JUNE 2022
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CAPE News

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

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Theme: Adrenal Disorders

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Editorial board

Dear ISPAE members,

It gives our team great pleasure to connect with ISPAE members through this June 2022 issue of CAPE News, themed on Adrenal Disorders. We have many interesting articles, mini reviews, journal scan, history corner, biochemistry corner and a case report, pertaining to childhood adrenal disorders. We also have reports of members' activities, useful information pertaining to pediatric endocrinology, learning pearls from ISPAE meetings and a Diabetes Educators' corner. Hope you have a good reading experience.

We look forward to contributions and suggestions from all members for the next issue, themed on "Childhood bone disorders".

Feedback is welcome at: *editor.capenews@gmail.com*

Thank You and Regards,
Team CAPE News 2021-22

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Office Bearers' Message

Dear ISPAE members,

Greetings from Team ISPAE 2021-22!

As we approach the last 6 months of our tenure, we are excited to share the ongoing and upcoming activities being planned by the ISPAE executive!

The IDEAL program has been a great success and owing to huge demand from physicians to get trained in basic aspects of type 1 diabetes, the third batch of IDEAL is exclusively oriented to the physicians. For this extensive modifications were done to the modules and the program is being conducted on Wednesdays and Sundays currently with much appreciation. Our sincere thanks to all the faculty for taking their time out and contributing to the success of this program.

Dr Shaila Bhattacharyya
President
ISPAE 2021-22

Dr Ganesh Jevalikar
Secretary cum Treasurer
ISPAE 2021-22

Dr Rakesh Kumar
Joint Secretary
ISPAE 2021-22

We have also invited applications for the second batch of ISPAE- BEST (Basic Education Series in Type 1 Diabetes). This is meant to train people with type 1 diabetes, their family members and all the interested health care and allied personnels.

The preparations for ISPAE ISPAD meeting in November 2022 are in full swing and the team led by Prof Devi Dayal is taking immense efforts to make this meeting a grand success. The conference website is now functional and can now be accessed on the home page of ISPAE website.

We continue our efforts for a better liaison with the Indian Academy of Pediatrics through the implementation of TOTs for pediatric endocrinology prepared by ISPAE membership under the supervision of Prof Vijaykumar, Prof Shaila Bhattacharyya and Prof PSN Menon.

We hope to continue with the good show for the rest of our tenure and need your constant support to make sure that it is a great success.

Best Wishes,
Drs Shaila Bhattacharyya, Ganesh Jevalikar, Rakesh Kumar,
Team ISPAE 2021-22

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Welcome to new ISPAE members

- Dr Manju Gupta, Consultant Pediatrician, Rajasthan Medical Centre, Tohana, Haryana
- Dr Vibha Yadav, Pediatric Endocrine Trainee, Regency CDER, Kanpur
- Dr Joewin Monteiro, Senior Resident, Raja Rajeswari Medical College, Bengaluru
- Dr Shantala J, Senior Resident, Indira Gandhi Institute of Child Health, Bengaluru
- Dr Jayashri MN, Fellow in Pediatric and Adolescent Endocrinology, JJM Medical College, Davanagere
- Dr Dileep Kumar Allagadda, Assistant Professor, Malla Reddy Institute of Medical Sciences, Hyderabad
- Dr Anusha CH, Assistant Professor, Mallya Hospital, Bengaluru
- Dr Dhruti Pandya, Pediatrician, CU Shah Medical College and Hospital, Surendranagar, Gujarat
- Dr Meetu Yadav, Assistant Professor, SHKM GMC, Mewat, Haryana
- Dr Arasavilli Manidurga Sai, Kalawati Saran Children's Hospital, Lady Hardinge Medical College, New Delhi
- Dr Nupur Singh, Post Graduate Institute of Child Health, Indergarhi, Uttar Pradesh
- Dr Shruthi R, Narayana Medical College, Nellore, AP
- Ms Banu Priya N, Dietitian, Manipal Hospital, Bengaluru
- Dr Yaramala Manjusha, Pediatrician, Keesari Hospital, Ongole, AP
- Dr Vinodhini V, Pediatrician, Kanyakumari, Tamil Nadu
- Dr Aarti Shroff, Oriental Insurance, Mumbai
- Dr Mousin Mustafa, Lecturer, Govt Medical College, Jammu, J & K
- Dr Rajnesh Kumar, Lecturer, Govt Medical College, Jammu, J & K

