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,

The preparations to elect the new office bearers of ISPAE for the term 2019-2020 have been initiated. Dr Rajni Sharma, Assistant Professor, Division of Pediatric Endocrinology, AIIMS, New Delhi, has been appointed as Election Officer, and will be in touch with all of us shortly. The next ISPAE Annual General Body Meeting will be held during the ISPAD 2018 conference, HICC, Hyderabad, on Friday, October 12, 2018 between 6:30 PM and 7:30 PM at Session Hall 3. Please save the date. We hope you have registered for ISPAD 2018, which is in association with ISPAE.

This issue of CAPENEWS carries a nice summary of the Endocrine Society Guidelines on hypothalamic–pituitary and growth disorders in cancer survivors and a mini-review on the new classification of pseudohypoparathyroidism and related disorders. It also features tabulated -3, -2.5 and -2.25 height z-scores for Indian children 5-18 years, and an interesting case of genetically proven X-linked hypophosphatemic rickets. It also brings you news of meetings past and forthcoming. I am sure all those interested in pediatric endocrinology will find this issue useful. I thank all my team members, Drs Rajni Sharma, Sachin Mittal, Sweta Budyal, and Vani HN for their active participation in designing this issue and for their valuable contributions. My special thanks to Dr Anju Virmani, for her tireless efforts to make this issue a fantastic one.

Dr Vijaya Sarathi,
Editor, CAPENEWS

Golden Opportunities for Learning Pediatric Endocrinology

DM courses in Pediatric Endocrinology

Divisions of Pediatric Endocrinology, Department of Pediatrics from PGIMER, Chandigarh as well as AIIMS, NewDelhi are ready to begin DM courses in 'Pediatric Endocrinology'. The course is expected to start from next academic year at both centers.

GROW Society Learning Online Course in Pediatric Endocrinology

GROW Society Learning in association with MedEClasses Private Limited is launching an online Pediatric Endocrinology Course on September 16, 2018. The course covers all aspects of pediatric endocrinology with six sections on Growth, Thyroid, Puberty, Calcium, Glucose and Electrolyte disorders with six modules in each. Each module includes a masterclass video (30-90 minutes), pathophysiology animations, approach algorithms, evidence-based management guidelines, interactive case scenarios (5-15 per module) and pre and post competency tests. The modules would be supplemented by periodic E-Classes and regularly updated as per latest management guidelines. The course is targeted at pediatric and adult endocrine trainees, practicing endocrinologists, pediatricians and pediatric trainees. Please logon to http://learning.growsociety.in or contact Dr Anurag Bajpai (info.dranuragbajpai@gmail.com) for details.

Hearty Welcome to New ISPAE Members

Deepika Harit, New Delhi	Zalak Upadhyaya, Bangalore
TamalLaha, Kolkata	Ram Menon, Michigan
Sajili Mehta, Mumbai	Amit Singhal, New Delhi
Mahesh Maheshwari, Bhopal	Anjali Verma, Rohtak
Mitrabhanu Satpathy, Jamshedpur	

Asia Pacific Paediatric Endocrine Society (APPES)

10th BIENNIAL SCIENTIFIC meeting

Chiangmai, Thailand
7-10 Nov. 2018

APPES 2018
Chiang Mai, Thailand

APPES
ASIA PACIFIC PAEDIATRIC ENDOCRINE SOCIRTY

THAI SOCIETY for PEDIATRIC ENDOCRINOLOGY

PROGRAM HIGHLIGHTS

- Adrenal steroidogenesis and its disorders
- Fibroblast growth factor-23 as a novel regulator of calcium and bone metabolism
- Translating real world data into improved diabetes outcomes
- New insights into human sex development
- Thyroid disorders following Fukushima Nuclear Power Plant accident
- Borderline neonatal TSH levels and educational and development outcomes
- Application of Next generation sequencing in bone-related disorders
- New technology and safety of GH
- Endocrine disruptors and its role on DSD
- Why prenatal treatment of CAH should not be done
- New technologies for the treatment of T1DM
- Stool microbiome and stool transplant

MEET THE WORLD RENOWNED SPEAKERS

- **John Achermann**, UK
- **Peter Adolfsson**, Sweden
- **Syed Faisal Ahmed**, Scotland
- **Viji Bhatia**, **India**
- **Narattaphol Charoenphandhu**, Thailand
- **Sung Yoon Cho**, Korea
- **Jin-Ho Choi**, Korea
- **Maria Craig**, Australia
- **Wayne Cutfield**, **New** Zealand
- **Chris Houk**, USA
- **Michelle Jack**, Australia
- **Tomoyuki Kawamura**, Japan
- **Peter Lee**, USA
- **Supawadee Likitmaskul**, Thailand
- **Kah Yin Loke**, Singapore
- **Pat Mahachoklertwattana**, Thailand
- **Ram Menon**, USA
- **Walter Miller**, USA
- **Noriyuki Namba**, Japan
- **Pisit Pitukcheewanont**, USA
- **Michel Polak**, France
- **Rodolfo Rey**, South America
- **Yiping Shen**, China
- **Vichit Supornsilchai**, Thailand
- **Shinichi Suzuki**, Japan





Deadline of Registration
Early Bird: 27th August 2018
Standard: 5th October 2018
Late: after 5th October 2018
Deadline of abstract submission: 30th July 2018
Registration is now open at www.appes2018.org

Summary of Recommendations from Endocrine Society Clinical Practice Guideline on Hypothalamic–Pituitary and Growth Disorders in Survivors of Childhood Cancer

Sklar CA et al, J Clin Endocrinol Metab. 2018;103:2761-84.

Short stature/impaired linear growth in childhood cancer survivors

Diagnosis and monitoring of short stature/impaired linear growth in childhood cancer survivors

- 1.1 We recommend prospective follow-up of linear growth for childhood cancer survivors at high risk for short adult height, namely those exposed to cranial radiation therapy, craniospinal irradiation, or total body irradiation at a young age and those with a history of inadequate weight gain or prolonged steroid requirement.
- 1.2 We recommend measuring standing height and sitting height in childhood cancer survivors treated with radiation that included the spine (*i.e.*, total body irradiation, craniospinal irradiation, as well as radiation to the chest, abdomen, or pelvis).
- ***Technical remark:*** Sitting height is measured directly using a sitting height stadiometer, and the lower segment can be determined by subtracting sitting height from standing height. Alternatively, the lower segment can be determined by measuring from the pubic symphysis to the floor, and the upper segment can be determined by subtracting leg length from height. The upper to lower segment ratio can then be calculated but differs depending on the method used and ethnicity. In situations where clinicians are unable to measure sitting height, measuring arm span and comparing it to standing height will provide an estimate of spinal foreshortening due to prior spinal radiation.

Treatment of short stature/impaired linear growth in childhood cancer survivors

- 1.3 We suggest against using growth hormone in cancer survivors who do not have growth hormone deficiency to treat for short stature and/or poor linear growth following spinal irradiation.
- 1.4 We suggest against treatment with growth hormone in children with short stature and/or impaired linear growth who are being treated with tyrosine kinase inhibitors.

Growth hormone deficiency in childhood cancer survivors

Diagnosis of growth hormone deficiency in childhood cancer survivors

- 2.1 We recommend lifelong periodic clinical assessment for growth hormone deficiency in survivors treated for tumors in the region of the hypothalamic–pituitary axis and in those exposed to hypothalamic–pituitary axis radiation treatment ≥18 Gy (*e.g.*, various brain tumors, nasopharyngeal carcinoma, acute lymphoblastic leukemia, lymphoma).
- ***Technical remark:*** The consensus of the writing committee is to assess height in children every 6 to 12 months.
- 2.2 We recommend against relying solely on serum insulin-like growth factor-1 levels in childhood cancer survivors exposed to hypothalamic–pituitary axis radiotherapy to make the diagnosis of growth hormone deficiency.

- 2.3 We advise using the same provocative testing to diagnose GHD in childhood cancer survivors as are used for diagnosing growth hormone deficiency in the noncancer population.
- 2.4 We recommend against the use of growth hormone– releasing hormone alone or in combination with arginine in childhood cancer survivors to diagnose growth hormone deficiency after hypothalamic–pituitary axis radiation.
- 2.5 We suggest against using spontaneous growth hormone secretion (*e.g.*, 12-hour overnight sampling) as a diagnostic test in determining GH deficiency in childhood cancer survivors.
- 2.6 We recommend that formal testing to establish a diagnosis of GHD is not required in childhood cancer survivors with three other confirmed anterior pituitary hormone deficits.
- 2.7 We recommend retesting adult cancer survivors exposed to hypothalamic–pituitary axis radiation treatment and with a diagnosis of isolated growth hormone deficiency in childhood.

Treatment of growth hormone deficiency in childhood cancer survivors

- 2.8 We recommend offering GH treatment in childhood cancer survivors with confirmed GHD based on the safety and efficacy demonstrated in that population.
- 2.9 We suggest waiting until the patient has been 1 year disease-free, following completion of therapy for malignant disease, before initiating growth hormone treatment. (2|⊕OOO)
- 2.10 In childhood cancer survivors who have chronic stable disease and thus may not ever be "disease-free" (particularly survivors treated for optic pathway tumors), we advise discussing the appropriateness of growth hormone treatment and its timing with their oncologist.
- 2.11 We advise treating GH-deficient childhood cancer survivors with similar GH treatment regimens as are appropriate for individuals with GHD from the noncancer population.

