, and learning how to make use of them; case conundrums - active discussion of various cases with short stature, obesity and puberty related problems; prevention of

exogenous obesity - a growth chart based approach. The total number of pediatricians who attended the event was 25. The event was sponsored by Novo Nordisk India Private Limited.

DIABETES UPDATE AND CAMP: RECENT ADVANCES IN TECHNOLOGY OF DIABETES - FOR SWEET KIDS - HYDERABAD. Dr Amarnath Kulkarni

A Diabetes Update and Camp was organised by Dr Amarnath Kulkarni from Department of Pediatric & Adolescent Endocrinology, Vivekananda Health Center, at Sri Ramakrishna Math, Domalguda, Hyderabad on 31-7-2019. The topics covered were ambulatory care of diabetes, various types of CGMS available for monitoring & their importance, types of bolus and basal settings in the insulin pump, troubleshooting in CGMS and insulin pump, role of spirituality in diabetes, monitoring and prevention of early and late complications in T1D. The event was attended by 20 T1D children and 25 family members. The speakers were Dr Silpa Nadella (Guest faculty from USA), Dr Amarnath Kulkarni, and Dr Kishore. It was organized in collaboration with CDiC (Changing Diabetes in Children).

TYPE 1 DIABETES SUPPORT GROUP - PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH, COIMBATORE. Dr Meena Kumari Mohan

A T1DM support group meeting was organised at PSG Institute, Coimbatore on 19th May 2019. The support group focused on two issues - 1. Dealing with adolescents for parents and dealing with parents for adolescents, from a diabetes point of view. 2. Insulin pump – discussing how to make the pump work better for you. This discussion was amongst young people already on the pump and those who wanted to know more about the pump and waiting to have a pump trial. Both sessions were well received, with both parents and teenagers feeling more relaxed and confident in dealing with day to day issues in a better way. In total, 55

members attended, and were hugely benefited. Diabetes educators from the hospital and educators from the pharmaceutical company facilitated the occasion.

TYPE 1 DIABETES MANAGEMENT SESSION-CUM-WORKSHOP - PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH, COIMBATORE. Dr Meena Kumari Mohan

An educational session was conducted for post graduates and faculty of the pediatric department, PSG Institute of Medical Sciences and Research, Coimbatore on 27th May 2019. A theory session followed by a workshop was conducted. About 30 members attended the meeting and it was well received. Insulin pen devices, various blood glucometers, carb counting booklets, blood monitoring booklets, sharps disposal boxes, etc were demonstrated during the workshop sessions. Diabetes educators helped to conduct the workshops.

4th PEDIATRIC ENDOCRINOLOGY CONCLAVE 2019 - T2T HORMONE CLINICS INDIA. Dr Abhishek Kulkarni

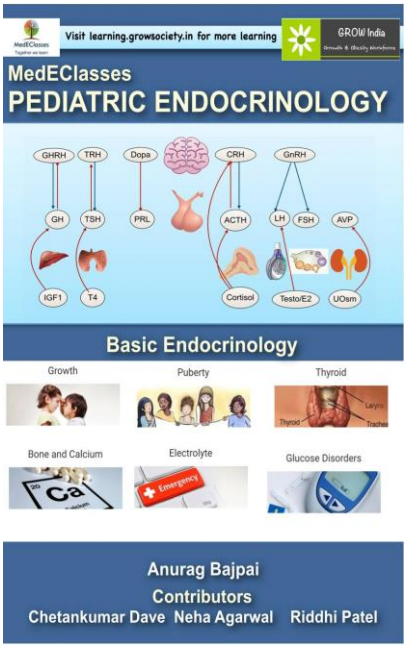
The 4th Pediatric Endocrinology Conclave, a day long pediatric endocrinology symposia with 7 guest lectures and 5 panel discussions on contemporary diagnostic and management protocols of common pediatric endocrine disorders, was held on Sunday, 16th June 2019 at Hotel Courtyard by Marriott, Mumbai. The event was attended by 300 registered delegates from various parts of the country. The faculty consisted of 12 eminent pediatric endocrinologists from India and one from UK. The event was supported by multiple academic partners. The Module for Screening and Management of Congenital Hypothyroidism under the action plan of the Indian Academy of Pediatrics was unveiled in the presence of the National President, Secretary and National Scientific Convener during this meeting.

