CAPE NEWS

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Contents

From the Editor's Desk

Dear members,

We are all keenly looking forward to our Biennial Meeting, ISPAE 2017, in Coimbatore, in November. Dr Raghupathy and Dr Ahila have put together an exciting program (details on 38-39 of this newsletter). I am sure you would have registered for it by now. If not, please click on this link to register.

This new issue of CAPENEWS brings you three interesting mini-reviews on various aspects of endocrine disorders in children. In the first mini-review Dr Ashok has briefly discussed the effects of exposure to endocrine disrupting chemicals in early life. In the second mini-review, I have discussed a new rule I have proposed recently to describe the characteristics of pheochromocytoma/paraganglioma in children. In the second mini-review I have discussed the expanding spectrum of genetics of familial hyperaldosteronism.

The issue also includes a few interesting case reports - of a child with VDDR type 1 with rare presentation, G6PD deficiency in a diabetic child, and two children with septo-optic dysplasia.

I am sure all those interested in pediatric endocrinology will find this issue useful. I thank all my team members, Dr Sachin Mittal, Dr Sweta Budyal, Dr Tushar Godbole and Dr Vani HN for their active participation in designing this issue and for their valuable contributions. My special thanks to Dr Anju Virmani, for her whole hearted efforts to make this issue a fantastic one.

Dr Vijaya Sarathi, Editor, CAPENEWS

ISPAE Biennial Meeting 2017: Coimbatore, Tamil Nadu, Nov- Dec 2017

Organizing Chairperson: Dr P Raghupathy, drp.raghupathy@gmail.com
Organizing Secretary: Dr Ahila Ayyavoo, ahila.ayyavoo@gmail.com

We proudly announce the 44th Annual ISPAD meeting, ISPAD 2018, will be held in Hyderabad, India, from Thursday 11th to Sunday 14th October 2018, in association with ISPAE. This will also be the ISPAE midterm meeting. Please see page no 40.
This is therefore the best time to become an **ISPAD member.** Membership runs from 1st July to 30th June, and the discounted 3 year membership for us in India (LMIC) is just $ 240, i.e. just $ 80/year. Membership allows discounted rates for attending the **43rd Annual ISPAD Conference, ISPAD 2017** in Innsbruck, Austria (18-21 October), and of course **ISPAD 2018.** Just click on ispad.org. In case of problems, please contact Dr Anju Virmani, virmani.anju@gmail.com

ESICON 2017, Thiruvananthapuram, Kerala on 13-15th October 2017. For Registration Form: http://www.esicon2017.com/wp-content/uploads/2017/01/Esicon2017_form.pdf
For Online Registration: http://www.esicon2017.com/online/
For More Details Log On: http://www.esicon2017.com/

Hearty Welcome to New ISPAE Members	
Akansha Parikh (Bengaluru)	Nithya T (Thrissur)
Aiswarya Yalamanchi (Bengaluru)	Poorvi Agrawal (Mumbai)
Alpesh Goyal (Delhi)	Rajkumar Goyal (Jaipur)
Amit Satapathy (Bhuvaneshwar)	Rakhi Malhotra (Delhi)
Chetankumar Dave (Kanpur)	Rini Shah (Mumbai)
Darshana Thakur (Thane)	Sadishkumar Kamalanathan (Pondicherry)
Deepak Chand Gupta (Meerut)	Sai Krishna Chaitanya P (Tirupathy)
Gayatri Ghanekar (Mumbai)	Saqib Khan (Meerut)
Kishore Baske (Bengaluru)	Varuna Vyas (Jodhpur)
Neha Agarwal (Kanpur)	Yeshiwas Sewagegn (Egypt)
Nikhil Lohiya (Pune)	

Effects of Exposure to Endocrine Disrupting Chemicals in Early Life

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Introduction:

There is growing evidence and interest in the threat posed by Endocrine Disrupting Chemicals (EDC) to the health of the general population. These EDC are naturally occurring or synthetic products in the environment that are associated with endocrine disorders. Just as exposure in fetal life to stressors such as maternal smoking, alcohol, diabetes mellitus, etc., can produce adverse lifelong consequences postnatally in the offspring, similarly, early exposure (neonatal period, infancy) to EDC can cause health problems in individuals.

WHAT ARE EDC?

The United State Environmental Protection Agency defined an EDC as “an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes.” How do they act? Initially it was proposed that these EDC can act through nuclear steroid receptors, but further research revealed that they can act even through non-nuclear receptors (membrane estrogen receptors), nonsteroid receptors (e.g. neurotransmitter receptors such as the norepinephrine receptor, dopamine receptor and serotonin receptor), and orphan receptors [e.g. aryl hydrocarbon receptor (AhR)].

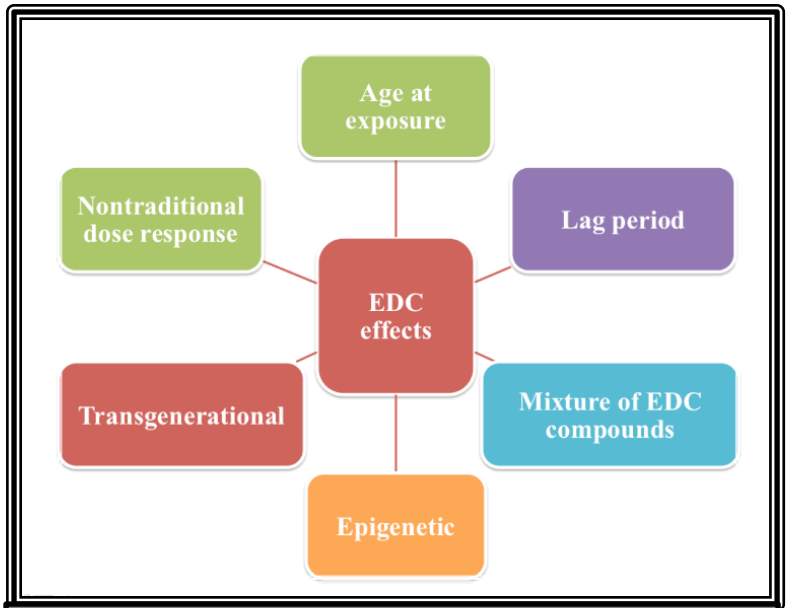

Figure 1: Important aspects of EDC effects

There are several important aspects of EDC effects, as shown in figure 1, a critical one being age at exposure. Exposure to EDC in fetal life leads to development of adult disease. Most EDC produce clinical effects after a latent period. Several mixtures of EDC may show more adverse manifestations due to their additive or synergistic effects. Some effects of EDC are non-genomic i.e. epigenetic origin due to DNA methylation and histone acetylation, and can, therefore, be transmitted via the germline from the exposed individual to the offspring, and even subsequent generations. These EDC may follow non-traditional dose responses, for example, significant clinical effects due to a small dose, or a U curve or inverted U curve response.

EDC are either synthetic or natural compounds and are highly heterogeneous. They include plastics [bisphenol A (BPA)], plasticizers (phthalates), synthetic industrial solvents/ lubricants and their by-products (polybrominated biphenyls (PBBs), polychlorinated biphenyls (PCBs), dioxins), fungicides (vinclozolin), pesticides [methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethane (DDD)], and pharmaceutical agents [diethylstilbestrol (DES)]. Few naturally occurring chemicals (e.g. phytoestrogens, including genistein and coumestrol) are also well known as EDC.

EFFECTS OF EXPOSURE TO ENDOCRINE DISRUPTORS IN EARLY LIFE

Exposure to EDC in early life (fetal life, infancy and childhood) may severely affect the neuroendocrine system, which in turn may affect growth, development, metabolism, appetite, adipogenesis and glucose homeostasis. It may also lead to future development of obesity, cardiometabolic dysfunction and dyslipidemia. Early exposure of EDC also has an effect on neuronal development, which can lead to development of autism, impaired memory, impulsive behaviour and attention deficit hyperactive disorders (ADHD).

Toxicokinetics may be different in early life: the lower levels of Cytochrome P450 enzymes may result in decreased degradation of toxic compounds, thereby increasing circulating and tissue concentration of EDC when compared to adults, for a given dose. In addition, EDC may synergistically or additively affect early neurodevelopmental processes, with more secondary consequences compared to adults, who have already completed their developmental process.

Exposure to EDC might also push the fetus or infant towards a ‘thrifty phenotype’, which efficiently stores excess calories in the postnatal period even with abundant calories and reduced physical activity. This phenotype would put individuals at risk of developing insulin

resistance and cardiometabolic disorders. The concept that many diseases in adults have origin in fetal life, called the 'developmental origins of health and disease' (DOHaD), tells us that early life exposures to environmental chemicals or poor nutrition can alter developmental processes in ways that lead to disease and/ or altered function in later life. Organisms are particularly susceptible to environmental chemicals in early life because of poor development /functioning of protective mechanisms.

EFFECTS OF EDC EXPOSURE IN EARLY LIFE

Cigarette smoke: There is evidence to suggest that maternal smoking is associated with increased risk of low birth weight (LBW), and later obesity or overweight, in the offspring.

Polycyclic aromatic hydrocarbons (PAHs): These chemicals usually occur in coal, oil, and tar products, and also as by-products from fuel burning. Animal and human studies revealed that exposure to PAH in pregnancy results in LBW, and later obesity.

Bisphenol A: It is a widely used chemical in the plastic industry, used in food containers, baby bottles, and reusable water bottles. Bisphenol A (BPA) binds to estrogen receptors to activate both nuclear and non-nuclear components. Some human cross-sectional studies showed that early life exposure is associated with increased weight in later life, but these observations do not address the temporality and causality of the obesity in exposed individuals. In animal studies it was found that exposure to BPA leads to altered proliferation of neuronal progenitor cells and neurogenesis, and also affects the hypothalamic circuits, which leads to hyperphagia, and subsequent weight gain. It was also shown to bind to the thyroid hormone receptor and antagonize its activation.

Tributyltin: It is used as a fungicide and also as a heat stabilizer in polyvinyl chloride. This is also an obesogenic agent. It causes activation of peroxisome proliferator-activated receptor γ (PPAR-γ), which results in increased fat cell differentiation (figure 2). Mice studies revealed that exposure to these compounds during pregnancy resulted in future development of obesity, which is also transmissible to future generations.

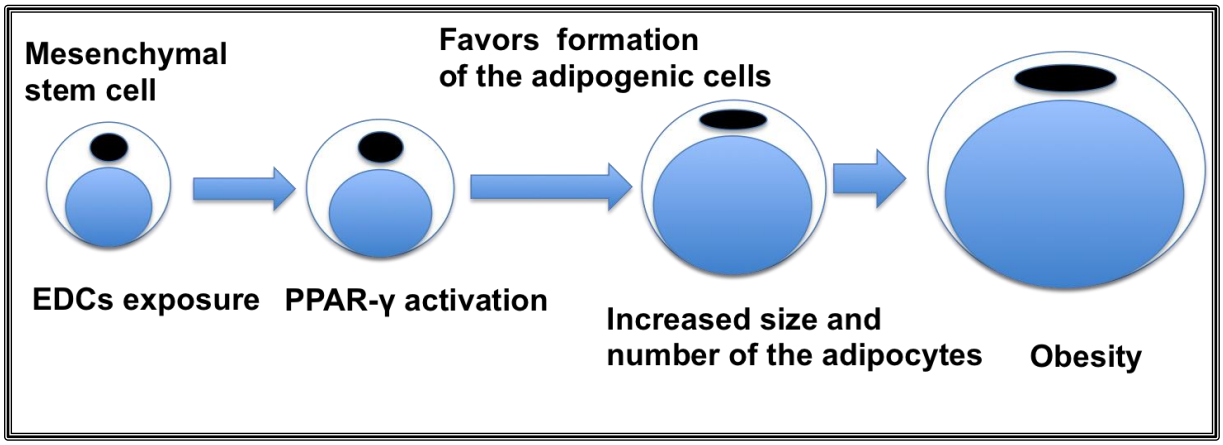

Figure 2: Mechanisms by which EDCs cause obesity

Polybrominated biphenyls and polybrominated diphenyl ethers: These chemicals are used as flame retards in a variety of materials such as electronics, construction materials, furniture etc. Basically they activate PPAR-γ, which results in adipogenesis. Prenatal and/ or childhood exposure leads to LBW, and altered thyroid function, by displacing T4 from the serum thyroid binding protein transthyretin, and by binding to the thyroid hormone

receptor. These compounds have also been linked to occurrence of early puberty, glucose intolerance and cardiac disorders.