Central precocious puberty in childhood cancer survivors

Diagnosis of central precocious puberty in childhood cancer survivors

- 3.1 We recommend periodically assessing childhood cancer survivors for evidence of central precocious puberty (CPP) if they have a history of hydrocephalus, tumors developing in/ near the hypothalamic region, and/or have been exposed to hypothalamic–pituitary radiation.
- 3.2 We recommend against using testicular volume as the primary or sole indicator of degree of sexual development in male childhood cancer survivors previously treated with gonadotoxic agents, such as alkylating agents or testicular radiotherapy.
- 3.3 We recommend measuring serum testosterone, preferably using liquid chromatography–tandem mass spectroscopy, and luteinizing hormone levels prior to 10:00 AM to complement the clinical assessment of male childhood cancer survivors who are suspected of or are at risk for developing central precocious puberty and were exposed to gonadotoxic treatments.
- ***Technical remark:*** Clinicians need to interpret plasma LH levels in patients exposed to gonadotoxic treatments in the context of their medical history and physical examination. Elevated LH levels in such patients may be due to primary gonadal injury rather than to the onset of central puberty.

Treatment of central precocious puberty in childhood cancer survivors

- 3.4 We advise that the indications and the type of treatment regimens for CPP in childhood cancer survivors should be similar to those used for CPP in the noncancer population.

Hypogonadotropic hypogonadism in childhood cancer survivors

Diagnosis of luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors

- 4.1 We recommend screening for LH/ FSH deficiency in childhood cancer survivors exposed to hypothalamic–pituitary axis radiation at doses ≥30 Gy and in those with a history of tumors or surgery affecting the hypothalamic–pituitary axis region.
- 4.2 We advise using the same strategies to diagnose LH/ FSH in childhood cancer survivors as are used in the noncancer population.

Treatment of luteinizing hormone/follicle-stimulating hormone deficiency in childhood cancer survivors

- 4.3 We advise following the same treatment approach to LH/FSHdeficiency in childhood cancer survivors as is appropriate in the noncancer population.

Central hypothyroidism–thyroid-stimulating hormone deficiency in childhood cancer survivors

Diagnosis of central hypothyroidism in childhood cancer survivors

- 5.1 We recommend lifelong annual screening for TSH deficiency in childhood cancer survivors treated for tumors in the region of the hypothalamic–pituitary axis and those exposed to ≥30 Gy hypothalamic–pituitary radiation.
- 5.2 We advise using the same biochemical tests to screen for TSH deficiency in childhood cancer survivors as are used in the noncancer population.
- 5.3 We recommend against using serum triiodothyronine, TSH surge analysis, or thyrotropin-releasing hormone stimulation to diagnose TSH deficiency.
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Treatment of thyroid-stimulating hormone deficiency in childhood cancer survivors

- 5.4 We advise using the same approach to treat TSH deficiency in childhood cancer survivors as is used in the noncancer population.

Adrenocorticotropic hormone deficiency in childhood cancer survivors

Diagnosing adrenocorticotropic hormone deficiency in childhood cancer survivors

- 6.1 We recommend lifelong annual screening for ACTH deficiency in childhood cancer survivors treated for tumors in the hypothalamic–pituitary region and in those exposed to ≥30 Gy hypothalamic–pituitary radiation.
- 6.2 We suggest screening for ACTH in childhood cancer survivors exposed to between ≥24 Gy and 30 Gy hypothalamic–pituitary radiation who are >10 years post-radiation or develop clinical symptoms suggestive of ACTH deficiency.
- 6.3 We advise using the same screening and dynamic testing procedures to diagnose ACTH deficiency in childhood cancer survivors as are used in the noncancer population.
- ***Technical remark:*** Clinicians should consider the influence of oral estrogen on total cortisol levels, as it can increase cortisol-binding globulin raising total, but not free, cortisol levels.

Treating adrenocorticotropic hormone deficiency in childhood cancer survivors

- 6.4 We advise that clinicians use the same glucocorticoid regimens as replacement therapy in childhood cancer survivors with ACTH deficiency as are used in the noncancer population with ACTH deficiency. (Ungraded Good Practice Statement)
- 6.5 We recommend that clinicians instruct all patients with ACTH deficiency regarding stress dose and emergency glucocorticoid administration and instruct them to obtain an emergency card/bracelet/necklace regarding adrenal insufficiency and an emergency kit containing injectable high-dose glucocorticoid.

Inactivating Parathyroid Hormone/Parathyroid Hormone-Related Protein Signalling Disorder (iPPSD): New EuroPHP network classification

SwetaBudyal, Consultant Endocrinologist, Fortis Hospital, Mulund, Mumbai, Maharashtra

Pseudohypoparathyroidism (PHP) is a highly heterogeneous group of disorders resulting from target organ resistance to the action of parathyroid hormone (PTH). Until now, PHP was classified based on clinical and biochemical criteria, like the presence of AHO (Albright's hereditary osteodystrophy), hormone resistance, urinary cAMP and phosphaturic response to exogenous PTH and *Gs*α activity. The old classification is illustrated in table 1.

However, several patients we see in our clinical practice do not fit well into any of the described classes due to overlapping features. The limitations experienced with the traditional classification are:

1. Mild resistance to PTH and other hormones has been described in patients with pPHP.
2. AHO phenotype has been one of the bases of the former classification. However, AHO phenotype has been described in patient with PHP1b resulting from epigenetic abnormalities of GNAS in previous case reports.
3. Clinical and biochemical overlap has been observed in PHP cases resulting from GNAS mutations and Gsα mutations.

To overcome these limitations and to create a uniform terminology based on current understanding of these disorders, the EuroPHP network has proposed a new classification. In this classification, the term "inactivating PTH/PTHrP signalling disorder" (iPPSD) has been used to describe the disorders related to abnormalities formerly termed as PHP and related disorders.

For the diagnosis of iPPSD, major and minor criteria have been laid down as depicted in table 2. A minimum of one major criterion is mandatory for the diagnosis of iPPSD. However, in patients with Brachydactyly type E as the only major criterion, two additional minor criteria must be satisfied to establish the diagnosis of iPPSD.

Table 1: Former classification with clinical, biochemical and molecular abnormalities

	PHP1a	PHP1c	pPHP	POH	PHP1b	Acrodysostosis type 1	Acrodysostosis type 2	HTN and Brachydactyly syndrome	Bloomstrand Chondrodysplasia	Eiken syndrome
Molecular defect	Inactivating Gsα mutations	Inactivating Gsα mutations	Inactivating Gsα mutations	Inactivating Gsα mutations	Methylation defects	Inactivating *PRKAR1A* mutations	Activating *PDE4D* mutations	Activating *PDE3A* mutations	Inactivating *PTH1R* mutations	Inactivating *PTH1R* mutations
Parental Origin	Maternal	Maternal	Paternal	paternal	Maternal	AD	AD	AD	AR	AR
Hormonal resistance	PTH, TSH, GHRH, FSH, LH, Calcitonin	PTH, TSH, GHRH, FSH, LH, Calcitonin	No	No	PTH TSH	PTH TSH	PTH, TSH, GHRH, FSH, LH, Calcitonin	Unknown	Unknown	Mild PTH
Additional clinical features	AHO +	AHO +		No	No	AHO+ Facies	AHO+ Facies	AHO + Hypertension	Lethal, Skeletal dysplasia, abnormal breast and tooth development Accelerated ossification	Severe skeletal dysplasia, dwarfism, Retarded ossification
Urinary CAMP to exogenous PTH	Blunted	Blunted	Normal	Normal	Blunted	Normal	Normal	Unknown	Unknown	Unknown
Urinary Phosphate to exogenous PTH	Blunted	Blunted	Normal	Normal	Blunted	Blunted	Blunted	Unknown	Unknown	Unknown
Erythrocyte Gsα activity	Reduced	Normal	Reduced	Reduced	Normal	Normal	Normal	Unknown	Unknown	Unknown

Table 2: Criteria for diagnosis of iPPSD

Major Criteria	Minor Criteria
1. PTH Resistance 2. Ectopic Calcification 3. Brachydactyly type E	1. TSH resistance 2. Other hormonal resistances 3. Motor or cognitive retardation 4. Antenatal or postnatal growth retardation 5. Overweight/Obesity 6. Flat nasal bridge and/or maxillary hypoplasia and/or round face

The new classification also has room to accommodate the disorders related to PTH/PTHrP signalling, with unknown molecular defects or new molecular defects which may be discovered in the future. This new futuristic classification based on molecular defects and corresponding entities from former classification is described in table 3.

Table3: New EuroPHP nomenclature based on molecular defects

iPPSD	Clinical/Biochemical diagnosis based on major/minor criteria
iPPSD 1	**Inactivating *PTH1R*mutations:**Bloomstrand and Eiken dysplasia
iPPSD 2	**Inactivating Gsα mutations:**PHP1a, PHP1c, pPHP, POH
iPPSD 3	**Methylation changes at *GNAS* DMRs:**PHP1b
iPPSD 4	***PRKAR1A* mutations leading to reduced PKA activity:** Acrodysostosis type 1
iPPSD 5	**Activating *PDE4D*mutations:**Acrodysostosis type 2
iPPSD 6	**Activating *PDE3A*mutations:**Hypertension with Brachydactyly syndrome
iPPSDx	**Unknown molecular defects**
iPPSD n+1	**Newer molecular defects**

PTH: parathyroid hormone, PHP: pseudo-hypoparathyroidism, pPHP: pseudo-pseudo-hypoparathyroidism, POH: progressive osseous heteroplasia

Thus, the new nomenclature takes care of the clinical overlap seen in different classes and provides greater flexibility to accommodate new defects. However, it does have a few limitations. The new classification does not consider the parental origin of genetic or epigenetic defects, which may be important in genetic counselling. Another point is the inability to classify patients just based on clinical and biochemical features in the absence of genetic information, which may be difficult to obtain in resource poor countries. Using a dual classification system may the more realistic and clinically relevant approach at this time.