II ADVANCED PEDIATRIC ENDOCRINOLOGY COURSE, KANPUR. Dr Anurag Bajpai

The II Advanced Pediatric Endocrinology Course (APES) was organized under the auspices of the GROW Society, MedEClasses, and Regency Center for Diabetes, Endocrinology & Research, on 18th – 19th May 2019. The course covered key areas of Pediatric Endocrinology using interactive case based modules by eminent faculty from across the country, including Drs Shaila Bhattacharya, Subrata Dey, Sangeeta Yadav, Rishi Shukla, Ahila Ayyavoo, Sudha Rao, Hemchand Prasad, Abhishek Kulkarni, Santosh Olety, Saurabh Uppal, Amarnath Kulkarni and Kumar Angadi. Key initiatives included Launch of MedEClasses Textbook of Endocrinology, MedEClasses Master Online Pediatric Endocrinology Course and Pediatric Endocrinology Primer for Pediatricians.

MEDECLASSES MASTER COURSE IN PEDIATRIC ENDOCRINOLOGY. Dr Anurag Bajapi

MedEClasses Master Course in Pediatric Endocrinology was launched during the II APES. The 18 month course encompasses 85 modules over 14 sections, covering all aspects of Pediatric Endocrinology, including growth, puberty, thyroid, calcium, glucose, electrolyte, adrenal, pituitary, bone, adolescent gynecology, MEN, APS, endocrine physiology and endocrine assessment using animated videos, extensive text, management algorithms, pre and post tests and real life case scenarios. The approximate time commitment is 400 hours (around 1 hour per day). The course is ideal for pediatric and adult endocrinology trainees, practicing pediatric and adult endocrinologists, and pediatricians with special interest in endocrinology. The course can be accessed at https://learning.growsociety.in.



MedEClasses Textbook of Pediatric Endocrinology, launched during the II APES, covers 42 modules across fundamentals of pediatric endocrinology, growth, thyroid, calcium, electrolyte, glucose, and puberty, using animated

diagrams and algorithms. Each chapter includes patho-physiology, algorithmic etiology, pointers, criteria, assessment, approach, management, case vignettes and learning points. The book provides over 200 animated images, 60 algorithms and 100 real life case scenarios to make Pediatric Endocrinology learning easy and is recommended for Pediatricians, Pediatric Trainees, Pediatric Endocrinologists and Endocrinologists. Print version of the book is available at https://learning.growsociety.in/books/ while the Kindle version can be accessed at amazon.in.

WORLD THYROID DAY CELEBRATION 2019 - SAMRAT ENDOCRINE INSTITUTE OF THYROID, DIABETES & OBESITY, and WOMEN'S DOCTOR WING OF IMA, AURANGABAD. Dr Priti Phatale

On the occasion of World Thyroid Day, Samarth Endocrine Institute conducted a program. The objective of this meeting was to create awareness regarding rising prevalence of thyroid disorders in all age groups - from intrauterine period to geriatric age. The topics included screening for Congenital Hypothyroidism, Thyroid disorder is not the only reason for obesity; Inverse relationship of TSH with intellectual development in babies, Uncontrolled hypothyroidism leads to physical, intellectual, emotional and mental disturbances, Myths and facts about dietary restrictions with thyroid disorders. The meeting was attended by more than 100 delegates.

Publications by ISPAE members

Anju Virmani

Virmani A. Throwing the Baby out with the Bath Water: The Need for Reviewing Ethics Requirements. Indian Pediatr. 2019;56:515.