Phthalates: These are derivatives of phthalic acid, used as flexibility imparting agents in the production of plastics, and as carriers in the cosmetic industry. These compounds also activate PPAR-γ. Prenatal and neonatal exposure to diethylhexylphthalate in pregnant mice lead to increased weight gain in the offspring. Degradation of phthalates by gram-negative bacteria results in the formation of dihydroxybenzoic acid (DHBA), known to possess anti-thyroid properties.

Polychlorinated biphenyls (PCB) and Polybrominated biphenyls (PBB): These are major components of organic pollutants, widely used in electric transformers, capacitors, and heat transformers**.** Exposure to these chemicals is ubiquitous, due to improper disposal and bioaccumulation. The NHANES 1999–2002 data reported that there is an association between obesity and detectable levels of persistent organic pollutants. Several other studies have also reported that early life exposure to these compounds may be responsible for childhood obesity.

Perfluorinated chemicals: Perfluorooctanoic acid and perfluorooctane sulphonate repel grease and oil, and are components of lubricants, nonstick coatings and stain-resistant compounds. These compounds are known to activate PPAR-γ, thereby increasing adipocyte differentiation and development of obesity, though human studies regarding the impact of prenatal exposure are not conclusive. These compounds may also affect neuronal development with early life exposure.

DDT: This is highly lipophilic and can accumulate in the food chain and in adipose tissue, with several adverse consequences. Animal studies have shown that early life exposure to DDT may cause nipple retention, hypospadias, cryptorchidism, small penis size, reduced weight of accessory sex organs, increased apoptosis of germ cells in testes, and reduced anogenital distance. Environmentally relevant doses of DDT cause reduced energy expenditure and impaired thermogenesis. DDT may act as an obesogenic/ diabetogenic agent in exposed individuals. DDT and its metabolites have been associated with testicular, endometrial and pancreatic cancers.

Fungicides: Fungicides like vinclozolin, procymidone and prochloraz showed several adverse effects in animals exposed in early life. Prenatal exposure to vinclozolin in rodents has also been shown to cause germ cell death and diseases of the prostate. In females, vinclozolin exposure caused more ovarian cysts and a reduced number of oocytes and primary follicles. Some of the effects of vinclozolin may be transgenerational, causing hypospadias, undescended testes, delayed puberty and prostate disease among subsequent generations.

Pesticides: Exposure to these chemicals is becoming more common due to increased usage in agriculture. Organochloride pesticide usage is associated with increased prevalence of type 2 diabetes, shown in both animal and human studies.

Diethylstilbestrol (DES): Exposure of pregnant women to DES in resulted in a 40-fold rise in the occurrence of vaginal adenocarcinoma in female off-springs and increased the risk of cryptorchidism, micropenis and epididymal cysts in male off-springs. Various effects of EDC exposure during early life are summarised in figure 3.

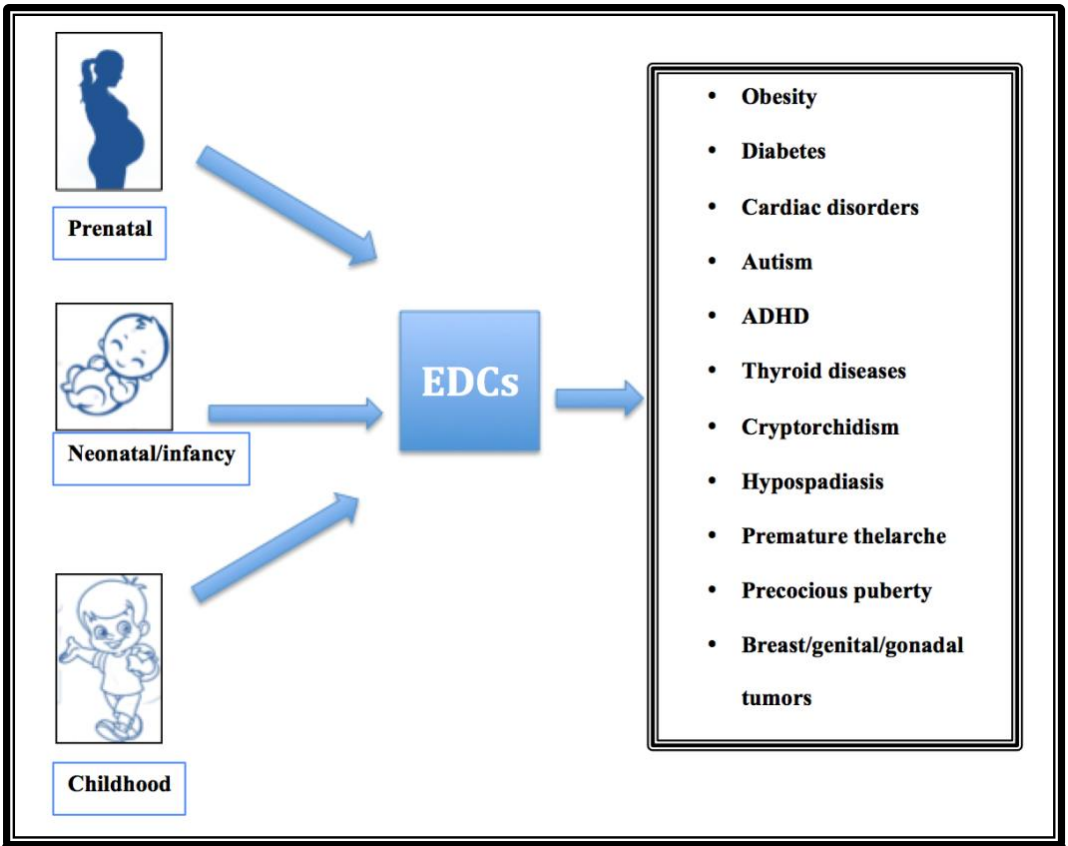

Figure 3: Effects of EDC exposure in early life

It is difficult to get incriminating evidence against EDCs because of slow accumulation and universal presence of EDCs, long time-gap between exposure to EDC and outcome and presence of other confounding factors.

Most of the animal studies are observational. In future, large multicenter, randomized and case control prospective studies may give a better idea about causality in disease occurrence.

In summary, available data suggests that the possibility of a health threat by EDCs. In exposed individuals, they may affect neurodevelopment, be responsible for future development of obesity and diabetes, and affect other hormonal functions, resulting in altered thyroid or gonadal function, and growth disorders. However, with most EDCs, good evidence data base for adverse consequences of early life exposure is still lacking in humans.

For further reading…

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The 10-90% rule: a new Rule to describe Characteristics of Pediatric Pheochromocytoma/ Paraganglioma

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Introduction

The "rule of 10" used to describe pheochromocytoma/paragangliomas (PCC/PGLs) is a good example of axioms that medical students often learn to remember the key characteristics of a disorder. The rule of 10 used to describe PCC/PGLs is as follows: 10% are extra-adrenal, and of those, 10% are extra-abdominal; 10% are malignant; 10% are found in children; 10% of patients are normotensive; and 10% are hereditary [1]. However, at the beginning of the 21st century, the 10% rule was dashed by a study from Neumann *et al*., which reported germline mutation in 24% of apparently sporadic PCC/PGL patients [2]. This study heralded the death of an axiom, as it was aptly called [1]. Data on characteristics, especially of germline mutations in patients with pediatric PCC/PGL were greatly limited till 2013 [3-5]. Thereafter, few studies have reported genotype and phenotype characteristics of PCC/PGL in pediatric cohorts. From these, it was appreciated that characteristics of pediatric PCC/PGL follow a pattern [3-5]. Hence, we have reviewed the available literature to verify this, the bulk of the data being derived from four studies with a sample size of more than 35. These are the pediatric PCC/PGL cohorts from the National Institute of Health, USA, European-American Pheochormocytoma Paraganglioma Registry (EAPPR), Spain and Russia [3-6]. We have compared the data from the current review with that of two previous reviews by Stackpole et al and Ross et al [7,8].

Proportion of children in pheochromocytoma/paragangliomas cohorts: According to the "10% rule," 10% of PC/PGL occur in children. In the current review pediatric PCC/PGL cases accounted 8.86% of the total PCC/PGL cohort, suggesting that this component of "10% rule" remains unchanged.

Age at diagnosis: In the review by Stackpole *et al*.,[7] in which children up to 15 years were included, the mean age of the pediatric PCC/PGL patients was 10.18 years. Referring to this review, the average age of PCC/PGL in children has been classically described as 11 years [8]. However, in the recent larger pediatric cohorts, which included children up to 17–18 years, the mean or median age is between 12 and 14 years, suggesting the average age of children with PCC/PGL is 13 years.

Proportion of boys: Classically, it has been described that ratio of boys to girls in pediatric PCC/PGL cohorts is 2:1 [8], mainly derived from the review by Stackpole *et al*. where children younger than 15 years were included [7]. The overall proportion of boys in the recently published cohorts (children up to 18 years included) is 61.94% [3-5].

Hypertension: According to the 10% rule, 10% of PCC/PGL patients are normotensive. In older studies, 95-100% of pediatric PPGL patients had hypertension. However, cohorts characterized by greater proportion of extra-adrenal PGL, such as Pham *et al*. (64%) and Babic *et al*. (37%), have reported hypertension in a smaller number of patients [3,9]. In the latter study, a larger proportion of patients identified during family screening (40%) might have also contributed for the lower prevalence of hypertension. With increasing availability

of routine genetic testing and family screening, it is likely that a greater proportion of PCC/PGL children will be identified before their symptomatic presentation.

It was classically described that the prevalence of sustained hypertension is more common in children (80 – 90%) than adults (50%) [7]. In the review by Stackpole *et al.*, sustained hypertension was reported in 88% of cases [6]. However, the lower prevalence (31 – 64%) of hypertension in the recent studies [3,8] suggests that it is not as high as previously thought, and approximately only 70% of pediatric PCC/PGL may have sustained hypertension.

Secretory status: The secretory status can reliably be obtained from only one study [EAPPR] in which catecholamine excess status was reported in 89% of patients [4]. However, in a few other studies, prevalence of secretory tumours is lower [3]. The proportion of secretory PCC/PGL depends on the proportion of head and neck paragangliomas (HNPGL) in the cohort, since they are most likely to be non-secretory; and the biochemical tests used for evaluating secretory status [3,4].

Bilateral pheochromocytoma: Simultaneous diagnosis of PCC in both the adrenal glands is called *synchronous bilateral PCC*, whereas the subsequent occurrence of PCC in the contralateral adrenal gland after excision of the initial unilateral PCC is called *metachronous bilateral PCC*. The prevalence of bilateral PCC at initial presentation is 20.75% and overall 33% [3-5]. The classic description of 20% patients with PCC/PGL 20% being bilateral, also reported by Stackpole *et al* [7], represents synchronous bilateral PCC. The overall prevalence of bilateral PCC is as high as 33%. In patients with tumors confined to the adrenals, proportion of bilateral PCC was 41.15% in pediatric cohorts. Hence, it can be remembered that 40% of adrenal-confined PCC will be bilateral in children.

Extra-adrenal paraganglioma: The prevalence of extra-adrenal PGL varied from 18 to 61.1%, and overall the prevalence of extra-adrenal PCC/PGL cohorts is 32.07% [3-9]. It is estimated from published pediatric PPGL cohorts that around 70% extra-adrenal tumors are confined to the abdomen, while the 30% extra-abdominal ones are located in the thorax or head and neck region.

Nonmetastatic recurrence (occurrence of a second paraganglioma): An important issue in children with PCC/PGL is the high rate of recurrence. In the EAPPR, overall non-metastatic recurrence rate during follow-up was about 25% at 10 years, 40% at 20 years, 50% by 30 years, reaching 80% for those with the longest follow-up [4]. During a median follow-up of 16 years, occurrence of a second PCC/PGL was 16%, 13%, and 18% in the ipsilateral adrenal gland, contralateral adrenal gland, and extra-adrenal ganglia, respectively. In the Spanish study, the recurrence risk was 22.22% (8/36) at 10 years; in the US study, the recurrence rate was about 40% (22/55) over 16 years with 27.27% (6/22) of them being ipsilateral, arising from sites of partial adrenalectomy [3,5].