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Excerpts from recent guidelines
Diagnosis and Treatment of Primary Adrenal Insufficiency (PAI): An Endocrine Society - Clinical Practice Guideline.

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North DMC Medical College & Hindu Rao Hospital, Delhi

PAI is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/ or mineralocorticoids. It is a severe and potentially life-threatening condition due to the central role of these hormones in energy, salt, and fluid homeostasis. The signs of PAI are mainly based on the deficiency of glucocorticoids and mineralocorticoids: weight loss, orthostatic hypotension due to dehydration, hyponatremia, hyperkalaemia, changes in blood count (anemia, eosinophilia, lymphocytosis), and hypoglycemia. Enhanced secretion of ACTH and other pro-opiomelanocortin peptides often leads to the characteristic hyperpigmentation of the skin and mucous membranes. PAI is a rare disease with a reported prevalence of about 100-140 cases per million and an incidence of 4:1 000 000 per year in Western societies. The most common cause of PAI is autoimmunity (up to 90% in Western countries), followed by infectious diseases such as tuberculosis, adrenalectomy, neoplasia, and various genetic causes; the last are more likely to be present and diagnosed in children.

Diagnosis of PAI

Diagnosis is traditionally based on low morning cortisol concentrations (measured in serum or plasma) and confirmed by low stimulated cortisol.

The diagnosis is highly likely if the cortisol is < 5 µg/dL in combination with plasma ACTH more than 2-fold above the upper limit of the reference interval for the specific assay.

The corticotropin stimulation test is currently regarded as the diagnostic "gold standard" for the diagnosis of primary (but not secondary) AI.

The standard dose (250 µg for adults and children > 2 y of age, 15 µg/kg for infants, and 125 µg for children < 2y of age) iv corticotropin stimulation (30 or 60 min) test is preferred over other existing diagnostics tests to establish the diagnosis of AI. Peak cortisol levels below 18 µg/dL (assay dependent) at 30 or 60 minutes indicate AI.

The low-dose (1 µg) corticotropin test is used for diagnosis of PAI only when the substance itself is in short supply, but it may be useful in settings where secondary AI is suspected.

An elevated plasma renin activity or concentration in combination with an (inappropriately) normal or low serum aldosterone concentration is also suggestive of PAI.

The etiology of PAI should be determined in all patients with confirmed disease.

Treatment of PAI

Treatment with hydrocortisone in 3-4 divided doses (total starting daily dose of 8 mg/m^2 body surface area) is preferred over other types of glucocorticoid replacement therapies, with doses adjusted according to individual need.

Avoid synthetic, long-acting glucocorticoids (e.g. prednisolone, dexamethasone).

Monitor glucocorticoid replacement by clinical assessment, including growth velocity, body weight, blood pressure, and energy levels.

In children with PAI and confirmed aldosterone deficiency, the recommended treatment is with fludrocortisone (starting dosage, 100 µg/d).

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For infants, sodium chloride supplements in the newborn period, up to the age of 12 months, is recommended. Inadequate weight gain, fatigue, anorexia, and hyperpigmentation suggest the need for increased medication dose.

Management and prevention of adrenal crisis in patients with PAI

Patients with suspected adrenal crisis should be treated with an immediate parenteral injection of 50 mg/m^2 hydrocortisone, followed by appropriate fluid resuscitation and 50–100 mg/m2 of hydrocortisone/24 hours (via continuous iv therapy or 6 hourly injections).