Shreya Sharma

Sharma S, Chandrashekhar SR. Refractory hypoglycemia in an infant with isolated severe primary hypothyroidism. Hormones (Athens). 2019 Jul 22.

Rakesh Kumar

1. Ayers K, Kumar R, Robevska G, et al. Familial bilateral cryptorchidism is caused by recessive variants in RXFP2. Journal of Medical Genetics. Published Online First: 05 June 2019. doi: 10.1136/jmedgenet-2019-106203
2. Kumar R, Patodia J, Malhi P, Dayal D. Quality of Life for Indian Diabetic Children. J Postgrad Med Edu Res 2019; 53(2):61-68.
3. Kumar R, Raviteja KV, Sachdeva N, Dayal D. Feasibility and Acceptability of Professional Continuous Glucose Monitoring System in Children with Type 1 Diabetes Mellitus: an observational study. J Diabetol 2019;10:15-20.

Awards and Fellowships

Dr Varuna Vyas, Assistant Professor in the Department of Pediatrics, AIIMS Jodhpur, was selected by the **Pediatric Endocrine Society (USA) for the International Scholars Program**. The award consisted of a scholarship amount of 8000 USD and an opportunity to visit a Pediatric Endocrinology center in North America for a period of 3 months. As part of the program she visited CS Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan, under the mentorship of Prof. Ram Kumar Menon. She also attended the Pediatric Endocrine Society - Pediatric Academic Societies joint Annual Meeting held from April 24 to May 1, 2019 at Baltimore.

Answer to Photo Quiz 1

CLEIDOCRANIAL DYSPLASIA

Cleidocranial dysplasia is also known as dento-osseous dysplasia or Marie-Sainton syndrome. It is a rare autosomal dominant disorder caused by mutations in the *RUNX2* gene located on chromosome 6p21, which is involved in the development and maintainence of bone, cartilage and teeth. One of the parents may be mildly affected in the form of hypolplastic or absent lateral end of the clavicles, necessitating radiological examination of both parents. Clinically, it is characterized by delayed closure of the anterior fontanelle (AF) (sometimes it never closes), brachycephaly, hypertelorism and depressed nasal bridge. Due to absence of clavicles, narrow sloping shoulders are observed, with the ability to voluntarily bring them together. Limb involvement can occur in the form of brachydactyly, broad thumb, clinodactyly and coxa vara. Dental changes such as retention of deciduous dentition with delayed eruption of permanent teeth, peg like teeth, supernumerary teeth and malocclusion can be seen. Radiological features include open sutures, multiple wormian bones as well as hypoplastic facial, scapulae and pelvic bones.

The characteristic findings such as open AF, absent clavicles, short stature and teeth abnormalities led to the clinical diagnosis of cleidocranial dysplasia in our patient.

Long term prognosis is good except for short final height, progressive kyphosis and scoliosis leading to spinal cord problems, and rarely irritation of brachial plexus due to compression by clavicular fragments.

The differential diagnoses of cleidocranial dysplasia are as follows:

Condition	Similarities	Differences
Pyknodysostosis	Wide open AF, dysplasia of the acromial ends of clavicles	Wrinkled skin appearance over dorsae of fingers and grooved nails, acro-osteolysis and bone sclerosis on radiology
Hajdu-Cheney syndrome	Absent or hypoplastic clavicles	Coarse facies, thickened skull vault, acro-osteolysis and narrow intervertebral spaces
Kenny-Caffey syndrome	Wide open AF	Primary hypoparathyroidism, thick cortices of long bones
Congenital clavicle pseudoarthrosis	Absent clavicle	Absent clavicle is almost always on right side; only 10% are bilateral, dextrocardia

Answer to Photo Quiz 2

LARON SYNDROME

In view of severe growth failure, open anterior fontanelle, midfacial hypoplasia, frontal bossing, shallow orbits, high pitched voice and truncal obesity in our child, Laron syndrome was suspected.