Reference

Thiele S, Mantovani G, Barlier A, et al. From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP. Eur J Endocrinol 2016;175:P1-P17.

-3, -2.5 and -2.25 height z-scores for Indian children between 5 and 18 years

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The Indian Academy of Pediatrics (IAP) recommends that all pediatricians use the IAP 2015 charts for assessment of growth in children more than 5 years.3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles for height, weight and body mass index have been reported earlier. However, other commonly used height z-scores in routine endocrine/pediatric practice such as -3, -2.5 and -2.25 are not reported. -3 height z-scores are essential to define pathological short stature whereas -2.5 and -2.25 height z-scores represent the auxological criteria for intervention in children born small for gestational age (SGA) with poor catch-up growth, and idiopathic short stature (ISS) respectively. Here, we provide height measurements corresponding to -3, -2.5 and -2.25 z-scores for Indian children aged between 5 and 18 years. These may be useful as a ready reckoner for an endocrinologist or a pediatrician who evaluates children with growth disorders.

	Boys			Girls		
Age (y)	-3 SD	-2.5 SD	-2.25 SD	-3 SD	-2.5 SD	-2.25 SD
5	93.5	95.9	97.3	92.2	94.4	95.8
5.5	96.0	98.5	99.9	94.6	96.9	98.3
6	98.5	101.0	102.5	96.9	99.3	100.8
6.5	101.0	103.5	105.1	99.1	101.7	103.3
7	103.4	106.1	107.7	101.4	104.1	105.8
7.5	105.8	108.5	110.2	103.6	106.5	108.3
8	108.1	110.9	112.6	105.9	108.9	110.8
8.5	110.4	113.3	115.0	108.2	111.4	113.3
9	112.6	115.5	117.3	110.5	113.9	115.9
9.5	114.7	117.7	119.6	113.0	116.4	118.5
10	116.8	119.9	121.8	115.5	119.1	121.2
10.5	118.9	122.1	124.1	118.1	121.8	124.0
11	121.1	124.4	126.4	120.8	124.5	126.7
11.5	123.2	126.7	128.8	123.5	127.2	129.4
12	125.5	129.0	131.2	126.1	129.7	131.9
12.5	127.7	131.4	133.7	128.5	132.0	134.2
13	130.0	133.9	136.2	130.7	134.1	136.2
13.5	132.3	136.3	138.7	132.6	135.9	137.9
14	134.5	138.6	141.1	134.3	137.4	139.4
14.5	136.6	140.9	143.4	135.7	138.7	140.6
15	138.6	142.9	145.5	136.8	139.8	141.6
15.5	140.4	144.9	147.5	137.8	140.7	142.4
16	142.1	146.6	149.2	138.7	141.4	143.1
16.5	143.7	148.2	150.9	139.5	142.1	143.7
17	145.3	149.8	152.4	140.2	142.7	144.3
17.5	146.8	151.4	154.0	140.9	143.3	144.8
18	148.4	152.9	155.5	141.5	143.9	145.3

Khadilkar V, Yadav S, Agarwal KK, Tamboli S, Banerjee M, Cherian A, et al. Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. Indian Pediatr2015; 52(1):47-55.

Friedreich's ataxia associated diabetes mellitus- Lessons from a case

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Introduction

Friedreich Ataxia (FA) is an autosomal recessive, progressive neurodegenerative disease caused in 96% cases by homozygous expansion of GAA repeats in the first intron of the *FXN* gene. It is characterized by neurologic abnormalities including ataxia, dysarthria, areflexia and loss of proprioception. In addition, non-neurologic problems like cardiomyopathy and scoliosis are very common. Diabetes mellitus (DM) has been reported in 8-32% of cases of FA.

We report a case snippet of a boy with FA who presented with incidentally detected severe hyperglycemia to highlight unique aspects of DM in FA.

Case Report

A 15 yo Indian boy presented with progressive difficulty in walking and fine motor activities, and frequent falls over a period of 2y. Considering his difficulties in reading and writing, he was initially diagnosed to have dyslexia. However, during evaluation of muscle weakness, he was diagnosed to have concentric left ventricular hypertrophy, and was put on beta blockers. On further testing, he was detected to have hyperglycemia (blood glucose 325 mg/dL, HbA1c 12.2%). No osmotic symptoms were present. The child was not obese (160 cm, 50 kg, BMI 19 kg/m2) and had no signs of insulin resistance. Urine ketones were positive, but there was no acidosis. The diabetes was initially managed with basal bolus insulin therapy. Genetic work-up confirmed homozygous expansion of GAA repeats in intron 1 of *FXN* gene, confirming the diagnosis of Friedreich's ataxia, along with point mutation in *ACO2* gene. Anti-GAD 65 antibodies were borderline positive (19.7 IU/L, N < 10) but other autoantibodies (ICA, IA2, ZnT8) were negative; 7 months after diagnosis of diabetes, C-peptide was documented to be high (5.57 ng/mL, N 0.8 – 3.8 ng/mL).

After initial glycemic control, insulin was tapered, and he was given sitagliptin 100 mg/day and metformin 1500 mg/day (gradually increasing doses), with which good glycemic control was achieved. However, because significant worsening of ataxia was noted on this dose of metformin, the dose was tapered to 850 mg/day and then to 500 mg/day over a period of 9 months, which was associated with improvement in ataxia. However, no increase in serum lactate was seen at any point of time. During tapering of metformin, basal insulin (glargine) was added for better control of blood glucose. Sitagliptin was stopped after 9 months and patient was continued on low dose metformin (500 mg/day) and basal insulin (0.35 unit/kg). On this, follow up HbA1c was 6.5% and most documented blood glucose values were between 100-130 mg/dL before meals and up to 180 mg/dL after meals.

Discussion

Diabetes mellitus is a well-known complication of FA. The average time of diagnosis is usually reported to be 10-15y after onset of neurological manifestations, but it can occur

even at the time of first presentation. Since the onset can be abrupt and severe, including ketoacidosis, all patients with FA should be screened annually for diabetes. HbA1c is not recommended as a screening test since hyperglycemia can develop acutely, hence screening should be done by fasting blood glucose and glucose tolerance test.

Several possible mechanisms of diabetes have been postulated. The gene product of *FXN* gene, frataxin is important in the assembly of iron-sulphur clusters in mitochondria, which in turn is important in ATP production. In pancreatic β cells, this failure causes uncoupling of stimulus- dependent secretion of insulin from β cells, triggering of apoptosis of β cells caused by excess iron accumulation, and production of reactive oxygen species. The mutation in *ACO2* gene found in our patient affects function of aconitase enzyme thereby interfering in ATP generation via Krebs's cycle. At the level of peripheral tissues, insulin resistance has been documented. Evidence of downregulation of the transcription coactivator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) has led to use of thiazolidinediones in this condition.

Several agents have been tried in the treatment of DM, but evidence-based guidelines are lacking. Insulin therapy should be given to those who present with significant hyperglycemia and ketoacidosis. Metformin inhibits complex 1 and 2 of the electron transport chain of mitochondria, therefore it needs to be used cautiously and in the lowest possible dose. Since downregulation of PPAR-γ/ PGC-1α is documented in FA, use of pioglitazone may lead to increased frataxin levels through a positive feedback mechanism between PGC-1α. However, thiazolidinediones are associated with fluid retention and can possibly worsen the risk of cardiac failure, the most common cause of death in FA. Incretin analogues have been shown to prevent apoptosis in both β-cells and neuronal cells however further data of their safety and efficacy is needed.

Summary

DM is a common complication in FA and is thought to result primarily from non-autoimmune β cell failure. Since the presentation can be acute and severe, all patients need to be screened annually, but HbA1c is not recommended. The pharmacologic management depends on the severity of hyperglycemia. Physicians need to be aware of the pros and cons of oral antidiabetic medications so that appropriate therapy can be given to the patients.

Suggested readings:

1. Corben LA, Lynch D, Pandolfo M, Schulz JB, Delatycki MB, Clinical Management Guidelines Writing Group. Consensus clinical management guidelines for Friedreich ataxia. Orphanet J Rare Dis. 2014; 9:184.
2. Cnop M, Mulder H, Igoillo-Esteve M. Diabetes in Friedreich ataxia. J Neurochem. 2013;126 S1:94–102.
3. Greeley NR, Regner S, Willi S, Lynch DR. Cross-sectional analysis of glucose metabolism in Friedreich ataxia. J Neurol Sci. 2014;342:29–35.
4. Pappa A, Häusler MG, Veigel A, Tzamouranis K, Pfeifer MW, Schmidt A, et al. Diabetes mellitus in Friedreich Ataxia: A case series of 19 patients from the German-Austrian diabetes mellitus registry. Diabetes Res Clin Pract. 2018;141:229–36.
5. Ran S, Abeti R, Giunti P. Diabetes in Friedreich's ataxia. In Barbetti F, Ghizzoni L, Guaraldi F (eds): Diabetes Associated with Single Gene Defects and Chromosomal Abnormalities. Front Diabetes. Basel, Karger, 2017, vol 25, pp 172−181.