Malignancy: The prevalence of malignancy varied from 9% to 16% in pediatric PCC/PGL cohorts [3-6], with overall rate of 11.5%. The statement that the pediatric prevalence of malignancy is less (3.5%) than in adults [8] is derived from studies with no or minimal follow-up. Recent data suggests that childhood PCC/PGL have similar malignant potential

as adults, and should be as closely followed-up and monitored for metastasis during follow-up as adults. Malignancy is the only component of the 10% rule which remains unchanged.

Familial/syndromic: The prevalence of familial disease varied from 30.5% to 40.7%, with overall prevalence of 39.2% [3-5], suggesting that 60% of pediatric PCC/PGL present as apparently sporadic. The EAPPR study reported extra-paraganglial tumors in 43% patients, with the highest prevalence among children with *VHL* mutations (65%) and *NF-1 (*100%).

Hereditary (germline mutations): It was previously believed that only 10% PCC/PGL are hereditary [1], but recent studies have demonstrated germline mutations in up to 40% patients [10]. In the rest, with no identifiable germline mutations, one-third have a somatic mutation in PCC/PGL associated genes [10]. The prevalence of germline mutations in pediatric PCC/PGL cohorts is even higher, varying from 69% to 81%; overall 79.4% [3-5]. Mutations in *VHL* were the most common: seen in 45.5% of pediatric patients; *SDHB* and *SDHD* mutations were the second (18.28%) and third (9.32%) most common. Mutations in other genes were significantly rarer. Altogether these mutations were observed in about 7% patients [3-5].
Even in children with apparently sporadic PCC/PGL, the prevalence of germline mutations is high (60-70%) [2-5,11]. The prevalence of germline mutations in solitary non-metastatic PCC with no family history is also high (50-60%) [3,11]. In addition, up to 60% of the mutation negative children may also have somatic mutations, increasing the presence of genetic drivers to around 75% of children with solitary PCC/PGL [11]. With rapidly evolving advances in the genetic understating of PCC/PGL, we are not too far from identifying the genetic drivers (germline and/or somatic) in 100% of pediatric PCC/PGL patients.

To summarize, pediatric PCC/PGLs appear to follow a pattern, which we call “10%–90% rule”, as mentioned below:

- **10%: Malignant**
- **20%: Synchronous bilateral**
- **30%: Extra-adrenal**
- **40%: Familial**
- **50%: Recur (second PCC/PGL) by 30 years**
- **60%: Boys**
- **70%: Sustained hypertension**
- **80%: Germline mutations**
- **90%: Secretory**
- **100%: Germline + somatic?!**

This new rule will help to understand and easily remember the characteristics of pediatric PCC/PGLs. However, this does need evaluation in larger cohorts from different parts of the world.

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Expanding genetic spectrum of familial hyperaldosteronism

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Introduction

Primary aldosteronism (PA) is a rare cause of hypertension in children; it should be suspected in children with resistant hypertension, spontaneous or diuretic induced hypokalemia, and/or family history of hypertension. Hypokalemia is not sine qua non feature of PA.

Familial hyperaldosteronism (FH), inherited by autosomal dominant pattern with variable penetrance, accounts for the majority of cases of primary aldosteronism (PA) in children. Although three forms of FH have been described for more than three decades, till the beginning of this decade, the genetic basis of only one type FH (FH-I) was known. However, recent advances in genetics have not only enhanced the understanding of genetic basis of previously known forms of FH (FH-III) but also led to the discovery of a new form: FH-IV.

Familial hyperaldosteronism type I: FH-I, also called glucocorticoid-remediable aldosteronism (GRA), is characterized by early and severe hypertension, usually before the age of 20 years. It is due to the formation of a chimeric gene due to fusion of genes coding for promoting region of CYP11B1 (11β-hydroxylase) and coding region of CYP11B2 (aldosterone synthase), both of which are located adjacently on chromosome 8. This gene determines the regulation of aldosterone synthase activity by adrenocorticotropic hormone (ACTH). Patients with GRA have increased risk of hemorrhagic stroke before 40 years of age. Hence, all patients with onset of confirmed PA earlier than 20 years of age, and those with a family history of PA or stroke at a young age (< 40 years), should undergo genetic testing for FH-I.

Familial hyperaldosteronism type II: FH-II is clinically and biochemically indistinguishable from sporadic forms of PA and is only diagnosed on the basis of two or more affected family members. No causal genes have been identified so far. Studies have demonstrated linkage to the locus 7p22. With advances in genetics, a few of the PA cases labelled previously as FH-II have been later regrouped as FH-III.

Familial hyperaldosteronism type III: FH-III is due to gain-of-function mutations in the *KCNJ5* gene, which codes for the potassium inwardly rectifying channel Kir 3.4. Mutations in *KCNJ5* impair the selectivity filter of the Kir3.4 K^+ channel, leading to angiotensin II-independent depolarization of adrenal cells, and constitutive aldosterone production. FH-III is characterized by severe and early-onset hypertension in children and young adults; the majority have resistant hypertension and massive bilateral adrenal hyperplasia, often requiring bilateral adrenalectomy to control hypertension. However, mild forms of PA resembling FH-II, have also been described in patients with *KCNJ5* mutations. It is recommended that all very young patients with PA should undergo genetic testing for *KCNJ5* mutations.

Interestingly, a child with FH-III who developed PA at 2 years age developed Cushing syndrome at 20 years of age. Surprisingly, the CYP11B1 expression in the adrenal glands was relatively low, so the hypercortisolism was ascribed to the large size of the massively hyperplastic adrenals.

Familial hyperaldosteronism type IV: FH-IV occurs due to a mutation in CACNA1H gene which encodes a voltage-gated calcium channel ($Ca_V3.2$) expressed in the adrenal glomerulosa. Mutations in *CACNA1H* lead to impaired channel inactivation and activation at more hyperpolarized potentials, producing increased intracellular Ca^{2+}, the signal for aldosterone production. The majority of patients with PA and germline mutations *in CACNA1H* are children younger than 10 years, but a few have presented after 40 years of age. Bilateral adrenal hyperplasia was observed in some patients who presented during adulthood, whereas it was absent in children with FH-VI. However, microscopic hyperplasia of the zona-glomerulosa has been described in one adolescent (17 years) despite the absence of macroscopic hyperplasia.

Primary aldosteronism, Seizures, and Neurologic Abnormalities [PASNA]: Although not yet classified as a separate form of FH, PASNA [Primary aldosteronism, Seizures, and Neurologic Abnormalities] is another type of PA with an underlying germline mutation. Mutations in *CACNA1D* gene have been identified with this disorder and cause alterations in the signal for aldosterone production, similar to *CACNA1D* mutations.

To summarise, all the recently identified forms of FH are channelopathies. Identification of the underlying genetics in children with PA has major implications for management. In FH-1, glucocorticoids are the mainstay of treatment whereas in FH-III bilateral adrenalectomy is most often required to control severe hypertension.

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Vitamin D Dependent Rickets Type 1: A rare entity with a rarer presentation

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A 2y 2mo old boy was admitted with complaints of acute onset fever and breathlessness. He had 4 episodes of recurrent lower respiratory tract infections needing hospitalization, since the age of 7 months. His gross milestones were severely affected, and he had recently begun standing with support. His dentition was also delayed. He had no previous history of seizures nor had the parents noticed any fracture at any time. Prior to this visit, he was diagnosed with vitamin D deficiency rickets (S. calcium: 7.6 mg/dl, S. phosphorus: 1.4 mg/dl, S. alkaline phosphatase: 917 IU/L, S. 25(OH)D_3: 19.6 ng/ml). He had received oral chole- calciferol (D_3) 30,000 IU weekly for 10 weeks, along with 2000 IU of oral D_3 and 500 mg of oral calcium daily.

On examination, he was a sick looking child with failure to thrive. His weight was 6.4 kg (<3rd centile) and length was 65 cm (<3rd centile). He had tachycardia (heart rate 130/min) and tachypnoea (respiratory rate 46/min). He also had signs of florid rickets with hypotonia, wide open anterior fontanelle, chest deformity, bilateral widened wrists, double malleoli and potbelly. He had deformities of both upper limbs, however there was no tenderness of bones or restriction of movements at any joint. He had clinical signs of bronchopneumonia. Rest of his systemic examination were normal.

On investigation, his S. calcium was 7.2 mg/dl, S. phosphorus 1 mg/dl, S. alkaline phosphatase 907 IU/L, and S. PTH 517 pg/ml. As he had received adequate treatment with vitamin D in the past, his serum 25(OH)D_3 was reassessed and found to be 53.46 ng/ml.

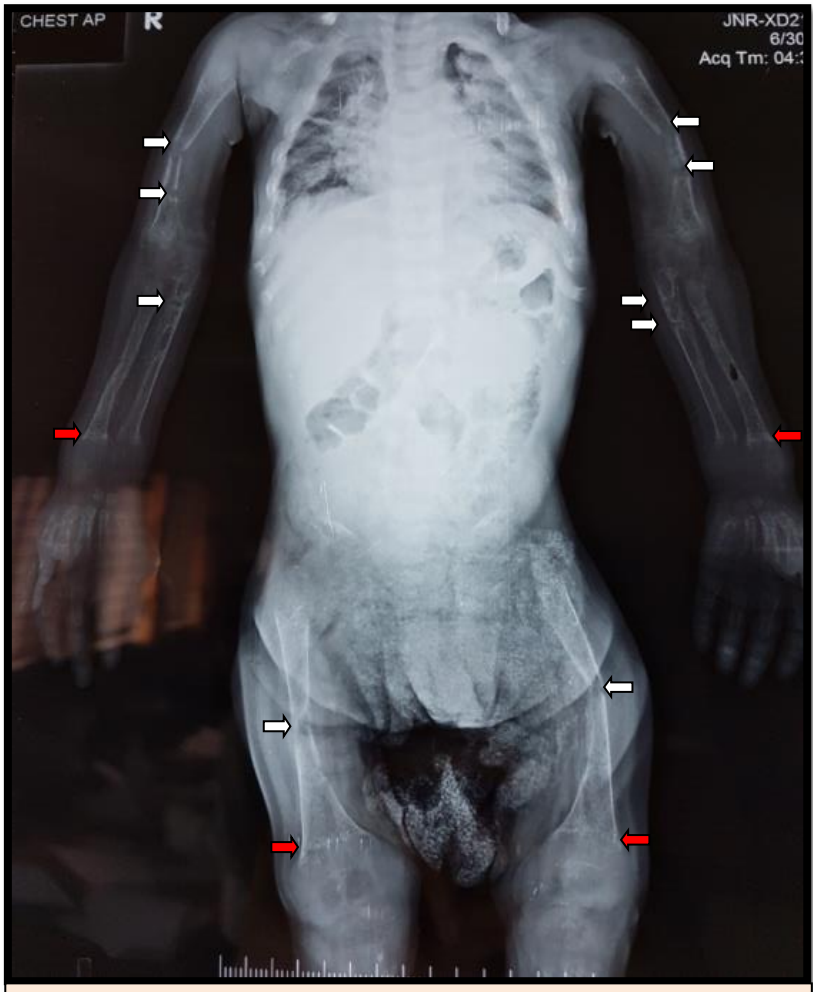

Fig 1: Lower respiratory tract infection with multiple bilateral complete fractures (white arrows) and rachitic features at growth plates (red arrows) of upper and lower limbs with bowing.

With this clinical and biochemical picture, a diagnosis of vitamin D dependent rickets (VDDR) was made. Serum $1,25(OH)_2D_3$ level was 8 pg/ml. Radiographic images (Fig 1) are consistent with bronchopneumonia and rickets. An unexpected finding was of multiple fractures of both upper and lower limbs.

Discussion

VDDR1 is a rare, autosomal recessive condition with a paucity of literature regarding its incidence and prevalence. It generally presents by two years of age, with features like growth failure, motor delay, hypotonia, dental enamel changes, joint pains, bowing of legs, and in more severe cases, with hypocalcemic convulsions or greenstick (cortical) fractures.

Radiological findings can include fractures and generalized osteopenia. Though fractures have been described in VDDR1, they are generally greenstick fractures involving the cortex, and not complete, as seen in our patient (Fig. 1). The profusion of fractures seen, especially without a relevant past history or clinical findings like pain and restriction of movement, is an oddity in our case.