During febrile illnesses, the glucocorticoid dose is typically taken orally at double or triple the usual daily dose, until recovery, usually of 2- to 3-day duration.

During minor to moderate surgical stress, im hydrocortisone 50 mg/m2 or hydrocortisone replacement doses doubled or tripled is recommended.

During major surgery with general anaesthesia, trauma, or disease that requires intensive care, a dose of hydrocortisone 50 mg/m2 iv followed by hydrocortisone 50–100 mg/m2/d divided q 6h is recommended.

Weight-appropriate continuous iv fluids with 5% dextrose and 0.2 or 0.45% NaCl, rapid tapering, and switch to oral regimen, depending on the clinical state should be used.

Technical remarks

Every patient should be equipped with a glucocorticoid injection kit for emergency use and be educated on how to use it.

All patients should be equipped with a steroid emergency card and medical alert identification to inform health personnel of the need for increased glucocorticoid doses to avert or treat an adrenal crisis.

Additional monitoring requirement

Children with PAI be seen by an endocrinologist or a healthcare provider with endocrine expertise at least annually. Infants should be seen at least every 3 to 4 months.

PAI patients be evaluated annually for symptoms and signs of over- and under-replacement.

Annual screening for autoimmune diseases is desirable: thyroid disease, diabetes mellitus, premature ovarian failure, celiac disease, and autoimmune gastritis with vitamin B12 deficiency.

Genetic counselling should be offered for patients with PAI due to monogenic disorders.

Reference:

Stefan R. Bornstein, Bruno Allolio, Wiebke Arlt, et al; Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, 2016 ;101(2):364–389

Prevention and management of adrenal crisis during COVID-19: Educate, Equip and Empower

Dr Medha Mittal[1], Dr Sumeet Arora[2]

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[2]Artemis Hospital, ArBor Multispecialty Clinic, Gurgaon

Patients of adrenal insufficiency (AI) may be at a higher risk of catching COVID-19 infection and are at higher risk of having an adrenal crisis during such an infection, though they may not have a more severe course of COVID itself. We summarize here the clinical practice guidance for management of patients of AI in circumstances of COVID-19.[1,2]

Educate: Patients of AI and their families must be educated not to miss their medications, and to increase their glucocorticoid doses during any intercurrent illness, including COVID-19. Patients with primary AI have significantly decreased natural killer cell cytotoxicity, which is crucial to combat viral infections, therefore they are at somewhat greater risk of COVID-19 (although not as much as those on immunosuppressive drugs). They must follow strict social distancing and wear appropriate masks.

Equip: Patients must be equipped with sufficient supplies of oral glucocorticoid preparations (at the increased dose, if required). Glucocorticoid doses need to be increased if there are systemic symptoms such as fever, myalgia, or arthalgia [2] . Fludrocortisone is continued at the prescribed doses. They should be encouraged to get vaccinated, and carefully monitored for any systemic effects.

Empower: Empower your patients with a card mentioning emergency treatment of adrenal crisis. This could prove life-saving when they land at a peripheral health facility.

Suspected or Confirmed COVID-19 infection in children:

Patients with AI receive replacement glucocorticoid doses to mimic physiologic cortisol levels. Asymptomatic patients who test COVID positive, say on family screening, do not need to increase their routine replacement dose. But with the onset of symptoms, there is need to ensure careful replacement at higher doses to combat the high inflammatory cytokine load caused by COVID-19, as well as continued need for close monitoring for the clinical deterioration which may occur 7-10 days after the acute presentation of COVID-19 infection.

The suggested stress dosing of hydrocortisone in children with suspected COVID-19 infection includes:

- Acute infection: During onset of symptoms suggestive of COVID-19 infection including fever, malaise, sore throat, dry cough:
  - The dose of hydrocortisone should be increased (at least doubled and then tailored to the condition), administered in four divided doses (to be given every 6 hours) [2].
  - Oral fluid and electrolyte intake should be maximized and adjusted as per the color of the urine (urine concentration).
  - Fludrocortisone dose needs to be continued as usual.
  - Management of fever should include: regular acetaminophen administration to control fever and supportive treatment.