X Linked Dominant Hypophosphatemic Rickets - A Case Report

Dhivya S, RV Jeyabalaji, Karthik Raj, Jenish Rajma, G Mathevan, Madhurai, Tamilnadu

A6yo girl was hospitalized for evaluation of bowing of both legs since the age of 2y, which increased gradually, leading to pain while walking for the last 1 month. Her paternal grand-mother and aunt had similar complaints. She was the first-born child of anonconsanguineous marriage. She was diagnosed outside as having nutritional rickets, and treated with vitamin D and calcium supplementation for past 6 months, but with no improvement.

On examination, the child had bilateral tibia vara (fig 1A), exaggerated lumbar lordosis, mild wrist widening, Harrison's sulcus and waddling gait. Her height was 103 cm (< -3SD) and weight was 22.5 kg. Biochemical evaluation results are summarized in table 1.

Table 1: Summary of biochemical results

Parameters	Patient values	Reference range
Serum calcium	9.3	8.8-10.8 mg/dl
Serum phosphorus	2.3	3.5-5.0 mg/dl
Serum alkaline phosphatase	294	40-140 IU/L
Blood urea	13	10-50 mg/dl
Serum creatinine	0.5	0.3-0.6 mg/dl
Serum potassium	4.2	3-5-5.0mEq/L
Arterial blood pH	7.40	7.35-7.45
Serum 25OH Vitamin D	49	20 -100 ng/ml
Serum 1,25$(OH)_2$ vitamin D	57.9	34.87-88.81 pg/ml
Serum intact PTH	82.4	14-72 pg /ml
Spot urine creatinine	74 mg/dl	
Spot urine phosphorus	31 mg/dL	
TMP/GFR	3.0	3.5-5
24h-urinary calcium	10	

Blood investigations revealed normal calcium, hypophosphatemia and normal alkaline phosphatase. Renal function tests, serum electrolytes, blood pH and 25(OH) vitamin D were normal. Serum 1,25$(OH)_2$vitaminD was inappropriately normal for low serum phosphorus. Serum intact PTH was slightly elevated. PTH. Urine examination revealed only phosphaturia; there was no proteinuria, glycosuria or hypercalciuria. Roentgenography revealed bilateral tibia vara and rachitic changes including cupping, fraying and splaying at the ends of the long bones (fig 1B and 1C). Bone age normal. Genetic analysis showed a pathogenic heterozygous 7 base pair duplication (c.1925-1931dup) in exon 19 of *PHEX* gene that results in frameshift and premature termination of the protein 4 amino acids downstream to the codon 645 (p.Ala645LysfsTer4). Hence, the diagnosis of X-linked dominant hypophosphatemic rickets was made.

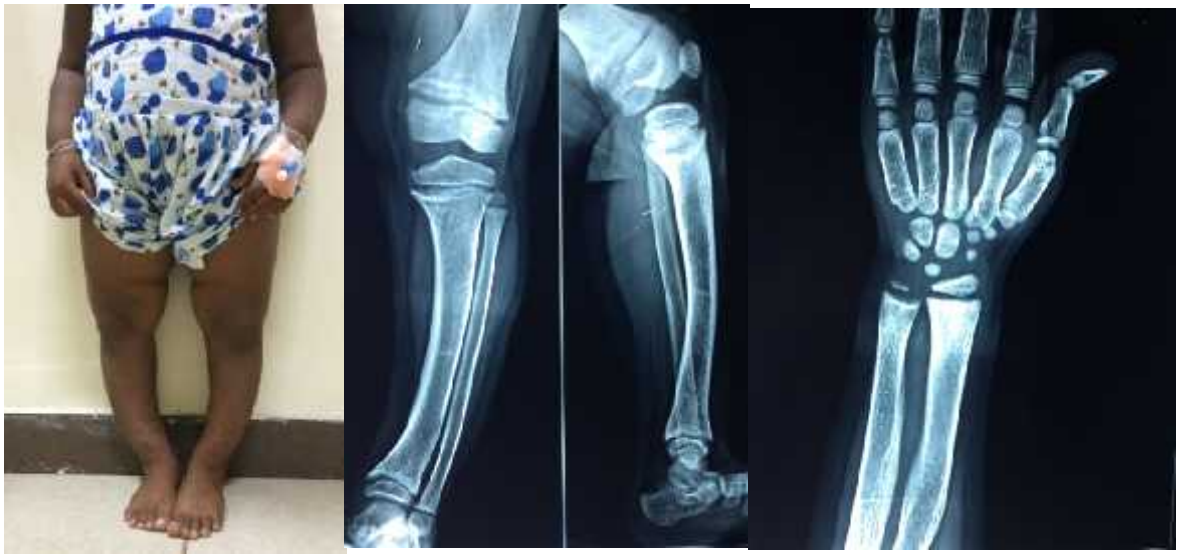

Fig 1: Clinical photograph depicting tibia vara both legs (1A) and roentgenograms showing rachitic changes at the ends of long bones (11B and 1C).

Patient was treated with oral alfacalcidiol 0.25 µg twice daily and phosphorus 500 mg twice daily, and is on follow up. Opinion was sought from an orthopedician, who advised corrective surgery once the child attains maturity.

Discussion

X-linked hypophosphatemic rickets (XLHR) is the commonest among the inherited hypophosphatemic rickets. Estimated incidence is 1:20,000 caused by mutation in **P**hosphate regulating gene with **H**omology to **E**ndopeptidases (PHEX) located on the **X** chromosome [1,2]. It is inherited as X-linked dominant. The classical physiologic defect in XLHR is impaired proximal renal tubular reabsorption of phosphate [3].

Inactivating mutations in *PHEX gene* result in increased synthesis and secretion of FGF23 [4]. The increased circulating concentration of FGF23 is responsible for the biochemical phenotype of XLH which includes phosphaturia, hypophosphatemia and inappropriately low or normal $1,25(OH)_2$ vitamin D [1,6].

XLHR is often misdiagnosed as nutritional rickets, as in our patient, who was treated with oral supplementation of calcium and cholecalciferol [5]. Clinical presentation in children with XLHR consists of predominant lower limb involvement. There is increased frequency of dental problems such as abscess or enamel problems. Our patient did not have any dental abnormalities. Identifying family history and screening in infancy leads to early recognition of XLHR, even before rachitic deformities are evident.

Diagnostic evaluation should include fasting serum and urine phosphate and creatinine to confirm hypophosphatemia, to determine the tubular threshold maximum for phosphate (TMP/GFR). 25-OHD is tested to exclude vitamin D deficiency, while 1,25(OH)2D in XLHR is inappropriately low or normal. PTH is frequently mildly elevated at diagnosis as like in our patient. Alkaline phosphatase is not much elevated in our patient as expected for this severity of bony changes.

Treatment of XLHR includes both activated vitamin D (calcitriol or alfacalcidol) and phosphate to correct these deficiencies [5]. It should be remembered that overtreatment with phosphorus and resultant secondary hyperparathyroidism may be harmful for the patient. We started both alfacaldiol and phosphate in therapeutic doses and she was followed up every 3 months on an outpatient basis, for monitoring her growth parameters, serum calcium, phosphate, alkaline phosphate and creatinine, and urine calcium. The patient was also advised annual ultrasound of the abdomen to rule out nephrocalcinosis. Radiological evaluation is needed to exclude the physiological bowing and bone dysplasia.

Growth hormone (GH) has been tried as an adjunct therapy in XLHR. Treatment with rhGH has been shown to result in an improvement in linear growth, a transient increase in serum phosphate and a transient decrease in urinary phosphate excretion [7,8,9]. Increased serum alkaline phosphatase activity, worsening leg deformities and worsening body disproportion have been reported after GH therapy [10]. We have not offered GH therapy to our patient. Recently, a monoclonal antibody against FGF23 (BUROSUMAB) has been approved by FDA for the management of XLHR.

Conclusion: Identification of genetic defects is useful to confirm the diagnosis of a child with refractory rickets and helps in optimization of therapy.

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My visit to University of Lübeck, Germany

Rajni Sharma, AIIMS, New Delhi

I had the privilege to visit Dr Olaf Hiort, Professor of Pediatric Endocrinology at University of Lübeck, Germany, under our collaborative ICMR-BMBF project "Improving Diagnosis and Management of Disorders of Sex Development in India". Dr Hiort has a long association with ISPAE; he was conferred Honorary Membership of ISPAE in 2015 in recognition of his immense contribution to our society.

Here I wish to share some informal observations with ISPAE members.

DSDs in childhood pose a challenge to pediatricians, both in terms of diagnosis and management. Moreover, socio-cultural taboos related to the subject pose an additional realm that needs to be considered when managing these disorders. We in India, have a long way to go in terms of improving the existing facilities for children with these conditions.

ProfHiort is a pioneer and one of the leads of the Euro-DSD network, which is an initiative of COST (European Cooperation in Science and Technology). DSD-net is a network of all people interested in DSD, including scientists, clinicians and patients with the aim to "*obtain new knowledge on the biological pathways of sex development in humans, and provide information on management for those physicians and psychologists caring for people with DSD*". (check out (www.DSD-net).