Alternative diagnoses considered were: pseudo-fractures, osteogenesis imperfecta, and child abuse. Pseudo-fractures or Looser zones are cortical infarctions, seen as transverse lucencies with sclerosed margins, traversing only part way through a bone, usually at right angles to the involved cortex, and are associated most frequently with osteomalacia and rickets. They occur due to presence of unmineralized osteoid at the sites of mechanical stress or entry of a nutrient artery. The biochemical findings of VDDR1 and absence of supportive historical and clinical features cannot be explained in the case of osteogenesis imperfecta or child abuse. Hence the child was considered to be a case of VDDR1 and commenced on appropriate treatment, which includes calcitriol (0.5 – 1 µg/day) and oral calcium. Long term prognosis is generally good.

We thus conclude that while greenstick fractures are commonly described in VDDR1, an unusual radiological picture showing numerous and complete fractures is a unique finding in our case.

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G6PD Deficiency: the Trojan among Diabetics.

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Introduction

Of the various complications of diabetes, hemolysis and unconjugated hyperbilirubinemia due to unmasking of previously undiagnosed Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency, is relatively unheard of. Sporadic case reports highlighting this association have appeared in literature but overall, the incidence appears to be under-reported. This case report describes this rather unusual phenomenon, with an attempt to explain the underlying pathophysiology, supported by a brief review of literature.

Case report

An 11 year old boy weighing 40 kg was diagnosed as a case of Type 1 Diabetes Mellitus (T1DM) after he presented with weight loss and tiredness for 2 months, and polyuria, polydipsia for 2 weeks. At presentation, he was hemodynamically stable without any evidence of dehydration. Investigations revealed a blood glucose (BG) of 267mg/dl, blood pH of 7.36, and negative urine ketones. HbA1C was 10.3%, Hb. 12.4g/dl, C-peptide 0.4ng/ml and Glutamic acid decarboxylase-65 (GAD-65) antibody value 1049.4 IU/ml. He was started on a basal-bolus insulin regimen with Glargine 11 units once daily and Aspart 6 units (titrated according to sliding scale) before the three major meals daily. Fasting and post meal BG within target range were achieved within 7 days. During this period, readings of low BG (up to 70mg/dl) were recorded on two occasions. On day 7 after initiating insulin, the child developed yellowish discolouration of sclera with deep lemon yellow coloured urine. There was no history of pain abdomen, vomiting, fever, loss of appetite, drug ingestion or any similar episode in the past or in any family member. However, on questioning, history of neonatal jaundice requiring phototherapy was elicited. On examination, scleral icterus and skin pallor were noted, but there was no hepatomegaly or abdominal tenderness. Investigations showed total bilirubin of 7.74mg/dl, indirect bilirubin of 6.54mg/dl, Hb. 9.2g/dl, SGPT 12 U/L, SGOT 25 U/L, GGT 10.4U/L, reticulocyte count 4.3%, and LDH 220 IU/L. Urine was negative for hemoglobin and RBCs. The peripheral smear was reported as showing no evidence of hemolysis and negative for P.falciparum. Direct and indirect Coombs test were negative. G6PD activity was found to be significantly

reduced at 0.1 U/gHb (normal range of 7.0-20.5 U/gHb), explaining the unconjugated hyperbilirubinemia and the clinical picture of hemolysis in our patient. The child was closely monitored. Jaundice abated over the next one week, hemoglobin levels returned to normal over the next 3 weeks, and BG were maintained well within the target range.

Discussion

G6PD deficiency is usually linked to drugs that induce oxidative stress. Association with diabetes mellitus is infrequently reported. This case highlights the fact that G6PD deficiency can be unmasked by hyperglycemia without any previous signs or symptoms.

In RBCs, G6PD enzyme is the key player for generating NADPH, which in turn maintains the sulfhydryl (SH) groups in the reduced state, safeguarding RBCs against oxidant damage. The energy required by the G6PD enzyme to generate NADPH is provided exclusively by glucose. In patients with diabetes, during periods of hyperglycemia (especially at diagnosis or when in DKA), there is a copious supply of glucose to the RBCs. However, with onset of treatment with insulin, and normalisation of BG, the glucose supply is progressively reduced. This eventually leads to the inability of the old RBC to generate enough NADPH to keep the SH groups in a reduced state, thus increasing RBC oxidant stress and ultimately results in RBC lysis, significantly more so in G6PD deficient cells (1-2).

In our patient, unconjugated hyperbilirubinemia and hemolysis were noted in the week following diagnosis of T1DM, when BG levels were markedly lower than the previous high levels (though he was never in DKA). Also of note is the fact that the hemolysis was precipitated in the absence of any infection or drug ingestion.

A few studies have demonstrated the occurrence of hemolysis after episodes of DKA in patients with diabetes and G6PD deficiency (3-5). Our patient and the cases published so far (1-5, 9) share the unique characteristic of hemolysis occurring after de-compensation of diabetes. There is now evidence to suggest that hyperglycemia can reduce expression of the G6PD gene and the activity of the enzyme (5). Conversely, G6PD deficiency can promote oxidative stress and impairment of insulin secretion in the islet cells of the pancreas (6).

A recent study proposes that alterations in the gene controlling both insulin secretion and G6PD mediated anti-oxidant defences may contribute to a predisposition to diabetes (7). This is supported by the finding of an increased prevalence of G6PD deficiency among patients with diabetes (8).

Interestingly, patients with G6PD deficiency have lower HbA1C compared to patients without the deficiency because the average lifespan of the RBC is reduced and the new RBCs are younger (9).

Finally, it is noteworthy that patients who develop hemolysis after initial DKA or hyperglycemia rarely require blood transfusions. The hemolytic anemia decreases spontaneously and disappears as new RBCs grown under normal glycemic conditions find a sufficient physiological source of energy to generate adequate NADPH to prevent oxidative damage (2).

For the sake of completion, other factors that may be responsible for the occurrence of hemolysis in patients with diabetes and G6PD deficiency, including use of drugs such as metformin and glibenclamide, should be considered.

Learning Points

1. G6PD deficiency should be thought of in all patients of diabetes who develop hemolysis.
2. In a patient with diabetes and G6PD deficiency, hemolysis may occur during normalization of blood glucose after diagnosis or DKA; during periods of hypoglycemia, or with use of drugs such as metformin and glibenclamide.

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Septo-Optic Dysplasia: Rare pituitary disorder with varied presentation

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Introduction

Septo-optic dysplasia (SOD) is a rare developmental disorder with an incidence of 1 in 10,000 [1]. It comprises of a clinical triad of midline brain abnormality, optic nerve hypoplasia and hypopituitarism. Diagnosis of this syndrome is clinical. It occurs with equal frequency in both the sexes. In recent times, various genetic mutations have been found causing this syndrome - HESX1, OTX2, SOX3 and SOX2, at the same time the yield of genetic diagnoses in less than 1%. We discuss here two unique cases of SOD, one with late

presentation with multiple pituitary hormone deficiencies, and another with normal pituitary functions and associated infantile obesity.

Case 1

An 11y 10mo old prepubertal female, belonging to the Sikh community, born of a non-consanguineous marriage, presented in the pediatric endocrine clinic with complaint of short stature. She was born at term by vaginal delivery, birth weight 2.5 kg, with no history of prolonged jaundice or hypoglycemia in the neonatal period. Her motor milestones were delayed. Dentition started at age 2y and deciduous tooth shed at age 10y. On enquiry, there was also history of nocturia since 8 years of age. She was doing well in school and had no behavioral problems. Family history was non-contributory. On examination, her weight was 22 kg (Z score -3.9), height 119 cm (Z score -4.1), with bone age of 7 years. She had phenotypic features of growth hormone (GH) deficiency: infantile voice, midfacial crowding and preserved truncal fat. She also had esotropia and nystagmus in the left eye (fig 1A). On complete ophthalmic examination, she had amblyopia with optic atrophy in the left eye (fig 1B), which had not so far been noticed by the parents. Anosmia was also reported on direct questioning. Hormonal evaluation showed normal serum free T4 (0.94 ng/dl), cortisol (9 µg/dl) and prolactin (16 ng/ml). Peak GH level on clonidine stimulation was 0.6 ng/ml. Serum sodium was 147mEq/L, with low urine osmolality of 93 mOsm/L and serum osmolarity of 301 mOsm/L. Hence, she was diagnosed with multiple pituitary hormone deficiencies (GH and Antidiuretic Hormone). MRI pituitary and brain showed absence of the septum pellucidum, hypoplastic pituitary gland with partially empty sella turcica (fig 1c). The posterior pituitary bright spot was not seen and there was absence of olfactory bulb. The rest of the brain parenchyma was normal. She was started on GH therapy and desmopressin; periodic surveillance for other pituitary hormones was planned. On follow up at 6 months, her height increased by 7 cm. She subsequently developed ACTH deficiency (serum 8:00 am cortisol 3.6 µg/dl), and was started on physiological replacement of steroids (10 mg/m^2/day of hydrocortisone), with stress dosing. Thyroid function is normal till date. She will be kept on lifelong hormonal surveillance, with monitoring of growth and puberty.

Case 2: A 2y old male, product of a non-consanguineous marriage, presented with rapid gain in weight, not recognising parents and surroundings, global developmental delay, and behavioral problems. Birth history was uneventful apart from physiological jaundice. There was no history of seizures, polyuria and temperature instability. On examination, his weight was 24 kg (Z score +5.47), length 89.5 cm, with BMI of 30.3 kg/m^2. He had mild dysmorphism in the form of epicanthic folds, low set ears, and depressed nasal bridge. Ophthalmic examination showed right eye squint and nystagmus (Fig 1D); fundus showed optic disc hypoplasia (Right > Left). Hormonal evaluation showed normal serum free T4 (1 ng/dl), 8 am cortisol (12.5 ug/dl), and prolactin (22 ng/ml). Fasting blood glucose, electrolytes and lipid profile were also normal. In view of global developmental delay and optic atrophy, neuroimaging was performed, which showed absence of septum pellucidum, confirming the diagnosis of SOD. He was managed with lifestyle modification, behavioral therapy and periodic monitoring for endocrinopathies.

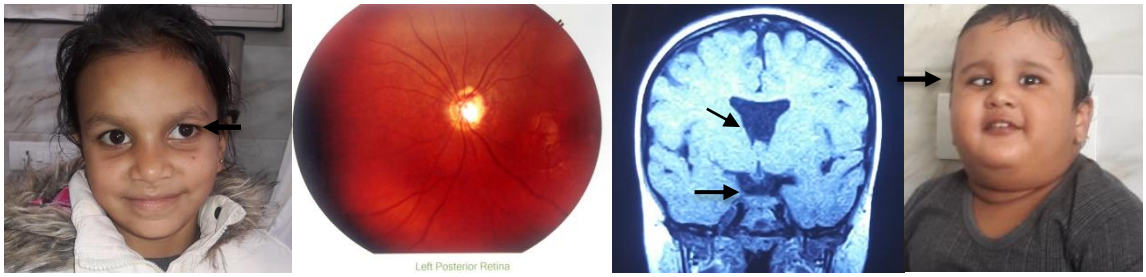

Fig 1: Clinical photograph of case 1 showing facial features of growth hormone deficiency and squint in left eye (1B), fundus photography of left retina of patient showing peripapilary atrophy and double ring sign (1B), coronal section of MRI brain absent showing septum pellucidum (thin arrow) and hypoplastic pituitary (thick arrow) (1C), and clinical photograph of case 2 with squint in right eye (arrow)

Discussion

Septo-optic dysplasia (SOD), also known as De Morsier's syndrome, is a rare and unique form of hypopituitarism in children. In 1941, Reeves first described the syndrome of lack of septum pellucidum with optic nerve disorder [2]. Both genetic and environmental factors play a role in its occurrence. It comprises of a clinical triad of absence of the septum pellucidum, congenital optic nerve dysplasia, and hypopituitarism, which occurs in almost 30% of patients [3]. Presence of two of three criteria is considered an atypical form of SOD. This syndrome is more common in children born of young nulliparous woman and in areas with high unemployment rate [4]. Cocaine or alcohol abuse have been postulated to be possible etiological factors. Two major theories have been described: the Developmental theory which suggests that teratogenic injury to the fetus at 6 weeks' gestation interferes with normal development of retinal ganglion cells, hypothalamus and septum pellucidum; and the Destructive theory which postulates damage to the already formed retinal pathway during any period of gestation [5]. Various developmental malformations have been described - corpus callosal agenesis, schizencephaly, holoprosencephaly, Duane syndrome, blepharophimosis, hemifacial atrophy, anophthalmia, olfactory tract agenesis (as present in case 1), autism, pineal gland cyst and arachnoid cyst. Rare associations reported include congenital hepatic fibrosis, cerebral cortical abnormality (SOD plus) and transverse limb defects. Neurological abnormalities like cerebral palsy, developmental delay or seizures can also occur in patients.