- Clinical deterioration: If any new severe symptom is seen, including dizziness, drowsiness, lethargy, vomiting, increasing respiratory distress or difficulty speaking, the following measures are to be taken immediately:
  - Hydrocortisone should be injected intramuscularly immediately at home or nearest health facility at a dose of 25 mg for infants, 50 mg for school children and 100 mg for adolescents (50mg/m)[2].
  - Immediate hospitalization is recommended for IV fluid and hydrocortisone administration.

- At Hospital: the patient should be admitted for:
  - Continuous IV infusion of hydrocortisone should be administered at a dose of 50 mg for children, and 100 mg for adolescents given over 24 hrs.
  - Fludrocortisone can be discontinued during the higher IV steroid infusion.
  - IV isotonic saline should be administered for fluid resuscitation.
  - Rest of the supportive and medical management for COVID-19 needs to be continued as per hospital protocol. Send samples for electrolytes and urea, and repeat as required. Assess and treat for coagulation abnormalities, if any.[2]
  - With improving respiratory and hemodynamic status as well as reducing temperature: tapering of stress dose of steroids can be started and fludrocortisone restarted.

Continuous IV infusion of hydrocortisone is preferred, as it has been shown to maintain a steady state of cortisol levels during stress as compared to split doses.

The data on severity of COVID-19 infection in those with known AI is scarce; nonetheless, a few retrospective and cross-sectional studies in adults with small sample size showed no significant increased rates of adrenal crisis or need for hospitalization in those with symptomatic COVID-19 infection when necessary glucocorticoid dose adjustments were made.[3] The use of steroids in COVID-19 management has been a matter of ongoing debate. The data on mortality reduction with use of hydrocortisone in management of COVID-19 is not robust in comparison to dexamethasone, but in patients with known AI, supraphysiological doses of hydrocortisone are a life-saving treatment to ensure adequate stress dosing cover, not a pharmacological measure for management of COVID-19. It is a must to continue the hydrocortisone replacement in stress doses until there is clear clinical improvement and only then gradually taper it off.

Reference:

1. Arlt W, Baldeweg SE, Pearce SHS, Simpson HL. Endocrinology in the time of COVID-19: Management of adrenal insufficiency. Eur J Endocrinol. 2020 Jul;183(1):G25-G32.

2. Puig-Domingo M, Marazuela M, Yildiz BO, Giustina A. COVID-19 and endocrine and metabolic diseases. An updated statement from the European Society of Endocrinology. Endocrine. 2021 May;72(2):301-316.

3. Chifu I, Detomas M, Dischinger U, Kimpel O, Megerle F, Hahner S, Fassnacht M, Altieri B. Management of Patients With Glucocorticoid-Related Diseases and COVID-19. Front Endocrinol (Lausanne). 2021 Sep 14;12:705214. doi: 10.3389/fendo.2021.705214. PMID: 34594302; PMCID: PMC8476969.

Biochemistry Corner
Measurement of blood 17-OHP on dried blood spots

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Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders caused by enzymatic defects in steroid biosynthesis. Newborn screening (NBS) for CAH is available at most centres in the West and at a few centres in India [1]. The most common first-tier method recommended for screening of CAH is by time-resolved fluoroimmunoassay (FIA) using dried blood spots (DBS). Other techniques like radioimmunoassay and ELISA have lower sensitivity and have been phased out in most NBS programs [2].

Principle of test: DELFIA (dissociation enhanced lanthanide fluorescence immunoassay) is the recommended technology in first-tier testing. Lanthanide chelate labeled reagents (Europium, Samarium, Terbium) are used to detect the presence of analytes in the blood sample. The measurement of TSH on DBS uses direct sandwich technique, thus the fluorescence signal is directly proportional to the concentration of the analyte. However, measurement of 17-OHP by DELFIA is indirect, where the analyte (17OHP) competes with europium-labeled 17-OHP for the binding sites on monoclonal antibodies. Thus, the fluorescence is inversely proportional to the content of the analyte [3].