Prof Hiort heads the Pediatric Endocrinology Unit of the University of Lübeck, which is a referral centre for management of DSD in Germany. He has an excellent team working with him, including Dr Ralf Werner who is a molecular geneticist. The DSD clinic starts at 8 am, with a meeting of the multidisciplinary team consisting of Dr Hiort, the pediatric surgeon, geneticist, psychologist, gynaecologist and residents. The cases scheduled for appointments are discussed in detail along with their biochemical, radiological and genetic reports before the clinic starts. It was indeed heartening to see to well-adjusted adolescent girls with androgen insensitivity syndrome with full knowledge of their condition. Parents of children with DSD had many questions for the team, which Dr Hiort answered with a lot of patience, explaining the pathophysiology and diagnostic plan in detail.

I had the opportunity to talk to Dr Marion Rapp who wasin-charge of the German arm of the DSD-life study. Briefly, this was a study with a large sample size (> 900) that assessed to the quality of care and patient satisfaction with care in individuals with DSD in 14 centers across six European countries. She informed me about the study design, proformas, outcomes and operational challenges of the study.

I also visited Prof Paul-Martin Holterhus at the Pediatric Endocrinology unit at the University of Keil, the sister-town of Lübeck. He has a very sophisticated laboratory that performs HPLC/LCMS for steroid profiling for adrenal and gonadal disorders, the ideal method for measuring steroids in small children. The Keil laboratory receives over 100 samples every day for steroid profiling and has immensely contributed towards creating a database for normative values of steroid levels in various age groups. Dr Alexandra, who is in-charge of laboratoryfunction, was considerate enough to show me the various protocols that they follow in the laboratory.

The electronic record system in Germany is very advanced, and patient records are meticulously digitalized. In addition, they maintain a comprehensive registry for type 1 diabetes (a database spanning the last 25 years), which the clinician updates after every clinical visit. This registry is very user-friendly, automatically calculating the insulin requirements of the patient and even generating a letter to the local general practitioner!

Since much more information is required for the clinical outcomes and natural history of DSD, the DSD-net has started an excellent initiative, the Anonymous International DSD registry (i-DSD) for clinical profiling of patients. As a user of this registry, I find it helpful to enter and record the clinical details of my patients. Moreover, DSD-net website has valuable resource materials for both clinicians and patients, as well as study material for students.

Photo Quiz

Zalak Upadhyay, Vani HN, Raghupathy P, Indira Gandhi Institute of Child Health, Bengaluru

A 14yo boy presented to us with history of short stature. He had recurrent respiratory infections in the past and suffered multiple fractures in both lower limbs. He was receiving empirical treatment for this since age 3y, but was lost to follow up for nearly 7y. On examination, his height was 138cm (<3rd centile), weight was 29 kg (<3rd centile), and head circumference 49 cm.

1. What are the clinical features?
2. What are the radiological features?
3. What is the diagnosis?

Pedendoscan

Sachin Mittal, Consultant Endocrinologist, Fortis Hospital, Mohali (near Chandigarh)

Diabetes/ Insulin Glucose Metabolism

Changes in diabetes medication regimens and glycemic control in adolescents and young adults with youth-onset type 2 diabetes: The SEARCH for Diabetes in Youth Study. Pinto CA et al. Pediatr Diabetes. 2018 May 15.

To describe recent medication patterns and changes in medication patterns and glycemic control in adolescents and young adults with incident type 2 diabetes (T2D), using data from the SEARCH for Diabetes in Youth Study, a cross-sectional analysis of treatments for 646 adolescents and young adults with incident T2D in 2 periods (2002-2005 vs. 2008/2012) and a longitudinal analysis of medications and glycemic control for a subset with baseline and follow-up visits. A majority in each period received metformin (64.9% vs 70.4%) and/or insulin (38.1% vs 38.4%), while fewer used sulfonylureas (5.6% vs 3.6%) with non-significant changes over time. There was a significant reduction in thiazolidinedione use (5.0% vs 2.0%, $P < .05$). In the longitudinal analysis, 322 participants were followed for 7y on average. Baseline metformin users had a lower A1C (6.4%) compared to insulin (8.4%, $P < .001$) or insulin plus any oral diabetes medication (ODM) users (7.7%, $P < .001$). Overall, 35% were at A1C goal (<7.0%) at follow-up. Youth-onset T2D is still largely being treated with metformin and/or insulin. The majority treated were not at American Diabetes Association (ADA)-recommended goal 7y after diagnosis.

A single exercise session increases insulin sensitivity in normal weight and overweight/obese adolescents. Short KR, Pediatr Diabetes. 2018 Apr 23.

To measure the effect of an aerobic exercise session on postprandial glucose control in adolescents with habitually low-physical activity, 11 normal weight, body mass index (NW, BMI = 48 ± 13 percentile) and 12 OW/Ob (BMI = 91 ± 5 percentile) participants completed 3 trials. In the no exercise (No Ex) trial, participants rested quietly before and after consuming a test meal. In the other 2 trials, a 45-minute aerobic exercise session was performed either 17h (Prior Day Ex) or 40 min (Same Day Ex) before the test meal. On all trials, the OW/Ob group had higher fasting glucose (~6%) and insulin (~66%), and lower insulin sensitivity (~9%) than the NW group. The Same Day Ex and Prior Day Ex trials resulted in reduced area under the curve for glucose (6% on both trials, $P < .01$) and insulin (15% and 13%, respectively, $P < .03$), and increased insulin sensitivity (8% and 6%, respectively, $P < .01$). The magnitudes of those effects did not differ between the NW and OW/Ob groups. The results demonstrate that moderate intensity aerobic exercise increases insulin sensitivity in NW and OW/Ob adolescents and that the beneficial effects of exercise last up to 17 hours. The acute impact of exercise on metabolic health in adolescents is not impaired in overweight/obese participants.

Intensive remote monitoring versus conventional care in type 1 diabetes: A randomized controlled trial. Gandrud L et al. Pediatr Diabetes. 2018 Feb 21.

To assess the impact of an intensive remote therapy (IRT) intervention, pediatric patients with T1D were randomized to IRT or conventional care (CC) for 6 months. Both cohorts continued routine quarterly clinic visits and uploaded device data; for the IRT cohort, data were reviewed, and patients were contacted if regimen adjustments were indicated.

Glycated hemoglobin (HbA1c) change from baseline was assessed at 6 and 9 months. Diabetes-related quality of life (QoL), healthcare services utilization, and hypoglycemic events were also tracked. Among 117 enrolees (60 IRT, 57 CC), mean (SD) 6-month %HbA1c change for IRT vs. CC was -0.34 vs -0.05 (P = .071). Diabetes-related QoL increased by 6.5 and 1.3 points for IRT and CC, respectively (P = 0.062). Three months after intervention cessation, %HbA1c changed minimally among treated children aged 8-12y but increased by 0.22 (0.89) (2.4 mmol/mol) among those aged 13-17y. IRT substantially affected diabetes metrics and improved QoL among pediatric patients with T1D. Adolescents experienced a stronger treatment effect but had difficulty in sustaining improved control after intervention cessation.

The influence of treatment, age at onset, and metabolic control on height in children and adolescents with type 1 diabetes - A SWEET collaborative study. Svensson J et al. Pediatr Diabetes. 2018 Aug 13.

To describe the association between height, demographics and treatment in youth with T1D participating in an international network for pediatric diabetes centers (SWEET), data was collected from 55 centers of subjects below 20y of age, diabetes duration >1y, and without celiac disease. Data of 22,941 subjects (51.8% male, median range for age 14.8y, diabetes duration 5.6y, and height z-score 0.34 was analysed. WHO growth charts were used to calculate height and BMI z-scores. Children were taller in the youngest age groups: adjusted height z-score of 0.31 and 0.39 respectively; with shorter diabetes duration (< 2y: 0.36, 2-<5y: 0.34, ≥ 5y: 0.21) and if they were pump users: 0.35 versus 0.25 (> 3 injections /day) and 0.19 (0-3 injections daily) respectively. High HbA1c and low to normal weight were associated with lower height z-score. No gender differences were found except in the final height model where females exhibited higher z-score than males. The authors concluded that for youth treated at centers offering modern diabetes management, major growth disturbances are virtually eliminated. For children with a young age at onset, high HbA1c, injections and/or non-intensive diabetes, treatment still requires attention in order to attain normal growth.

Type 1 Diabetes Outcomes: Does Distance to Clinic Matter? Fox DA, Islam N, Amed S. Pediatr Diabetes. 2018 Aug 12.

To determine whether HbA1C and patient reported outcomes were associated with (i) distance to clinic and (ii) tertiary vs. community care, 189 patients with similar age and duration of T1D were recruited from T1D clinics across British Columbia (BC). Clinical chart review and patient surveys were completed, including the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Clinic type was categorized as tertiary (BCCH) or community, and travel time to BCCH was categorized as <1h, 1-2h, or >2h. Mean number of visits/year for BCCH groups were 2.23, 2.24 and 2.05 for the <1h, 1-2h and >2h groups, respectively, vs. 3.26 for the community group. Adjusted mean difference in HbA1C was +0.65% and +0.52% for the BCCH >2h group compared to BCCH <1h group and community group, respectively. Child DTSQ scores were significantly lower in the BCCH >2h group compared to the BCCH <1h and community groups. The authors concluded that children travelling >2h to T1D clinic at BCCH had significantly higher HbA1C values and lower satisfaction with care vs. those travelling <1h to BCCH and those receiving communitycare. Access to care closer to home may benefit glycemic control in children with T1D and improve treatment satisfaction.