The most common endocrine abnormalities are hyperprolactinemia and GH deficiency (73% and 58% respectively), followed by central hypothyroidism (39%), adrenal insufficiency (31%) and gonadotropin deficiency. On the other hand, they can also have precocious puberty due to hypothalamic damage, which may mask GH deficiency. Pituitary involvement can occur at any age, and can vary from a single hormone deficiency to multiple deficiencies occurring gradually over time. Long term surveillance is needed to prevent life threatening adrenal crises due to ACTH deficiency. Diabetes insipidus leading to hypernatremia, and thermal dysregulation are other important causes of sudden death. Many children may become obese due to hypothalamic involvement [6].

Neuroimaging in SOD

MRI findings are heterogeneous, including morphological anomalies of the cortex and malrotation of the hippocampus, and a variety of midline abnormalities (agenesis of corpus

callosum, absence of the septum pellucidum, cerebellar hypoplasia, aplasia of the fornix and schizencephaly). Neuroradiological anomalies are present in up to 75-80% of the patients with optic nerve hypoplasia. Ectopic posterior pituitary predicts the existence of hypopituitarism, while hemispheric migration anomalies are predictors of neurodevelopmental deficits [7].

Ophthalmologists and neurologists should be aware of the syndrome, and if they find any of the features, timely referral to a pediatric endocrinologist is important, since the pituitary deficiencies may present at any age, and lead to permanent sequelae or even a crisis.

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Hyperprolactinemia in children with subclinical hypothyroidism

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Prevalence of hyperprolactinemia in children with subclinical hypothyroidism (ScH) is not known. We conducted a study to determine the occurrence and predictors of hyperprolactinemia in children with euthyroidism, ScH, and overt primary hypothyroidism (OPH). Consecutive children <18 years age, with known thyroid status (normal, ScH or OPH) underwent serum prolactin estimation. Children with pituitary adenomas, secondary hypothyroidism, multiple pituitary hormone deficiency, comorbid states and drug-induced hyperprolactinemia were excluded. 791 children were screened among whom 602 children who fulfilled inclusion criteria were analysed. Of these 71 (11.79%) had ScH, and 33 (5.48%) had OPH. Occurrence of hyperprolactinemia was highest in OPH (51.51%), followed by ScH (30.98%) and euthyroid children (4.41%) ($P<0.001$). Median [25^{th}-75^{th} percentile] values of serum prolactin in euthyroid children, ScH and OPH were 13.3 [9.4-17.95], 19.15 [15.97-30.12] and 28.86 [17.05-51.9] ng/ml respectively ($P<0.001$). Serum prolactin levels were comparable in boys and girls. A secular trend of increase in serum prolactin with age was noted in euthyroid children, which was statistically significant in post-pubertal (16-18 years) children. AUC for TSH in predicting hyperprolactinemia in

children was 0.758 (95% CI: 0.673-0.829; P <0.001). TSH ≥ 4.00 mIU/L had a sensitivity of 69.4% and specificity of 77.6% in detecting hyperprolactinemia. Another study done by our group in adult subjects also found similar results of hyperprolactinemia in females and males- OPH (42.95%: 39.53%) (n=192), ScH (35.65%: 31.61%) (n=770) and euthyroid individuals (2.32%: 2.02%) (n=1886) (P<0.001). ROC analysis revealed that TSH ≥7.51mIU/L in females and ≥8.33mIU/L in males had a sensitivity of ≈50% with a very high specificity of >90% in detecting hyperprolactinemia. When compared to this, serum TSH threshold for predicting hyperprolactinemia was lower in children as compared to adults.

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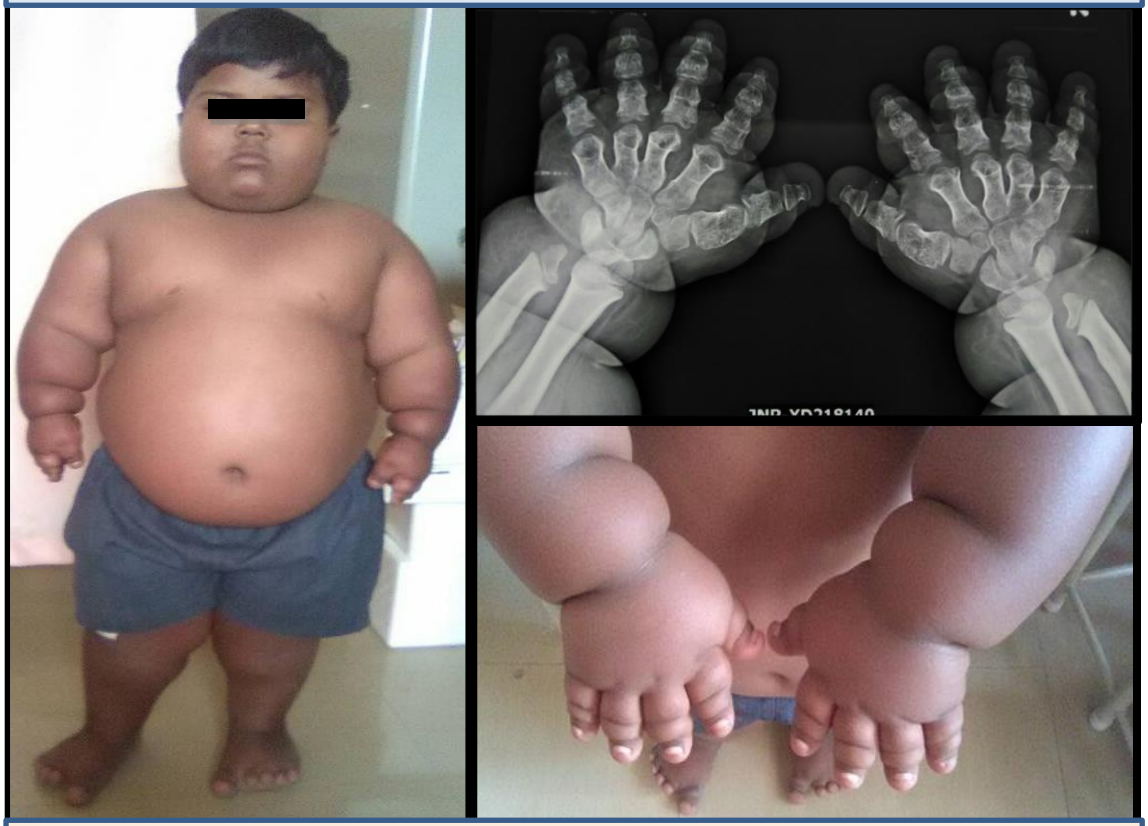
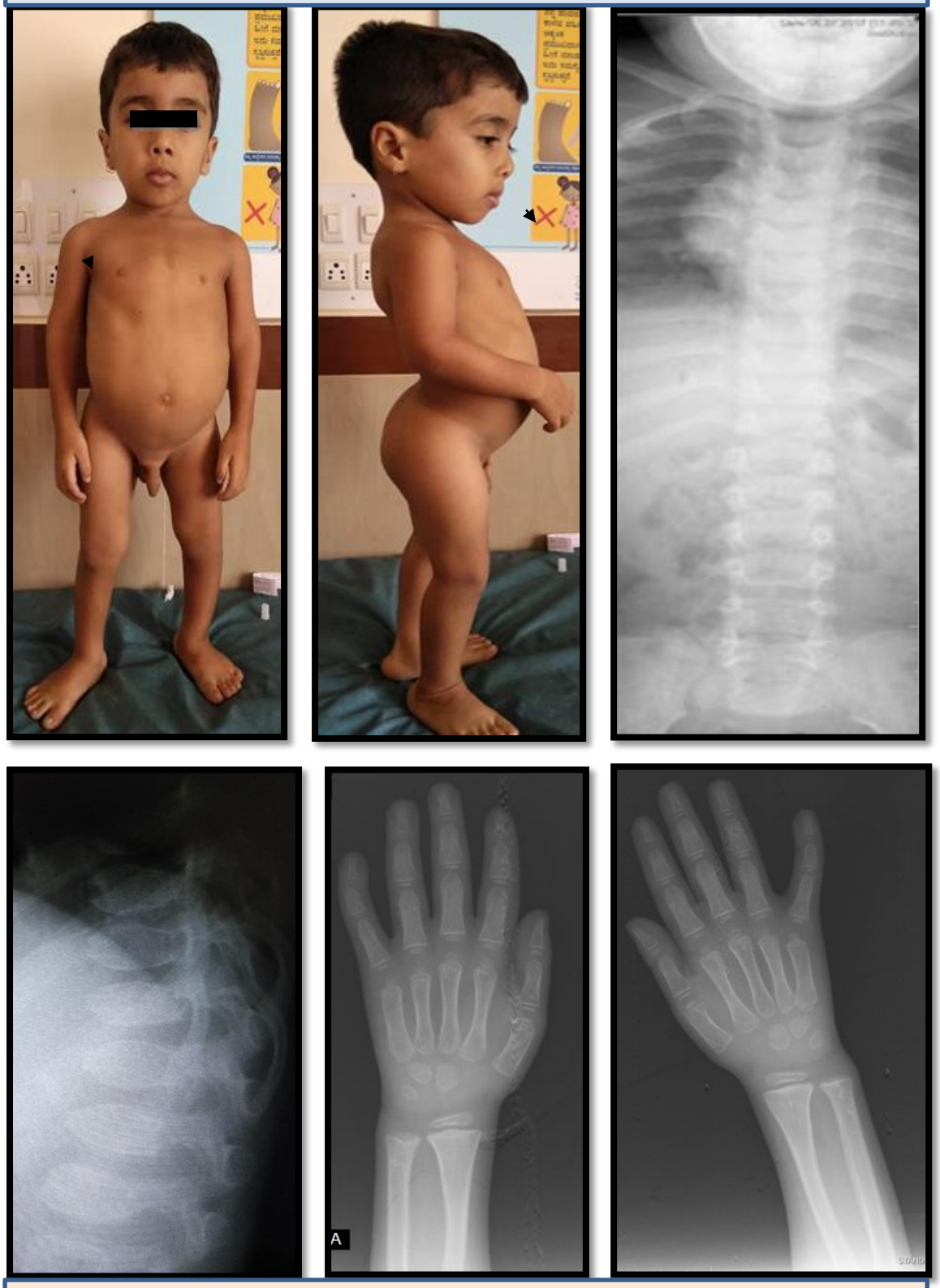
Photo Quiz 1



11 yo boy presented with disproportionate short stature, dysmorphism and obesity

Questions: What are the findings noted in the clinical picture? What are the X-ray findings seen? What is the diagnosis? What are the differential diagnoses for brachydactyly?

Photo Quiz 2



A 6yo boy presented with short stature.

Questions: What are the clinical findings? What are the x ray findings? What is the diagnosis?

Pedendoscan

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GROWTH AND PUBERTY

Meta-Analysis of Paediatric Patients with Central Precocious Puberty Treated with Intramuscular Triptorelin 11.25 mg 3-Month Prolonged-Release Formulation. Durand A et al. Horm Res Paediatr 2017;87:224–232

A meta-analysis involving 153 children (13 boys, 140 girls) was undertaken to assess the effect of triptorelin 11.25 mg 3-month prolonged-release formulation in central precocious puberty (CPP). The primary outcome was the proportion of children with suppressed luteinising hormone (LH) response (peak LH ≤3 IU/L) to the gonadotrophin-releasing hormone (GnRH) test 3 months after triptorelin 11.25 mg injection. Secondary outcomes included: the proportion with suppressed peak LH response at 6 months and the proportion with suppressed peak follicle-stimulating hormone (FSH) response (≤3 IU/L), suppressed oestradiol (≤20 pmol/L) in girls or suppressed testosterone (≤30 ng/dL) in boys at 3 months. The proportion with a suppressed peak LH response to the GnRH test was 87.6% and 92.8% at 3 and 6 months, respectively. FSH peak, oestradiol, and testosterone were suppressed in 86.7%, 97.1%, and 72.7% of children at 3 months, respectively. The authors concluded that Triptorelin 11.25 mg 3-month formulation is efficacious in suppressing LH peak and other gonadal hormones and in slowing the progression of CPP in children.