Laron syndrome is characterized by growth hormone (GH) resistance which occurs due to defects in the GH receptor or post-receptor pathways. Unlike with GH deficiency, many patients are short at birth and continue to grow at a lower velocity throughout childhood. They have small hands and feet (acromicria), as well as small internal organs (organomicria), giving the illusion of macro-cephaly. Facial features include a protruding forehead, saddle nose, and midfacial hypoplasia. Thin and sparse hair, slow nail growth, delayed dentition with overcrowding due to a small mandible may be observed. The voice is typically high-pitched due to a narrow oropharynx. These patients are predisposed to hypoglycemic events throughout their life span. Although onset of puberty may be delayed (more often in boys than girls), their reproductive functions remain normal.

Elevated basal GH, and undetectable or very low IGF-1 establish the diagnosis of Laron syndrome. IGF-1 levels do not increase even after exogenous GH administration. Our child had a significantly delayed bone age of 1y6mo. Her basal GH level was very high (40 ng/ml) and basal IGF-1 was low (34.4 ng/dl), thus confirming the diagnosis.

The only treatment is subcutaneous administration of IGF-1 in a dose of 80-120 µg/ kg/ day. Prolonged treatment improves linear growth and body proportions, including growth of hands, feet, chin, and nose, and also normalizes the onset of puberty.

Supplement to CAPE News April 2019

Dr Ashok Venkatanarasu, Secunderabad, Telangana, received the **"RSSDI/ USV Excellence in Diabetes Care Award - 2018"** at RSSDI-2018, Ahmedabad.
He also received the "**Best Doctor - 2019 Award"** from the SAT Foundation on 10th February, 2019, Hyderabad.
Congratulations!

ISPAE 2019: 6th Biennial Meeting of the Indian Society for Pediatric & Adolescent Endocrinology: 29th, 30th November & 1st December, 2019
ISPAE PET School: 26-28 November, 2019
KOLKATA

Dear ISPAE Members,

The Organizing Chairperson and the ISPAE 2019 Committee are excited to welcome you to the 6th Biennial Conference of ISPAE to be held from 29th November to 1st December 2019, in ITC Sonar Kolkata, in the historic City of Joy, Kolkata, in collaboration with the West Bengal Academy of Pediatrics. A galaxy of international speakers of immense stature have confirmed participation in this event. We are finalizing the National speakers. Prior registration is mandatory for Faculty considerations. There will be 6 Meet The Professor sessions, and several symposiums (pediatric endocrine research, growth hormone therapy, insulin pumps, and many more). Get updated about pediatric endocrine research in India.
There have been many registrations thus far, but many more ISPAE members have not yet registered. We exhort all ISPAE members to demonstrate allegiance to the Society and register. We need to disseminate the gospel of Pediatric Endocrinology. We are empowered by our
Advisors - Dr Raghupathy, Dr PSN Menon and Dr Nalini Shah
Chair, Scientific Committee - Dr Vaman Khadilkar
Convener PET School - Dr Sudha Rao
Abstracts Coordinator - Dr Anurag Bajpai
Organizing Secretary - Dr Abhishek Kulkarni

Abstract submission is open. The last date of submission is 17 Sept 2019.

visit **www.ispae2019.com**
for online registration and abstract submission

Preceding the main meeting is the PET School, the Gurukul, will be based at Vedic Village, an idyllic resort to promote learning. There will be more than 12 faculty for intensive training of the 36 candidates selected.

My very best regards,
Subrata Dey
Organizing Chairperson, ISPAE 2019

Other upcoming Endocrine Conferences

1. ESPE, 19-21 September, 2019, Vienna.
2. ISPAD, 30 October - 2 November,2019 Boston.
3. RSSDI, 7-10 November, 2019, Jaipur.
4. ESICON, 21-24 November, 2019 Nagpur.
5. PEDICON, 6-9 February, 2020, Indore.