Adrenal

Longitudinal Assessment of Illnesses, Stress Dosing, and Illness Sequelae in Patients With Congenital Adrenal Hyperplasia. Diala El-Maouche et al. JCEM, 2018;103:2336–45.
Longitudinal analysis of 156 patients with CAH followed at the National Institutes of Health clinical center over 23y was performed to evaluate rates of illnesses and associated factors. The rates of illnesses and stress-dose days, emergency room (ER) visits, hospitalizations, and adrenal crises were analyzed in relation to phenotype, age, sex, treatment, and hormonal evaluations. A total of 2298 visits were evaluated. Patients were followed for 9.3 ± 6.0y. During childhood, there were more illness episodes and stress dosing than adulthood ($P < 0.001$); however, more ER visits and hospitalizations occurred during adulthood ($P \leq 0.03$). The most robust predictors of stress dosing were young age, low hydrocortisone and high fludrocortisone dose during childhood, and female sex during adulthood. Gastrointestinal and upper respiratory tract infections (URIs) were the two most common precipitating events for adrenal crises and hospitalizations across all ages.

Thyroid

Epidemiology of Childhood Hyperthyroidism in France: A Nationwide Population-Based Study. Simon M et al. JCEM, 2018;103:2980–2987.
To perform a nationwide epidemiological survey of hyperthyroidism in children and adolescents (age 6 mo-17y), a cross-sectional descriptive study was carried out in 2015, by identification of entries corresponding to reimbursements for antithyroid drugs in the French National Insurance database. A total of 670 cases of childhood hyperthyroidism were identified. Twenty patients (3%) had associated autoimmune or genetic disease, with type 1 diabetes and Down syndrome the most frequent. The annual incidence for 2015 was 4.58/100,000 person-years (95% CI 3.00 to 6.99/100,000). Incidence increased with age, in both sexes. This increase accelerated after age 8y in girls and 10y in boys and was stronger in girls. There was an interaction between age and sex, the effect of being female increasing with age: girls were 3.2 times more likely to be affected than boys in the 10-14y age group and 5.7 times more likely to be affected in the 15-17y age group. No conclusions about spatial pattern emerged.

Permanent Decompensated Congenital Hypothyroidism (CHT) in Newborns with Whole-Blood Thyroid-Stimulating Hormone Concentrations between 8 and 10 mU/L: The Case for Lowering the Threshold. McGrath N et al. Horm Res Paediatr 2018;89:265–270.
The Newborn screening (NBS) program in the Republic of Ireland has used a cut-off of 8 mU/L since 1979. The aim of this study was to determine if raising the cut-off to 10 mU/L would have resulted in undetected cases of permanent or decompensated CHT. Of 2,361,174 infants screened between July 1979 and December 2016, a total of 1,063 babies were diagnosed with CHT and treated with levothyroxine. This included 33 (3.5%) infants with a whole-blood TSH concentration between 8 and 9.9 mU/L. 13 of these 33 infants had decompensated hypothyroidism with low plasma free thyroxine level at diagnosis and 9 (41%) of the 21 evaluable cases have confirmed permanent CHT. Although lowering screening TSH cut-offs can increase the cost of NBS, as well as anxiety for families, many infants with borderline increases in whole-blood TSH concentrations on NBS have persistent CHT and low thyroxine concentrations in infancy. The authors recommend that this is considered when developing and reviewing NBS protocols for identifying infants with CHT.

Puberty

Sex Differences in Reproductive Hormones During Mini-Puberty in Infants With Normal and Disordered Sex Development. Johannsen TM et al. JCEM;103:3028–3037.

To evaluate sex differences in reproductive hormone concentrations in serum from healthy infants to define sex-specific cut-off values and to apply these in infants with DSD, a cross-sectional study involving 1840 healthy infants and 27 patients with DSD, aged 2-5 months, was done at a tertiary center for pediatric endocrinology at the University Hospital of Copenhagen. LH and FSH concentrations showed overlap between sexes, with LH being highest in boys and FSH being highest in girls. The LH/FSH ratio separated infant boys from girls with minimal overlap at a cut-off value of 0.32. Inhibin B and AMH concentrations were markedly higher in boys compared with girls, with minimal or no overlap. In infants with Klinefelter syndrome, 45,X/46,XY mosaicism and male phenotype, and Turner syndrome, the LH/FSH ratio matched the gender of rearing. However, infants with complete androgen insensitivity syndrome had LH/FSH ratios within the male range. Reference ranges for reproductive hormones and LH/FSH ratio during mini-puberty were established in this study. The classifiers that best separated sex in mini-puberty were AMH, LH/FSH ratio, and Testosterone. Use of the LH/FSH ratio may add valuable information in the workup of infants suspected to have DSD.

Prediction of Spontaneous Puberty in Turner Syndrome (TS) Based on Mid-Childhood Gonadotropin Concentrations, Karyotype, and Ovary Visualization: A Longitudinal Study. Hankus M et al. Horm Res Paediatr2018;89:90–97

The data from 110 TS girls aged >13y at the end of the study (1,140 visits between 1996 and 2015) was analysed to investigate whether karyotype, mid-childhood (6–10y) follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, and ultrasound ovary visualization results can be used as indicators of spontaneous puberty in Turner syndrome (TS). The study population was divided according to karyotype: 45,X and non-45,X. Spontaneous puberty was confirmed in 48% and menarche in 20% of the subjects, less frequently in 45,X girls. The mean age at Tanner stage B2 was 13.7 ± 2.4y and that at menarche 14.2 ± 1.7y, regardless of the karyotype. The median FSH level at 6–10y was 8.16 IU/L, which was significantly lower than <6y and >10y. The median LH level at 6–10y was 0.35 IU/L, which was lower than >10y. The chance of spontaneous menarche was decreased in girls with FSH ≥6.7 IU/L between 6 and 10y. The authors opined that although spontaneous puberty and menarche occur more frequently in non-45,X girls, the karyotype cannot be used to predict them. However, the chance of spontaneous menarche can be predicted based on gonadotropin cut-off values. There was no correlation between ultrasound ovary visualization results and spontaneous puberty.

Testicular Function and Bone in Young Men with Severe Childhood-Onset Obesity. Laakso S et al. Horm Res Paediatr2018;89:442–449.

To describe the effects of severe childhood-onset obesity on the cross talk between metabolic state, testes, and skeleton at late puberty, a cohort of adolescent and young adult males with severe childhood-onset obesity (n = 21, mean age 18.5y) and an age-matched control group were assessed for testicular hormones and X-ray absorptiometry-derived bone mass. Median BMI for obese and control subjects were 37.4 and 22.9 kg/m^2.

Severe early-onset obesity manifested with lower free testosterone (244 vs. 403 pmol/L, p = 0.002). Lower insulin-like factor 3 (1.02 vs. 1.22 ng/mL, p = 0.045) and lower ratio of testosterone to LH (2.81 vs. 4.10 nmol/IU, p = 0.008) suggested disrupted Leydig cell function. The degree of current obesity inversely correlated with free testosterone (τ = –0.516, p = 0.003), which in turn correlated positively with bone area at all measurement sites in males with childhood-onset obesity. The authors concluded that severe childhood-onset obesity is associated with impaired Leydig cell function in young men and lower free testosterone may contribute to impaired skeletal characteristics.

Pituitary

Evaluation of Hypothalamic-Pituitary-Adrenal Axis Suppression following cutaneous Use of Topical Corticosteroids (TCS) in Children: A Meta-Analysis. Wood HeickmanLK et al.Horm Res Paediatr 2018;89:389–396.

A meta-analysis was performed of all published pediatric clinical trials evaluating TCS use with pre- and post-treatment HPA axis assessment by cosyntropin stimulation testing to determine the likelihood of hypothalamic-pituitary-adrenal (HPA) axis suppression following short-term cutaneous TCS treatment of atopic dermatitis. Of 128 eligible trials, 12 were selected, with a total of 522 participants. There were 20 observed cases of HPA axis suppression (3.8%). The percentage of HPA axis suppression with low, medium and high-potency TCS use was 2%, 3.1% and 6.6% respectively. The authors concluded that there is a low rate of reversible HPA axis suppression with the use of mid- to low-potency TCS compared to more potent formulations. In pediatric clinical practice, the limited use of mid- to low-potency TCS is rarely associated with clinically significant adrenal insufficiency or adrenal crisis. In the absence of signs and symptoms of adrenal insufficiency, there is little need to test the HPA axis of these patients.

Clinical Features and Response to Treatment of Prolactinomas in Children and Adolescents: A Retrospective Single-Centre Analysis and Review of the Literature. BreilT.a et al. Horm Res Paediatr 2018;89:157–165.

To investigate the clinical features and outcome of pediatric patients with prolactinomas, a single-centre retrospective analysis of clinical, biochemical, and radiological features of all pediatric patients with pituitary adenomas diagnosed between 2000 and 2016 was done. Of 21 patients with pituitary adenomas, 12 had prolactinomas (median age 14.2y, range 11–16.6y, 8 females, 7 macro- and 5 micro-prolactinomas). The most common clinical symptoms were headaches (67%) and pubertal delay (67%). All patients with macroprolactinomas with prolactin concentrations >10,000 mU/L had at least 1 pituitary hormone deficiency. Cabergoline as first-line treatment (n = 11, median follow-up of 37 months, range 12–89 months) induced normoprolactinemia (n = 8), reduced the mean tumour volume by 80%, and ameliorated headaches (p = 0.016) and pubertal delay (p = 0.031), whereas intermittent moderate side effects occurred in 55%. The authors opined that the adolescents with headaches and pubertal delay should be investigated for prolactinomas. Treatment with cabergoline is well tolerated and effective in reducing clinical symptoms and prolactin concentrations as well as inducing tumour shrinkage.