Metabolic Outcomes, Bone Health, and Risk of Polycystic Ovary Syndrome in Girls with Idiopathic Central Precocious Puberty Treated with Gonadotropin-Releasing Hormone Analogues. Faienza M.F. Horm Res Paediatr 2017; 87:162–169

To assess the effects of Gonadotropin-releasing hormone analogues (GnRHa) treatment on metabolic outcomes, bone status, and polycystic ovary syndrome (PCOS) prevalence in young girls with idiopathic CPP (ICPP), 94 girls who were at least 2 years after menarche and had already attained adult height at the time of the study: 56 previously treated with depot triptorelin and 38 untreated were studied. The 2 groups were similar for body mass index (BMI) and waist circumference. HOMA-IR, DHEAS, androstenedione were higher in the treated than in the untreated subjects. The prevalence of PCOS was higher in the treated than in the untreated subjects. The authors concluded that GnRHa therapy is associated with hyperandrogenism and an increase in insulin resistance and PCOS prevalence, but not with increased BMI or lipid profile alterations. Long-term evaluations at the time of expected peak bone mass achievement are needed to understand the persistent or transient nature of subtle bone abnormalities.

Endocrine Long-Term Follow-Up of Children with Neurofibromatosis Type 1 and Optic Pathway Glioma. Sani A et al. Horm Res Paediatr 2017;87:179–188:

To assess the prevalence of hypothalamic-pituitary dysfunction in children with neurofibromatosis type 1 (NF1) and optic pathway glioma (OPG) who did not receive radiotherapy or surgical resection, a retrospective follow-up study of 36 children was undertaken. Endocrinopathies were diagnosed in 55.6% children during a mean follow-up of 9.1 years. The first endocrinopathy was found at a mean age of 7.4 years, 2.4 years after tumor diagnosis. The most prevalent abnormalities were growth hormone deficiency (36.1%), central precocious puberty (33.3%), obesity with insulin resistance/ impaired glucose tolerance (11.1%), early puberty (5.5%), GH excess (5.5%), ACTH deficiency (5.5%), hypogonadotropic hypogonadism (2.7%), and thyrotropin deficiency (2.7%). The authors concluded that this population is at high risk of endocrinopathies due to tumor location. Lifelong endocrine follow-up is recommended.

THYROID: Characterization of Thyroid Abnormalities in a Large Cohort of Children with Down Syndrome. Pierce MJ et al. Horm Res Paediatr 2017;87:170–178.

Retrospective records of 508 patients with Down syndrome (DS) were reviewed to assess thyroid abnormalities. 24% had a thyroid-related diagnosis, the majority having elevated thyrotropin, treated with levothyroxine. A Kaplan-Meier estimate projects that 50% have thyroid disorder by adulthood, with 20% of hypothyroidism diagnosed before the age of 6 months. When tested, approximately 50% had positive anti-thyroid antibodies, though this rate was 100% in overt hypothyroidism. There was no association between congenital or acquired hypothyroidism and common comorbidities. The authors concluded that thyroid disease in DS is more common and occurs earlier than in the general population, and is often transient. Apart from overt hypothyroidism, much of hypothyroidism in DS appears unrelated to autoimmunity. Authors recommend not checking anti-thyroid antibodies expect in select cases; and an additional screen for thyroid disease between the newborn screen and the 6-month well-child visit to detect early cases of hypothyroidism in those who passed their newborn screen.

DSD: The Spectrum of Ovotesticular (OT) Disorders of Sex Development in South Africa: A Single-Centre Experience. Ganie Y et al. Horm Res Paediatr 2017;87:307–314.

A retrospective subset analysis of 64 cases of histologically confirmed OT DSD was done to describe the clinical characteristics, biochemistry, histopathology, and long-term outcomes. All subjects were South African; 97% (n = 62) were African and 92% (n = 59) were of Zulu ethnicity. The most common karyotype was 46,XX (88%; n = 56), followed by 46,XY (8%), 46,XY/45,X (3%), and 46,XX/46,XY (1%). The median age at presentation was 7 months (0.5 months to 5.1 years). 95% of the subjects presented with DSD. The ovotestis was the most frequent gonad (56%), followed by the ovary (23%) and the testis (16%). Testes were more commonly located on the right and ovaries on the left. The male gender was the predominant sex of rearing in two-thirds of the subjects. Gender dysphoria was noted in 8 subjects (11%) at a median of 6.4 (4.3–9.3) years. Long-term follow-up (n = 14) revealed spontaneous puberty in 5 subjects, gender dysphoria in 2 subjects, and neuropsychiatric disorders in 4 subjects.

OBESITY

Determinants of Advanced Bone Age in Childhood Obesity. De Groot CJ et al. Horm Res Paediatr 2017;87:254–263.

Childhood obesity is associated with advanced bone age (BA). A correlation analysis of BA standard deviation score (SDS) with age- and sex-specific SDS for androgens, estrogens, and with indicators of insulin secretion derived from oral glucose tolerance testing, was performed in a group of obese children (n = 101; mean age 10.9 years; mean BA 11.8 years; mean BMI SDS 3.3). In this cohort BMI SDS was significantly correlated to BA SDS ($r = 0.55$, $p < 0.001$). Dehydroepiandrosterone sulphate (DHEAS) showed a positive, independent association with BA SDS. No association with indicators of insulin secretion was found.

Hormonal and Metabolic Responses to a Single Bout of Resistance Exercise in Prader-Willi Syndrome. Rubin DA et al. Horm Res Paediatr 2017;87:153–161.

Prader-Willi syndrome (PWS) is characterized by excessive adiposity. Excess adiposity negatively affects hormonal and metabolic responses to aerobic exercise. To determine whether PWS and/or adiposity affected hormonal and metabolic responses to resistance exercise, 11 children with PWS (11.4 ± 3.1 years, 43.9 ± 7.5% body fat), 12 lean children (9.3 ± 1.4 years, 18.3 ± 4.9% body fat), and 13 obese children (9.6 ± 1.3 years, 40.3 ± 5.2% body fat) stepped onto an elevated platform while wearing a weighted vest for 6 sets of 10 repetitions per leg (sets separated by 1 min of rest). Blood samples were obtained before, immediately after, and during recovery from exercise (+15, +30, and +60 min). All groups had similar catecholamine, insulin, and glucagon responses. The PWS children demonstrated earlier increases in fatty acids during recovery and higher glycerol and ketone levels than the controls. The authors suggested that PWS children demonstrated largely intact hormonal, glycolytic, and lipolytic responses to lower-body resistance exercise. Elevated ketone levels in PWS suggest incomplete fat oxidation.

Alterations in Glucose Effectiveness and Insulin Dynamics: Polycystic Ovary Syndrome or Body Mass Index. Vuguin P et al Horm Res Paediatr 2017;87:359–367

To delineate the relationship of polycystic ovary syndrome (PCOS), obesity, and hyperandrogenism (HA) with glucose and insulin dynamics in adolescents across a broad range of body mass index (BMI), 74 PCOS subjects (age 16y) and 82 controls (age 16y) were evaluated by an oral glucose tolerance test. Subjects were categorized by BMI as normal weight, overweight/obesity, and severe obesity. Indices of glucose and insulin dynamics were determined. BMI was significantly associated with systolic and diastolic blood pressure and insulin resistance. A significant interaction between BMI and PCOS and indices of post-glucose load was observed. In PCOS subjects, testosterone was positively associated with BMI, fasting insulin, early insulin response, and diastolic blood pressure. The authors observed that the combination of PCOS and severe obesity has a synergistic effect on glucose dynamics when compared to other groups.

DIABETES

Predictors of Loss to Follow-Up among Children with Type 2 Diabetes. Shoemaker A et al. Horm Res Paediatr 2017;87:377–384

To determine which demographic and clinical factors differ among youth with T2D lost to follow-up, data was analyzed from 496 subjects in the Pediatric Diabetes Consortium registry. The factors analysed included age, race/ethnicity, parent education, and estimated distance to study site. The odds ratio of loss to follow-up was 2.87 for those aged 15 to <18 years and 6.57 for those aged ≥18 years versus those aged 10 to <13 years. Among patients living more than 50 miles from the clinic, the odds ratio of loss to follow-up was 3.11 versus those living within 5 miles of the site. The authors concluded that older adolescents with T2D are more likely to be lost to follow-up. Other socioeconomic factors were not significant predictors of clinic follow-up.

Improvement in glycemic control through changes in insulin regimens: findings from a Japanese cohort of children and adolescents with type 1 diabetes. Mochizuki M et al. Pediatr Diabetes. 2017 Sep;18(6):435-442

HbA1c values, proportion of insulin regimens, incidence of severe hypoglycemic events, and pubertal increase in HbA1c were compared in three cohorts of childhood-onset Japanese T1D patients (567 subjects in the 1995 cohort, 754 subjects in the 2000 cohort, and 806 subjects in the 2008 cohort). Glycemic control and incidence of severe hypoglycemic events improved chronologically, especially in female adolescents. Mean HbA1c values tended to decrease [9.33% in the 1995 cohort, 8.39% in the 2000 cohort, and 7.75% in the 2008 cohort; $P < .0001$]. The proportion of patients who received basal-bolus treatment tended to increase with statistical significance, as did the proportion on insulin analogs.

Factors contributing to partial remission in type 1 diabetes: analysis based on the insulin dose-adjusted HbA1c in 3657 children and adolescents from Germany and Austria. Nagl K et al. Pediatr Diabetes. 2017 Sep;18(6):428-434

To investigate the prevalence of partial remission (PREM) defined by Insulin dose-adjusted hemoglobin A1c (IDAA1c) ≤9, in 3657 children with new-onset T1D who were continuously followed over 6 years. PREM occurred in 71% of patients. Median duration was 9 months. Compared to children <5 years at T1D onset, those aged 5-10 and ≥10 years had twice the chance of developing PREM. Boys were more likely to develop PREM than girls. Further predictors for PREM were: ketoacidosis, autoantibodies, and HbA1c at T1D onset. As IDAA1c does not discriminate between insulin sensitivity and secretion, available data cannot resolve whether the sex-difference in PREM reflects innate higher insulin resistance in girls, or better beta-cell recovery in boys. Further research is needed to clarify the usefulness and performance of IDAA1c in clinical practice.

Activities by ISPAE Members

Master Class in Pediatric Endocrinology 2017, Dr Shaila Bhattachryya, Bengaluru

The '2nd Annual Master Class for Fellows in Pediatric Endocrinology 2017' was organised by Dr Shaila Bhattacharyya at Manipal Hospital, Bengaluru, on 30th April and 1st May 2017. The program, using case based modules, covered important topics related to pediatric endocrinology, with national and international experts among the faculty. The delegates, pursuing pediatric endocrinology fellowship or DM endocrinology courses, were from across the country. Each session started with case presentation by the fellow followed by a faculty talk.

The program began with a lecture by Dr Santosh Olety on 'neonatal endocrinology', emphasising the need of newborn screening for endocrine disorders. Dr Vaman Khadilkar discussed the role of human growth hormone in SGA babies who fail to show catch up growth. He later provided insights into the recent trends in childhood obesity and summarised the 2017 pediatric obesity guidelines by Endocrine Society, USA. Dr Zulf Mughal briefed the global guidelines on prevention and treatment of nutritional rickets; Dr Ahila Ayyavoo highlighted the unique problems of rickets in Indian children. Dr Ayyavoo later discussed common causes of hypothyroidism, including congenital hypothyroidism. Dr Belinda George delivered a lecture on 'childhood Graves' disease'. Dr Sridevi Hedge, a clinical geneticist at Manipal Hospital, Bengaluru spoke on various genetic tests and their implications in the diagnosis of pediatric endocrine disorders. Dr Vijaya Sarathi discussed practical issues of hormone assays in endocrine practice. Management of Type 1 and Type 2 Diabetes in childhood were touched upon by Dr Olety and Dr Shaila Bhattacharyya respectively.