Sample collection: DBS are easy to collect using standard heel lancets. Samples for steroid profiling should be collected preferably after 48-72 hours, but at least 24 hours after birth. Small circles are punched out from DBS from which blood is eluted in closed automated machines that process the samples. The same DBS can be preserved for testing of other analytes/ molecular testing after due consent of the parents.

Interpretation: Blood 17-OHP values more than 30-37.5 nmol/L (10-12.2 ng/mL)are considered abnormal. [3] Levels may be falsely elevated in preterm or sick babies [2] and should be repeated after two weeks of life or after stabilization, whatever is later. NBS data from Italy showed a reduction in false positive rates after increasing the cut-off of 17-OHP from 30 to 50 nmol/L in preterm babies [4]. Likewise, multiple courses of steroids can affect the estimation of 17-OHP, leading to false negative values and indicate a repeat screen after 2-3 weeks [2]. Indian data on gestation-wise cut-offs reported a cut-off of 37.5 nmol/L (12 ng/mL) for term babies and 42 nmol/L (14 ng/mL) for preterm babies (33-36 weeks) as abnormal [4,5]. A multiplication factor of 0.66 with whole blood units (in nmol/L) may be used to obtain serum units (in ng/mL) of 17-OHP cut-offs [3].

The incidence of CAH as per NBS programs in the world is approximately 1:14,000 to 1:18,000, lower than most reports from India that report an incidence of 1:2575 to 1:6873 [6-8].

This could reflect the lack of confirmatory second-tier testing, or probably a higher rate of endogamy contributing to a higher incidence in India, similar to an incidence of 1:7785 in Turkey [9].

Confirmation: The elevated 17-OHP values obtained on first tier testing by time-resolved FIA require confirmatory testing using liquid chromatography–tandem mass spectrometry (LC-MS/MS) in view of high number of false positives on FIA [1]. LC-MS/MS can perform complete steroid profiling to measure androstenedione, 11-deoxycortisol, 21-deoxycortisol, and cortisol, and can differentiate falsely elevated 17-OHP levels in stressed or sick babies. The Australasian screening programs reported a four-fold reduction in false positive rate, with an increase in positive predictive value from 2 to 11%, within two years of adopting LC-MS/MS for CAH-NBS [1]. However, LC-MS/MS platforms require stringent monitoring of quality control (QC) samples for validation and quality assurance. Few laboratories have investigated in-house QC methods for LC-MS/MS [10].

Conclusion: NBS is a cost-effective method for early identification of serious life-threatening disorders like CAH. The collection of heel-prick sample as DBS after 24 hours is required to screen levels of 17-OHP that should be interpreted as per laboratory specific and gestation-wise cut-offs. Confirmatory testing using LC-MS/MS reduces the false positive rates and should be offered with molecular diagnosis where facilities are available.

References:

1. Heather NL, Nordenstrom A. Newborn Screening for CAH-Challenges and Opportunities. Int J Neonatal Screen. 2021;7(1):11.

2. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital Adrenal Hyperplasia-Current Insights in Pathophysiology, Diagnostics, and Management. Endocr Rev. 2022;43(1):91-159.

3. GSP Neonatal 17α-OH-progesterone kit. Available at URL https://resources.perkinelmer.com/lab-solutions/resources/docs/BRO_GSPNeonatalKit_HR_low.pdf

4. Cavarzere P, Camilot M, Teofoli F, Tatò L. Neonatal screening for congenital adrenal hyperplasia in North-Eastern Italy: a report three years into the program. Horm Res. 2005;63(4):180-186.

5. Vats P, Dabas A, Jain V, et al. Newborn Screening and Diagnosis of Infants with Congenital Adrenal Hyperplasia. Indian Pediatr. 2020;57(1):49-55.