Activities by ISPAE Members

Rajesh Khadgawat, Dept Endocrinology & Metabolism, AIIMS, New Delhi

Symposium on "Growth Disorders: Theory to Practice" (28-29 April, 2018)

The one and half day Symposium was jointly organized by the Dept of Endocrinology, All India Institute of Medical Sciences, New Delhi, in collaboration with ISPAE and Growth Hormone Research Society (GHRS) on "Growth Disorders: Theory to Practice" at Holiday Inn, Aerocity, New Delhi, supported by an educational grant from Novo Nordisk India.The basic purpose of the conference was to discuss complex clinical problems faced by endocrinologists/ pediatric endocrinologists while managing growth disorders. The target audienceof130 pediatric and adult endocrinologists from all over the India, and two each from Myanmar and Nepal,were those already working in this area.

The meeting started with a post-lunch session on 28th April with a lecture on normal growth including growth velocity, pubertal growth spurt and effect of age of onset of pubertal growth by Prof Sangita Yadav (Head, Pediatrics, MAMC, Delhi). This was followed by Prof Nalini Shah (Head, KEM Hospital, Mumbai)discussingpriming with sex steroids during GH stimulation tests and other biochemical modalities which can be of some help in the diagnosis of GHD. Dr VamanKhadilkar(Bhartiya Vidyapeeth, Pune) discussed optimization of GH therapy in IGHD and CPHD, while Dr Tushar Bandgar (KEM Hospital, Mumbai) discussed optimization of GH therapy in Turner syndrome. Prof P Raghupathy (IGICH, Bengaluru) deliberated on assessment of poor response to GH therapy in a child with GHD. The complex issue of prediction of response to GH therapy by using various prediction models, and the possibility of using Indian data for our own prediction model was discussed by Dr MK Garg. The last lecture of the day, a review of published literature of GH therapy in GHD in the last 5y by Dr Rajni Sharma (AIIMS, Delhi) was very well appreciated.

The next day started with a lecture on Initiation of therapy in ISS – diagnosis, therapy and follow-up, by Prof Vandana Jain (AIIMS, Delhi). One of the least discussed areas of GH therapy is possible side effects. This difficult area was well covered during the meeting: early side effects of GH therapy Dr Anju Virmani (Max Hospital, Delhi), and late side effects by Dr Rakesh Kumar (PGI, Chandigarh). Prof Anju Seth (President, ISPAE) discussed the use of GH therapy for augmentation of height in various skeletal dysplasias, while Dr Sudha Rao (BJ Wadia Hospital, Mumbai) discussed the use of GnRH + GH therapy for augmentation of the pubertal growth spurt. Dr IPS Kochar (Secretary GHRS), reviewed published data on daily vs. weekly GH therapy in GHD and other new developments in GH therapy. Dr Sanjay Bhadada (PGI, Chandigarh) deliberated on the current status of GH deficiency and GH therapy in adults. Use of GH in patients operated for craniopharyngioma and other tumors was discussed by Prof Satinath (Kolkata).

Nowadays GH is also abused as a performance enhancing drug in sports. To increase awareness about abuse of GH, Dr S Perumal, National Anti-Doping Agency (NADA) was invited to talk about the current status of abuse, and modalities to detect such abuse. Last but not least, one of the most important aspects of GH therapy is cost of therapy. As we are all aware, most of our patients with GHD cannot afford GH, so Mr BR Shekhar, medical social support officer (MSSO), AIIMS, New Delhi was invited to discuss all possible government and non-government resources which can be used for GH therapy in non-

affording patients. Prof Rajesh Khadgawat, Organizing Secretary, thanked all delegates and faculty members.

Rajni Sharma, Division of Pediatric Endocrinology, Dept of Pediatrics, AIIMS, New Delhi

AIIMS CME on Pediatric Endocrinology (1st July 2018)

The Dept of Pediatrics, AIIMS, New Delhi organized a Pediatric Endocrinology CME for postgraduates on 1st July 2018, at Lecture Theatre, AIIMS, New Delhi, and accredited by the Delhi Medical Council.The response to the CME was overwhelming, with over 100 participants consisting mainly of MD/DNB students, Fellows in training, and Senior Residents of Pediatrics as well as DM Endocrinology.

The faculty included Prof PSN Menon (Jabber Al Ahmad Armed Forces Hospital, Kuwait), Prof Ram Menon (University of Michigan, USA), Prof Anju Seth (KSCH & LHMC, Delhi), Prof), Prof Sangeeta Yadav (MAMC, Delhi), Prof Vandana Jain (AIIMS, New Delhi), Dr Rajni Sharma (AIIMS, New Delhi), Dr Mahesh Maheshwari (AIIMS, Bhopal), Dr Amit Satapathy (AIIMS, Bhuvaneshwar) and Dr Varuna Vyas (AIIMS, Jodhpur). An array of topics covering the vast spectrum of Pediatric Endocrinology were discussed, including growth charts, short stature,growthhormone disturbances, disorders of puberty, neonatal endocrine disorders, ambulatory management of type 1 diabetes, diabetic ketoacidosis, childhood obesity and metabolic syndrome, disorders of sex development, and a potpourri of endocrine cases. There was a panel discussion on the scope of DM in Pediatric Endocrinology, a new course being introduced at AIIMS from next year. The faculty told the rapt audience what a career in the field of pediatric endocrinology offers,what attracted them initially and what fascinates them about the specialty. 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.

Nalini Shah, Department of Endocrinology, Seth GSMC and KEMHospital, Mumbai

KEMH CME "Intricacies of Pediatric Endocrinology: A Pragmatic Approach" (12 Aug 2018)

The Dept of Endocrinology, KEMH conducted a CME "Intricacies of Pediatric Endocrinology: A Pragmatic Approach", attended by over 130 pediatricians and general practitioners. Dr Anurag Lila talked about the rational approach towards short stature with case-based discussions. Prof Nalini Shah spoke about optimizing growth in short stature and overview of disorders of sex development (DSD). Prof Tushar Bandgar discussed evaluation and management of rickets, with special emphasis on resistant rickets. Pubertal disorders were discussed by Dr Swati Ramteke Jadhav giving an overview of physiology and pathology,and Dr Virendra Patil talking about treatment. All the attendees greatly appreciated the CME and said they eagerly awaited the next one.

Meena Mohan, Coimbatore

Support Group Programs (April, May, August 2018)

We conducted three support group programs, at PSG Hospital auditorium, Coimbatore, in April, on 6thMay and on 11-12thAugust, of which the May one was special. Ms Sheryl Salis, Nutritionist from Mumbai, explained about healthy eating and carb counting. A specially designed book for blood glucose monitoring in T1DM children was released and distributed by the Dean, PSG Institute of Medical Sciences & Research. A few nursing students from PSG Nursing College dressed up like clowns and helped to look after the children, while parents attended the sessions. The program was well attended by 60 children with T1D and their families. About 250 members in total were benefited; they all enjoyed the day.

A residential support group for children and families was conducted over two days: 11-12th August 2018 at Lima Gardens, Madhampatty, Coimbatore. The highlight of the occasion was the presence of Sister Judith Campbell, Advanced Nurse Practitioner, specialised in pediatric diabetes. She has a vast experience of paediatric diabetes, having trained and worked in Manchester, UK, for 25 years, and currently working in Sidra Hospital, Doha, Qatar.

The first day was planned to focus more on insulin pumps in T1D children and adolescents. 25 children and their families attended, of whom 15 were on insulin pumps. The rest of the families were keen to explore the advantages and uses of pumps in day to day T1D management.The day began with testing of HbA1c and blood glucose comparison between lab and three different glucometers namely Abbott, Johnson & Johnson, and Roche. The samples were done as fasting, random or post-prandial, depending on the time of their

attendance in relation to breakfast, after obtaining consent from children/parents. A presentation by Sister Campbell on the advantages and uses of insulin pumps, was followed by a discussion on the different models of Medtronic insulin pumps available in the Indian market. Adolescents on 640G pump had a one to one session with Sister Campbell, to discuss the various options available and to make the best use of the latest pump. All her presentations were translated in local language Tamil, as very few could understand English. Children were entertained separately by an entertainer, away from the parents, which enabled the parents to focus on, and make the best use of the sessions, while the children were equally happily occupied.

The second day focussed more on T1D in general, and was attended by 35 children and families. Again we began with testing of HbA1c and fasting, random or post-prandial BG, with comparison between lab and Abbott, J&J and Roche glucometers. Emphasis was laid on exercise management and carbohydrate counting, illustrating the importance of carb counting, irrespective of MDI or pumps therapy. The differences in managing diabetes using pump or MDI was explained. The children benefitted from a yoga session, in which a few exercises were taught, to reinforce the importance of exercise in day to day management of diabetes, and to make everyone aware of the advantages of different yoga postures. The highlights of the afternoon included a motivational talk by psychologist Dr Radhakrishnan. He stressed on the importance of being happy and contented, in order to face the everyday challenge of insulin injections and blood sugar monitoring. A discussion on millets and millet-based recipes was given by Ms Saraswathy, to increase intake of low GI foods, to reduce glycemic variability. Once again, children were entertained separately by an entertainer.