The second day began with a lecture on 'Disorders of Puberty' by Dr Vageesh Iyer, and discussion of different mind-boggling cases related to pubertal disorders. Later Dr Mughal delivered lectures on 'Vitamin D nonresponsive rickets' and 'pediatric hypercalcaemia'. Dr Sarah Mathai dealt with the nuances in management of Osteogenesis Imperfecta. Dr Amisha Sawkar, a pediatric radiologist from Sakra Hospital, Bengaluru discussed the use of various imaging modalities in pediatric endocrinology. Dr Mathai delivered lectures on 'disorders of fluid and electrolyte balance' and 'chronic steroid therapy. Dr Sarathi discussed endogenous Cushing syndrome in children, and Dr George presented an

overview of approach to a child with disorders of sex development.

Finally, Dr Mughal enlightened the delegates on the role of dual-energy X-ray absorptiometry and its interpretation in the pediatric population.

The intensive Masterclass in Pediatric Endocrinology was truly an enriching experience for all the participants.

Growth Symposium - 2017, Dr P Raghupathy, Bengaluru

Growth Hormone Research Society (GHRS), India, conducted Growth Symposium 2017 on 22-23 July at Taj Vivanta, Yeshwantpur, in Bengaluru. The theme for this year's Symposium was 'Recent trends in Management of Growth Disorders'. This national conference involved 42 faculty from all over the country and an international speaker, addressing nearly 150 delegates. The event was also attended by 10 delegates from Egypt and Dubai.

The key objective of this meeting was to generate awareness on all aspects of short stature, with a focus on clinical approach to diagnosis and management of growth hormone deficiency. This year, special emphasis was laid on current topics such as the new Pediatric Endocrine Society Guidelines (2016) for growth hormone and IGF-1 deficiencies, the new country-specific growth standards which were recently published by Indian Academy of Pediatrics, along with interesting panel discussions and case discussions, on topics such as importance of early diagnosis and initiation of treatment in management of growth disorders, optimisation of growth outcomes with appropriate dosing, importance of adherence to therapy and factors affecting adherence.

Professor P. Raghupathy, President of GHRS, and Organising Chairperson of this Conference, in his welcome address, highlighted the importance of treatment of short stature and the associated adverse psychological changes suffered by untreated children. He stressed the need to create awareness not only among health care providers, but also among central and state government health care authorities. This program was sponsored by Novo Nordisk India Pvt Ltd.

3rd AIIMS-LHMC CME on Pediatric Endocrinology, Dr Rajni Sharma, New Delhi

The Departments of Pediatrics of AIIMS, New Delhi and Kalawati Saran Children's Hospital (KSCH, Lady Hardinge Medical College, New Delhi), jointly organized the annual Pediatric Endocrinology CME for postgraduates in association with ISPAE on 29-30 July 2017. It was held at the Conference Hall, AIIMS, New Delhi, and was accredited by the Delhi Medical Council.

The response to the CME was overwhelming; though initially it was planned for 60 participants, the final number exceeded 90, with a fully packed hall. The participants consisted mainly of MD/DNB students, and Senior Residents of both Pediatrics and DM Endocrinology: from various parts of India including Jaipur, Hyderabad, Aligarh, Jamnagar, Chandigarh, Lucknow etc.

The faculty included Prof PSN Menon (Jabber Al Ahmad Armed Forces Hospital, Kuwait), Prof Anju Seth (KSCH & LHMC), Prof Sangeeta Yadav (Maulana Azad Medical College, New Delhi), Prof Vandana Jain (AIIMS), Dr Rajni Sharma (AIIMS), Dr. Preeti Singh (KSCH), Dr Aashima Dabas (Maulana Azad Medical College, New Delhi), Dr Swati Dublish (KSCH), Dr Ganesh Jevlikar (Medanta Medcity, Gurgaon), Dr Bhanukiran Bhakhri (SSPHPGTI, NOIDA) and Prof Naval Kishore (Department of Medicine, AIIMS).

An array of topics covering the vast spectrum of Pediatric Endocrinology were discussed, including growth charts, short stature, Growth Hormone disturbances, disorders of puberty, persistent hypoglycemia in neonates, nutritional and refractory rickets, thyroid disorders, hyponatremia, neonatal thyroid reports, ambulatory management of type 1 diabetes, diabetic ketoacidosis, childhood obesity, and disorders of sex development.

The sessions were case-based and the faculty encouraged interaction with the participants. It was a pleasure for the faculty to have such a rapt and attentive audience who proactively took part in the discussions. The participants gave a very positive feedback, saying that the CME made them more confident of managing pediatric endocrine disorders; many expressed their interest in pursuing the specialty in future.

Dr Anurag Bajpai, Kanpur

GROW India Congenital Hypothyroidism Support Group Meeting and Camp, May 27 2017

ISPAE-GROW India Thyroid Support Group meeting and Congenital Hypothyroidism (CH) Camp provided an opportunity to provide holistic care to 50 children with CH. Children were assessed by developmental physician, pediatric neurologist, speech therapist and occupational therapists. Infographics on thyroid disorders and an Awareness Video were launched on the occasion of World Thyroid Week.

V GROW India Educationalists Brainstorming session

The session, attended by around 50 educationalists from the region, dwelt on ways to improve early detection and treatment of growth disorders. 'Road to Growth, Fat to Fit, Period Plus and Type 1 DM Together We Win' projects were conceptualized in the meeting.

Student Sensitization Workshop on Female Adolescent Endocrine Disorders at GD Goenka School, Kanpur: July 22 2017

GROW India Student Sensitization Program on Female Adolescent Endocrine Issues was conducted at GD Goenka School, Kanpur. The program provided information about growth, obesity, pubertal problems and bone health to young girls.

IV GROW India Day August 13 2017

IV Grow India Day witnessed participation of over 200 children with endocrine disorders, educationalists, physicians, social activists, and GROW India Members. The key attractions of the event included launch of Type 1 Diabetes book, infographics on Celiac Disease, Growth Failure, Thyroid and Pubertal Disorders. The event was presided by Mr Alok Singh, IPS, IG Kanpur Zone who dwelt on the importance of promoting awareness about growth disorders. Key school projects like Road to Growth, Fat to Fit, Type 1 Together We Win, and Period Plus were launched to increase awareness about growth, obesity, type 1 DM and pubertal issues, and to support children with these disorders. Novel initiatives launched by GROW India on the day included Teacher Training Module to train teachers regarding growth disorders, GROW India Clinics to provide free services to poor children with endocrine disorders, and Kanpur Kreative Kids Club to enhance creativity in children. School children participated in Design Workshop and Poster Competition and provided innovative solutions about challenges of Type 1 Diabetes.

Type 1 Diabetes- Hum Honge Kamyab

GROW Society has published Patient Education Book ***"Type 1 Diabetes- Hum Honge Kamyab"*** for empowering children with diabetes. The book covers all aspects of disease, including Physiology, Insulin types and use, Nutrition, Sick day care, Hypoglycemia, Glycemic adjustments and Social issues in a pictoral form. The Hindi Version can be obtained at print cost and English pdf version for free by contacting at dr_anuragbajpai@yahoo.com.

Infographics on Pediatric Endocrine Disorders

GROW Society has published infographics on Growth, Congenital and Acquired hypothyroidism, Celiac disease and Early and Delayed puberty in Hindi and English. These infographics aim to provide practical information to children and parents in an illustrative manner. The print and pdf versions can be obtained from dr_anuragbajpai@yahoo.com.

School Projects

GROW Society has launched a number of school projects to increase awareness about growth failure, obesity, Type 1 DM and Period Plus by close interaction with schools. Key part of the initiative is implementation of ***"GROW Society Teacher Training Module"*** a validated four session module to impart knowledge about pediatric endocrine disorders to teachers, who would then act a s bridge between the Society and the children. This would be followed by supervised growth monitoring, awareness sessions and assessment of children with endocrine disorders. A special section is devoted to training school staff about Type 1 DM management, including glucose monitoring, insulin injections, and sick day management. The Period Plus Arm would sensitize teachers, parents and young girls about period problems and help them cope with the them. Fat to Fit project has drafted age specific guidelines for tiffin food, canteen food and physical activity. These projects would be implemented in 10 schools as a pilot project followed by wide implementation.

Type 1 diabetes – Parents' meet, Dr Sirisha Kusuma B, Dr Leenatha Jakkidi, Hyderabad

On 2nd July we organized a meet for children with Type 1 diabetes (T1D) and their parents at Rainbow Children's Hospital, Banjara Hills, Hyderabad. We had small group discussions between parents and diabetes educators. Topics ranged from a brief talk by the educators refreshing parents' and children's understanding of the pathophysiology of T1D, to common and important topics like identifying and treating hypoglycemia, managing sugars at school, preventing long term complications by trying to achieve Hba1c goals, options for healthy diet etc. The program ended with a question and answer session with parents. In addition to the daily diabetes management related questions, one particularly important and relevant concern raised by a couple of parents was the widely varying levels of acceptance and cooperation from different school authorities. Some schools have been very open to the idea of helping children with checking blood glucose (BG) and taking insulin at school lunch hours. But certain other schools (one of those being, to our surprise, a high profile international school), despite having school nurses, refuse to help. Even when parents take responsibility of managing diabetes at school, the school authorities insist that any checking of BG or injecting Insulin be done in a secretive way, away from the other kids. The root cause seems a lack of understanding of what is meant by T1D, and having endless misconceptions about its treatment. Ignorance begets fear. Fear clouds judgement.

Though we usually provide all the parents with a detailed letter to be given at the school, it is evident that the schools need more education on the issue. Ultimately our goal of treating a child with T1D is not just achieving a good HbA1c, but also making sure that diabetes does not come in the way of a child's access to quality education, and his/her ability to reach full potential as a happy, healthy and successful adult. At the end, we decided to have some awareness meetings with school authorities in association with parent groups.

Kids drew some pictures depicting what they think of their condition and how they deal with it on a daily basis. Parents had time to interact with each other, exchange ideas on day to day management, and get moral support from the feeling that they are not alone in this fight. We dispersed with plans for the next meet.

This is a picture drawn by 6 year old girl about herself.

Dr Anju Virmani, New Delhi

International Yoga Day: On the occasion of International Yoga Day, on Sunday 18th June 2017, the Yog Dhyan Foundation and Revord organized a celebration, with a special yoga session and drawing competition at the Nirankari School, Tilak Nagar, Delhi. YDF has been working with poor families with type 1 diabetes (T1D), providing free glucostrips, quarterly A1c tests, annual eye and other checks, financial help, weekly yoga classes, networking,

and other help. It was a joyous function with 70 children and youth with T1D and their families participating. The volunteers were also those with T1D. After the prize distribution, sugar checking and dispensing glucostrips, everyone was treated to home made chole, fruit and other healthy snacks.

Parental Meet of Type 1 diabetes Children: On 12th August there was a meeting of parents of T1D children, from Delhi, Jaipur, Sikar, Haridwar, Gurgaon, Faridabad, and Ghaziabad, with older persons with T1D, to discuss psychological issues in coping with diabetes. Ms Srishti Puri, counsellor and diabetes educator, conducted the meeting. Parents found it useful to discuss problems and solutions in person, as an extension of the discussions they have been having on a Whatsapp group. Issues such as surreptitious insulin injections to induce hypoglycemia, stealing food, refusing to exercise or eat in a disciplined manner, refusing to test BG regularly, temper tantrums, school issues, were brought up by the parents. A question asked was: "what do we tell our children when they ask us when the diabetes will be cured". Some mothers were also bothered by the fathers expecting them to handle all problems single-handedly. The fathers agreed they would be more involved in diabetes care and work as a team.

The children had a parallel session wherein they made friends with each other, went out and played for a while, took their pre-lunch tests and doses before having lunch. Then they put forward their point of view to the parents of how difficult it was for them to cope with diabetes and also handle their parents. They explained that the constant restrictions, need for discipline, pressure to obey instructions, were exhausting, and they would like parents to be more understanding and less interfering. The newly diagnosed children benefitted from seeing the older children self-inject and decide their doses.