6. ICMR Task Force on Inherited Metabolic Disorders. Newborn Screening for Congenital Hypothyroidism and Congenital Adrenal Hyperplasia. Indian J Pediatr. 2018;85(11):935-940.

7. Kaur G, Thakur K, Kataria S, et al. Current and future perspective of newborn screening: an Indian scenario. J Pediatr Endocrinol Metab. 2016;29(1):5-13.

8. Kommalur A, Devadas S, Kariyappa M, et al. Newborn Screening for Five Conditions in a Tertiary Care Government Hospital in Bengaluru, South India-Three Years Experience. J Trop Pediatr. 2020;66(3):284-289.

9. Güran T, Tezel B, Gürbüz F, et al. Neonatal Screening for Congenital Adrenal Hyperplasia in Turkey: A Pilot Study with 38,935 Infants. J Clin Res Pediatr Endocrinol. 2019;11(1):13-23.

10. Grecsó N, Zádori A, Baráth Á, et al. Comparison of different preparation techniques of dried blood spot quality controls in newborn screening for congenital adrenal hyperplasia. PLoS One. 2021;16(5):e0252091.

History Corner
Thomas Addison (1793-1860)

Dr Nikhil Lohiya, Consultant Pediatric & Adolescent Endocrinologist
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Born in April 1793, at Long Benton, Newcastle-upon-Tyne, at 15 Wellington Villas, Brighton Thomas Addison was the son of Sarah and Joseph Addison, a grocer and flour dealer in Long Benton. He was first sent to school in a roadside cottage where his teacher was John Rutter, the parish clerk, who years later also taught Robert Stephenson.

Thomas became a medical student at the University of Edinburgh in 1812 and in August 1815 he gained an MD. His thesis was 'Concerning Syphilis and Mercury' (now in the Wellcome Library, London). The same year he become house surgeon at the Lock Hospital, and entered as pupil to the Public Dispensary. His interest in skin disease was due to Thomas Bateman. He was promoted to assistant physician after he obtained his LRCP in 1819. In 1827 he became lecturer at materia medica. His lectures were very popular with fees assessed at £700 or £ 800 a year. In 1837 Addison became full physician to Guy's Hospital. Samuel Wilks describe Addison as "a quick hasty and impassioned manner of expression is not unfrequently the result of a deficient controlling power. We know . . . that, although wearing the outward garb of resolution, he was beyond most other men, most liable to sink under trial".

Story of Addison disease - Addison first wrote a short article in the London Medical Gazette (1849): 'Anaemia—disease of the suprarenal capsules in which the disease is not distinctly separated from a new form of anaemia'.

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One of the great works in 1855 was when Addison described for the first time two chronic diseases which he could not clearly separate: 'On the Constitutional and Local Effects of Disease of the Suprarenal Capsule'. The entity was confirmed by Trousseau (1801–1867) in Paris, who recognized supra-renal failure and named it Addison's disease. The monograph describes how, when investigating a peculiar form of anaemia, he found pathological changes in both suprarenal glands that appeared to be independent of the anaemia. He had, with Samuel Wilks, collected and described 11 patients.
In 1824 Addison founded the Department of Dermatology at Guy's. The department still possesses a collection of wax models of skin disorders prepared under his supervision. Addison married Catherine Hauxwell at Lanercost Church in September 1847. They were childless. For many years his life was blighted by depression and, along with his innate shyness, this probably accounted for some aspects of his behavior. It also deprived him of the affection and understanding of certain colleagues. This precipitated his retirement in 1860. Within 3 months of his retirement, he was no more, due to suicide. His remains were taken for burial to Lanercost Abbey, Cumberland, near his childhood home.