Apart from the families, four diabetes educators and a dietician from PSG Hospitals and two educators from Sanofi attended and were benefited. Overall, the sessions were very fruitful on both days, and was thoroughly enjoyed by one and all. A photo session was conducted at the end to mark the function.

Kumar Angadi, Pediatric Endocrinologist, Gulbarga, Karnataka

Pediatric& Adolescent Endocrine Academic Activities in north Karnataka

A day-long pediatric& adolescent endocrine Update-cum-Workshop was held on 22 July 2018 in MR Medical College, Gulbarga, under the aegis of IAP Gulbarga, in association with the Dept of Pediatrics, MR Medical College. The Update was attended by 148 delegates, including Medical College faculty members, private practitioners, and postgraduates in Pediatrics, from all the four medical colleges in the city of Gulbarga. Dr Abhishek Kulkarni from Mumbai, Dr Ganesh Jevalikar from Gurugram and Dr Kumar Angadi gave talks on the obesity pandemic, pubertal disorders, and short stature, and had panel discussions on diabetes in the young, and hypothyroidism in children. A special attraction of the Update was the post-lunch hands-on Workshop on “Use of growth charts in clinical practice”, which was widely appreciated by all the delegates.

Apart from this workshop, north Karnataka witnessed other academic activities on pediatric endocrinology, notably an Update in Hospet on 22-5-2018 under the aegis of IAP Vijayanagar branch, attended by 41 pediatricians in and around Hospet, where Dr Abhishek

Kulkarni and Dr Kumar Angadi participated as faculty. A Workshop on ambulatory care of type I diabetes and hands-on use of different insulin delivery devices was held at S. Nijalingappa Medical College, Bagalkot, on 11-8-2018 under the aegis of IAP Bagalkot district branch, in association with the Dept of Pediatrics, SN Medical College, Bagalkot. This workshop was attended by 40 delegates, including faculty members of SNMC, practicing pediatricians and postgraduates.

Publications by ISPAE Members

Pragya Bajaj Mangla, SGPGI, Lucknow

1. Mangla P, Gambhir PS, Sudhanshu S, Srivastava P, Rai A, Bhatia V, Phadke SR. Pyruvate carboxylase deficiency mimicking diabetic ketoacidosis. Indian J Pediatr. 2017;84:959-960.
2. Mangla P, Hussain K, Ellard S, Flanagan SE, Bhatia V. Diazoxide toxicity in a child with persistent hyperinsulinemichypoglycemia of infancy: mixed hyperglycemic hyperosmolar coma and ketoacidosis. J Pediatr Endocrinol Metab. 2018 ;31:943-945.

Sarala Kannan, Tata Memorial Hospital, Mumbai

Kannan S, Singh A. Compliance score as a monitoring tool to promote treatment adherence inchildren with thalassemia major for improved physical growth. Asian J Transfus Sci 2017;11:108-14.

Shreya Sharma, BJ Wadia Hospital for Children, Mumbai

Sharma S, Joshi R, Kalelkar R, Agrawal P. Tuberculous adrenal abscess presenting as adrenal insufficiency in a 4yearold boy. Journal of Tropical Pediatrics, fmy046, https://doi.org/10.1093/tropej/fmy046.

Alpesh Goel, AIIMS, New Delhi

Goyal A, Gupta Y, Kalaivani M, Sankar MJ, Kachhawa G, Bhatla N, Gupta N, Tandon N. Long term (>1year) postpartum glucose tolerance status among Indian women with history of Gestational Diabetes Mellitus (GDM) diagnosed by IADPSG criteria. Diabetes Research and Clinical Practice 2018:142:154-161.

Answers to Photo Quiz:

1. Clinical findings are short stature, frontal bossing, proptosis (figure 1A), and short fingers with dystrophic nails (figure 1B).

Other findings in classical cases are disproportionate short stature, macrocranium and open cranial sutures, high forehead, small facial features, proptosis, bluish sclera, beaked and pointed nose, micrognathia, high arched palate, retained primary teeth, short fingers with hypoplastic nails, narrow thorax, pectus excavatum, and kyphoscoliosis with lumbar lordosis.

2. Radiological findings are increased bone density, acro-osteolysis of distal phalanges (figure 1C), open fontanelles and cranial sutures and wide angle of mandible (more obtuse than normal) (figure 1D).

Radiologically, in classical cases, there is increased bone density that becomes progressively worse with age despite which susceptibility to fractures is increased. Other characteristics include open fontanelles, impaction of permanent and supernumerary teeth, clavicles that are slim and hypoplastic laterally, partial or total absence of the ribs and hyoid bone, and acro-osteolysis of the distal phalanges (a pathognomonic characteristic).

3. Pycnodysostosis

It is one of the sclerosing bone dysplasias. Inheritance - autosomal recessive, due to mutations in the cathepsin K, a cysteine protease gene (CTSK) that is highly expressed in osteoclasts [1].

Growth hormone therapy when commenced early has been found useful in improving the height of children with pycnodysostosis [2].The growth promoting effects of GH occur through the generation of an excess of IGF-I release locally at the growth plate level.

References

1. Maroteaux P, Lamy M. Pycnodysostosis. Presse Med. 1962;70:999-1002.

2. Rothenbuhler A, Piquard C, Gueorguieva I, Lahlou N, Linglart A, Bougneres P. Near normalization of adult height and body proportions by growth hormone in pycnodysostosis. J Clin Endocrinol Metab2010;95:2827-2831.

All India Association for Advancing Research in Obesity (AIAARO) Conference

AIAAROCON 2018: Here is an opportunity to update ourselves to tackle one of the important Public Health challenges of the 21st century, that is, obesity. The 13th National Obesity Conference 'AIAAROCON 2018', a state of the art conference will be held from 7-9th Sep 2018 at Aurangabad, Maharashtra. Dr PritiPhatale, the Organising Secretary, and Dr Hemanth Phatale, Organising Chairperson,are both ISPAE members. The conference features a pre-conference workshop-cum-certificate course with the theme 'Basics to Clinical Practice'.

For further information contact @ **www.aiaarocon2018.com**

ISPAD 2018 Hyderabad, India

44th Annual Conference
Thursday, October 11– Sunday, October 14, 2018

Reaching the Unreached




ISPAD 2018

The INTERNATIONAL SOCIETY for PEDIATRIC and ADOLESCENT DIABETES (ISPAD) is the only international professional society focusing specifically on all types of childhood diabetes. It aims to promote clinical and basic science, research, education and advocacy in childhood and adolescent diabetes. The strength of ISPAD lies in the scientific and clinical expertise of its members: committed medical professionals (pediatricians, internists, other disciplines), non-medical professionals (diabetes nurses, dieticians, psychologists, social workers, other members of diabetes teams) and scientists. The ISPAD Clinical Practice Consensus Guidelines for the management of diabetes in children and adolescents are well known and much consulted.

We are proud that ISPAD is coming to India, indeed South Asia, for the first time, and warmly invite you to the 44th Annual Conference, from October 11-14, 2018, in Hyderabad, with the theme "reaching the unreached". The city, like the meeting, combines old and new, bringing together all these experts from all corners of the world.

The Scientific Program is now online!

Highlights

- Release of ISPAD Guidelines 2018
- Another first: a parallel stream on "Diabetes 101": basic diabetes for pediatricians and allied professionals, covering the entire gamut of care
- Also NEW this year: Special low rates for attendees from SAARC countries: we can register and pay in Indian rupees!

Main meeting

- Sessions on Acute complications
- Communication: crucial aspect
- Closing the Loop
- Complications and Co-morbidities
- Epidemiology
- Handling technology
- Living with diabetes, not for diabetes
- Need for Mental health professionals
- Reaching the disadvantaged
- Registries

Joint Sessions

- Interventions today (with ESPE)
- Newer treatments (with ADA)
- Technology Today (with ATTD)
- Under to Over Nutrition (with APPES)
- Winners All (with JDRF)

Confirmed speakers so far

Carlo Acerini - Francesca Annan - Ana Maria Arbelaez - Kishwar Azad - Tadej Battelino - Viji Bhatia - Petter Bjornstad - Natasha Bratina - Stuart Brink - Fergus Cameron - Vinay Chauhan - Shuchy Chugh - Ethel Codner - Dana Dabalea - Thomas Danne - Ashok Das - Carine de Beaufort - Subrata Dey - Linda DiMeglio - Kim Donaghue - David Dunger - Gun Forsander - Sujoy Ghosh - Eveline Goethals - Rose Gubitosi-Klug - Santosh Gupta - Ragnar Hanas - Dhruvi Hasnani - Leenatha Jakkidi - Muhammad Yazid Jalaludin - Elisabeth Jelleryd - Sanjay Kalra - Lori Laffel - Feihong Luo - Maddalena Macedoni - Farid Mahmud - Beata Malachowska - Elizabeth Mayer-Davis - Angela C. Middlehurst - Helen Phelan - Kuben Pillay - Hemchand Prasad - Marie-Béatrice Saade - David Sacks - Archana Sarda - Andrea Scaramuzza - Rishi Shukla - Rekha Singhal - Tim Skinner - Carmel Smart - Nikhil Tandon - Martin Tauschmann - Gianluca Tornese - Matthias Von Herrath - Jill Weissberg-Benchell - Billy White - Michael Witsch - Jamie Wood - Chittaranjan Yajnik - Philip Zeitler

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