National Symposium on Growth, Paediatric and Adolescent Endocrinology, Dr. IPS Kochar, New Delhi

National Symposium on Growth, Pediatric and Adolescent Endocrinology was organised by Growth Hormone Research Society along with Indraprastha Apollo Hospital, Delhi Medical Association and Delhi-IAP on 10th & 11th of June, 2017. It was two days brainstorming session of paediatric endocrinology in which the first day, there was a hands on insulin pump workshop and extensive sessions covering pediatric and neonatal endocrine emergencies. Second day sessions were more of daily case scenario based management including common pediatric endocrine problems such as Growth monitoring, Bone age estimation, Newer guidelines of growth hormone therapy, management of Turner

syndrome, Obesity, PCOS, Gynecomastia in adolescent males, Early Puberty management, Neonatal Diabetes, MODY, Artificial Pancreas, Thyroid dysfunction in Obesity, sub clinical Hypothyroidism and Non-thyroidal illness syndrome. More than 30 national faculty and 40 experienced senior faculty chairpersons shared their experience and knowledge, benefiting over 150 delegates. Delhi Medical Council granted 11.5 credit hours for the symposium.

Dr Divyalakshmi, Chennai

"CME on Congenital Hypothyroidism" was organized by Division of Pediatric Endocrinology, Sri Ramachandra Medical College and Research institute (SRMC & RI), Chennai on 24th June 2017. Dr Anna Simon (CMC, Vellore) and Dr Sujatha Jagadeesh (Mediscans, Chennai) were the invited speakers. Dr Shriram Mahadevan (HOCS, Department of Endocrinology, SRMC & RI) was the chairperson. Around 70 delegates attended the CME. The program was highly interactive and well appreciated by the delegates.

Dr Meena Mohan, Coimbatore

A support group camp for children with diabetes was conducted on 30th April 2017, at Botanic Gardens, Coimbatore. The camp was attended by 25 children and their families. Experienced parents helped to troubleshoot the problems faced by parents of recently diagnosed children with type 1 diabetes. Children too enjoyed playing in the park.

A similar activity was conducted in Masonic Hospital auditorium on 22 January, in which 22 children and their families participated. Apart from emphasizing the importance of blood glucose monitoring, there was a magic show, which was enjoyed by all children and parents alike. A few mothers shared tips on millet cooking.

Dr Ahila Ayyavoo, Coimbatore

The annual camp for children with type 1 diabetes was conducted at G. Kuppuswamy Naidu Memorial Hospital, Coimbatore on 3rd of May 2017. Education was carried out on all aspects of management of T1D. The children had artistic activities such as drawing, colouring and music. They shared their practical experiences. Free HbA1c test was offered to the children attending the camp.

2nd Insulin Pump workshop for families, April 2017 , Dr Santosh Olety, Bengaluru

An annual meeting was held for families using insulin pumps, for empowering them with knowledge, problem sharing and parental interaction. Discussion regarding both medical and nonmedical issues such as making best use of insulin pump, financial schemes for pump purchase, discount price for insulin and consumables, non-permission of pumps to exam halls, overseas / domestic air travel requirements, portable insulin cold storage devices etc. were found useful by all.

Awards and Fellowships: Congratulations!

Dr Naina Bhat, Senior Resident in Pediatrics and in-charge of Pediatric Endocrinology at St Johns Medical College Hospital has been awarded the Allan Drash Fellowship 2017. She will start her observership in the Division of Pediatric Endocrinology and Diabetes at Stanford University School of Medicine from January 2018.

Dr Garima Chawla, Fellow in Pediatric Endocrinology at Sir Gangaram Hospital, New Delhi, has been awarded 1st Prize for her abstract on "Growth hormone therapy in Turner syndrome: Indian experience" and 3rd prize for her abstract on "Optimisation of growth in central precocious puberty with GnRH analogues" in oral paper presentation section at PEDICON 2017 held at Bengaluru.

Dr Mohammad Hayat Bhat, Lecturer, Department of Medicine, Govt Medical College, Srinagar, was awarded Fellowship of the American College of Endocrinology (FACE) in May 2017 at Austin, Texas.

Publications

Dr Shaila Bhattacharyya, Dr, Shobhi Anandi, Manipal Hospital, Bengaluru

1. Anandi VS, Shaila B. Evaluation of factors associated with elevated newborn 17 hydroxyprogesterone levels. J Pediatr Endocrinol Metab 2017 May 24;30(6):677-81.
2. Anandi VS, Bhattacharyya S, Banerjee B. Hashimoto's encephalopathy in a 10-year-old girl. Thyroid Res Pract 2017;14:89-91.

Dr Subramanian Kannan, Narayana Health City, Bommasanadra, Bengaluru

1. Akunuri S, Vuppu DK, Sapare AK, Bagde A, Murthy RV, Kannan S. Rapid onset obesity and Ondine's curse: a deadly syndrome. Int J Contemp Pediatr. 2017 May;4(3):1110-1114.
2. Mahadevan S, Sadacharan D, Kannan S, Suryanarayanan A. Does Time of Sampling or Food Intake Alter Thyroid Function Test? Indian J Endocrinol Metab. 2017 May-Jun;21(3):369-372.
3. Ramakrishna SH, Patil SJ, Jagadish AA, Sapare AK, Sagar H, Kannan S. Fructose-1,6-bisphosphatase deficiency caused by a novel homozygous Alu element insertion in the FBP1 gene and delayed diagnosis. J Pediatr Endocrinol Metab. 2017 May 23. doi: 10.1515/jpem-2017-0078. [Epub ahead of print].
4. Kannan S, Kulkarni P, Lakshmikantha A, Gadabanahalli K. Extramedullary Haematopoiesis Presenting as an Adrenal Mass. J Clin Diagn Res. 2017 Mar;11(3):TJ01.
5. Kannan S, Raju N, Kekatpure V, et al. Improving Bethesda Reporting in Thyroid Cytology: A Team Effort Goes a Long Way and Still Miles to Go….Indian J Endocrinol Metab. 2017 Mar-Apr;21(2):277-281.
6. Kannan S, Jain A, Tripathy R, Mahadevan S. Resistance to Thyroid Hormone - A Novel Mutation in THRβ-Gene from India. Indian J Pediatr. 2017 Mar;84(3):238-239.

Answers to Photo Quiz

Photoquiz 1:

1. Disproportionate short stature, acromelia, brachydactyly, upturned nose, hypertelorism, folds of skin seen over hands (Michelin baby appearance).
2. X-ray findings: Short metacarpals and phalanges, Cone shaped epiphysis
3. Acrodysostosis
4. DD for brachydactyly: Acrodysostosis, Pseudohypoparathyroidism, Pseudopseudohypoparathyroidism

Acrodysostosis is a rare primary bone dysplasia with only about 80 reported cases in literature. It is characterized by severe brachydactyly, peripheral dysostosis with facial dysostosis, nasal hypoplasia, and developmental delay. It is inherited in autosomal dominant or sporadic manner. In a few cases, it may be associated with resistance to multiple hormones like parathyroid, thyrotropin, calcitonin, GHRH and gonadotropins. Other x-ray findings include thickened skull bone and acetabular dysplasia.

Photoquiz 2:

1. Disproportionate short stature (short hands and legs), normal facies, head size appears normal, lumbar lordosis.
2. X-ray findings: Anterior beaking of vertebral body, platyspondyly, normal interpeduncular distance, short metacarpals and phalanges with metaphyseal changes.
3. Diagnosis: Pseudoachondroplasia

Pseudoachondroplasia is an autosomal dominant disorder due to mutation of COMP (cartilage oligomeric protein gene) gene. This is a rare disorder with incidence of 1 in 30,000. Clinical features include normal length at birth, decline in growth rate by age 2 years, leading to moderately severe disproportionate short-limb short stature, normal facies, waddling gait recognized at the onset of walking, brachydactyly, ligamentous laxity and joint hyperextensibility, valgus/ varus/ windswept deformity of the lower limbs, lumbar lordosis and mild scoliosis.

Radiological findings include normal skull and facial bone, anterior beaking of the spine, platyspondyly with normal interpeduncular distance, poorly formed acetabulum, late appearance and poorly formed femoral head epiphyses, medial beaking of femoral neck, short with flared metaphyses, small, irregular and fragmented epiphyses of long bones, proximal pointing of metacarpals, small irregular carpals and short phalanges.

Differences between Pseudoachondroplasia and Achondraplasia

Features	**Pseudoachondroplasia**	**Achondroplasia**
Skull & face	Normal	Abnormal
Spine	Platyspondyly +	No platyspondyly
Interpeduncular distance	Normal	Progressively decreases in lumbar spine
Epiphysis	Abnormal	Normal
Metaphysis	Abnormal	Abnormal
Trident hand	Absent	Present
Champagne pelvis	Absent	Present

ISPAE 2017 Scientific Programme

Day 1, 24th November 2017

0800 – 0830	**Registration**
0830 – 1100	**CSII (INSULIN PUMP) WORKSHOP** Insulin Pump Introduction, Indications & CGMS (30 min) Carbohydrate Counting (15 min) PUMP Nuts & Bolts (30 min) Hands on pump usage (30 min) Limitations / Difficulties of Pump Therapy (20 min) Future of T1DM Management (25 min)
1100 – 1130	**Tea**
1130 – 1300	**Growth** Molecular Genetics of GH Deficiency and Response to Treatment in India (30 min) Estrogen Receptor Blockade in Promotion of Growth (30 min) Safety of Growth Hormone Therapy (30 min)
1300 – 1400	**Lunch and Posters**
1400 – 1600	**Faculty Lectures on Novel Therapeutics** Genotype Phenotype Correlation in Hypogonadotropic Hypogonadism with special reference to Emerging Treatment Regimens (30 min) Closing the Loop: Artificial Pancreas (30 min) Novel Therapy in Adrenoleukodystrophy (30 min) Achondroplasia: Novel Therapies (30 min)
1600 – 1615	**Tea**
1615 – 1700	**Key Note Lecture** Bottoms Up: The Gut Microbiomes and Obesity and Diabetes (45 min)
1700 – 1830	**Faculty Lectures – Bone & Calcium** Newer Therapies in Bone Disease (30 min) Management of Hypocalcaemia (30 min) Management of Hypercalcemia (30 min)
1900	**Inauguration and Cultural Programme**
2030	**Dinner**

Day 2, 25th November, 2017

0800 – 0900	**Meet the Professors** Pubertal Induction Disorders of Adolescent Endocrinology
0900 – 1000	**Year in Review** GH, Thyroid, Type 1 DM, Adrenal, Puberty, Obesity
1000 – 1100	**Faculty Lectures on Management issues** Management of Resistant Rickets (30 min) Puberty & Fertility in Turner Syndrome (30 min)
1100 – 1115	**Tea**

1115 – 1215	**Faculty Lectures** Management of 46 XY DSD (30min) SGA: Management (30 min)
1215 – 1315	**Oral presentations**
1315 – 1415	**Lunch and Poster walk**
1415 – 1600	**Potpourri** Endocrine disruptors in the environment (15 min) Genetic Diagnosis in Infantile/Childhood Obesity (30 min) 2016 PES Guidelines for GH Therapy (20 min) Indian Experience: DXA Scan in Children (20 min) Craniopharyngioma (20 min)
1600 – 1700	**Thyroid** Thyrotoxicosis (30 min) Thyroid nodule: Panel discussion **(**30 min)
1700 – 1715	**Tea**
1715 – 1815	**Faculty Lectures** Update on DKA: ISPAD Guidelines (30 min) CAH–Neonatal Screening, Recent Advances in Management (30 min)
1815 – 1845	**Panel discussion:** PCOS & Hirsutism
1845 – 1945	**GBM**
2000	**Conference Banquet**

Day 3, 26th November 2017

Practical Pediatric Endocrinology

0800 – 0830	**Registration**
0830 – 0900	Endocrine Hypertension in Childhood
0900 – 0930	**Approach to Short Stature: Panel discussion**
0930 – 1000	Growth Charts – Current Views
1000 – 1030	Diabetic Ketoacidosis in resource poor settings
1030 – 1100	Childhood Obesity
1100 – 1115	**Tea**
1115 – 1145	Approach to DSD
1145 – 1215	Neonatal thyroid screening
1215 – 1245	Neonatal Hypoglycaemia and Beyond
1245 – 1315	**Neonatal Endocrinology: Panel discussion**
1315 – 1400	**LUNCH**
1400 – 1430	Vitamin D supplementation – for whom and how much?
1430 – 1500	Rickets Revisited
1500 – 1530	Management of Osteogenesis Imperfecta
1530 – 1600	**Electrolyte Disorders in Childhood: Panel discussion**
1600 – 1630	**Approach to Disorders of Puberty: Panel discussion**
1630 – 1700	How to Diagnose and How not to Misdiagnose Hypothyroidism
1700 – 1730	**Valedictory Function**

General Information

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ISPAD 2018

Reaching the Unreached

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