PedEndoScan

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Musa SA, Hassan SS, Ahmed AI, Ngwiri T, Fadlalbari GF, Ibrahim AA, Babiker OO, Abdullah MA. Clinical profile, etiology, and diagnostic challenges of primary adrenal insufficiency in Sudanese children: 14-years' experience from a resource limited setting. Journal of Pediatric Endocrinology and Metabolism. 2022 Feb 1;35(2):231-7.

Primary adrenal insufficiency (PAI) in children is an uncommon condition. Congenital adrenal hyperplasia (CAH) is the commonest cause, followed by autoimmune disorders. Diagnosis and management are challenging, especially in resource-limited settings. The authors describe for the first time the clinical presentation, possible etiologies, and challenges in diagnosis and management of PAI in a large cohort of Sudanese children. They conducted a descriptive hospital-based study where all patients diagnosed with PAI between 2006 and 2020 were reviewed. The diagnosis was based on clinical presentation, low morning cortisol ± high adrenocorticotropic hormone (ACTH), or inadequate response of cortisol to synacthen stimulation. Challenges faced in diagnosis and management were identified. Of 422 PAI suspected patients, 309 (73.2%) had CAH, and 33 (7.8%) had PAI-like symptoms and were not discussed further. Eighty patients (19%) fulfilled the study criteria: 29 had Allgrove syndrome, nine auto-immune polyendocrinopathy syndrome, seven adrenoleukodystrophy, and one had an adrenal hemorrhage. Hyperpigmentation was the cardinal feature in 75 (93.8%), while an adrenal crisis was not uncommon. Lack of diagnostic facilities obscured the etiology in 34 (42.5%) patients. **The authors concluded that PAI is not uncommon in Sudanese children where genetic causes outweigh the autoimmune ones. Many cases were missed due to nonspecific presentation, lack of awareness, and difficult access to tertiary health care facilities. In addition to the clinical findings, early morning cortisol ± ACTH levels can be used for making the diagnosis where facilities are limited, particularly if the synacthen stimulation test is not available.**

Seneviratne SN, Jayarajah U, Gunawardana S, Samarasinghe M, de Silva S. Gender-role behaviour and gender identity in girls with classical congenital adrenal hyperplasia. BMC Pediatrics. 2021 Dec;21(1):1-6.

Girls with classical CAH are exposed to excess fetal adrenal androgens in utero, and are often born with masculinised genitalia. They are conventionally reared as females, but show more "boyish" gender-role behaviour (GRB) and gender-identity (GI) issues in childhood and adolescence. Male-rearing is also reported, mainly due to delayed treatment and/or socio-cultural factors. In this study, the authors compared GRB/GI in 27 girls with CAH using the Gender Identity Questionnaire for children (GIQC), with 50 healthy age-matched children as controls, and

explored for associations with socio-demographic and diagnosis/ treatment related factors. It was observed that girls with CAH had lower total GIQC scores compared to healthy children (3.29 vs. 4.04, p = < 0.001) with lower GRB score (3.39 vs. 4.23, p < 0.001), and tendency for lower GI score (3.19 vs. 3.5, p = 0.08). Exploratory analysis showed no differences based on diagnosis/treatment factors including age, degree of virilisation at diagnosis and surgical procedures. and only subtle changes based on ethnicity and maternal education. Girls with CAH managed at a specialised center showed more masculinised GRB and tendency for ambiguous GI, which did not vary with diagnosis/ treatment related factors, suggesting that prenatal androgen exposure was the likely contributor. **The authors suggest that clinicians should be vigilant about the increased risk of gender-related problems in girls with CAH, irrespective of sociocultural background and despite early treatment.**

Merke DP, Mallappa A, Arlt W, Brac de la Perriere A, Lindén Hirschberg A, Juul A, Newell-Price J, Perry CG, Prete A, Rees DA, Reisch N. Modified-release hydrocortisone in congenital adrenal hyperplasia. Journal of Clinical Endocrinology & Metabolism. 2021 May;106(5):e2063-77.
Standard glucocorticoid therapy in CAH regularly fails to control androgen excess, causing glucocorticoid overexposure and poor health outcomes. The authors in the current study investigated whether modified-release hydrocortisone (MR-HC), which mimics physiologic cortisol secretion, could improve disease control. It was a 6-month, randomized, phase 3 study comparing MR-HC vs standard glucocorticoid, followed by a single-arm MR-HC extension study. Primary outcomes were change in 24-hour SD score (SDS) of androgen precursor 17-OHP for phase 3, and efficacy, safety and tolerability of MR-HC for the extension study. The phase 3 study, which recruited 122 adult CAH patients, failed its primary outcome at 6 months, but there was evidence of better biochemical control on MR-HC, with lower 17-OHP SDS at 4 (P = .007) and 12 (P = .019) weeks, and between 07:00h to 15:00h (P = .044) at 6 months. The percentage of patients with controlled 09:00h serum 17-OHP (< 1200 ng/dL) was 52% at baseline, while at 6 months it was 91% for MR-HC and 71% for standard therapy (P = .002), and at 18 months extension, it was 80% for MR-HC. The median daily hydrocortisone dose was 25 mg at baseline, at 6 months 31 mg for standard therapy, and 30 mg for MR-HC, and after 18 months 20 mg for MR-HC. Three adrenal crises occurred in phase 3, none on MR-HC, and 4 in the extension study. MR-HC resulted in patient-reported benefit including menses restoration in 8 patients (1 on standard therapy), and 3 patient and 4 partner pregnancies (none on standard therapy). **The authors concluded that MR-HC improved biochemical disease control in adults with CAH, with reduction in steroid dose over time and patient-reported benefits.**

Buonocore F, Maharaj A, Qamar Y, Koehler K, Suntharalingham JP, Chan LF, Ferraz-de-Souza B, Hughes CR, Lin L, Prasad R, Allgrove J. Genetic analysis of pediatric primary adrenal insufficiency of unknown etiology: 25 years' experience in the UK. Journal of the Endocrine Society. 2021 Aug;5(8):bvab086.
Although PAI in children and young people is often due to congenital adrenal hyperplasia (CAH) or autoimmunity, other genetic causes occur. The relative prevalence of these conditions is poorly understood. With this in mind, the authors investigated genetic causes of PAI in children and young people over a 25 year period. They reviewed unpublished and published data for 155 young people in the United Kingdom who underwent genetic analysis for PAI of unknown etiology in three major research centers between 1993 and 2018. They pre-excluded those with CAH, autoimmune, or metabolic causes. They also obtained additional data from NR0B1 (DAX-1) clinical testing centers. Genetic analysis involved a candidate gene approach (1993 onward) or next generation sequencing (NGS; targeted panels, exomes) (2013-2018) were noted. The results showed that genetic diagnosis was reached in 103/155 (66.5%) individuals. In 5 children the AI resolved and no genetic cause was found. Pathogenic variants occurred in 11 genes: MC2R (adrenocorticotropin receptor; 30/155, 19.4%), NR0B1 (DAX- 1; 7.7%), CYP11A1 (7.7%), AAAS (7.1%), NNT (6.5%), MRAP (4.5%), TXNRD2 (4.5%), STAR (3.9%), SAMD9 (3.2%), CDKN1C (1.3%), and NR5A1/steroidogenic factor-1 (SF-1; 0.6%). Additionally, 51 boys had NR0B1 variants identified through clinical testing. Although age at presentation, treatment, ancestral background, and birth weight can provide diagnostic clues, genetic testing was often needed to define the cause. **The authors concluded that PAI in children and young people often has a genetic basis. Establishing the specific etiology can influence management of this lifelong condition. NGS approaches improve the diagnostic yield when many potential candidate genes are involved.**

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The Transgender Persons (Protection of Rights) Act, 2019

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Children and adolescents who experience a marked incongruence between the gender assigned at birth and their gender identity are 'transgender' and 'gender-nonconforming' individuals. Gender identity and gender role are determined by genetic, environmental and socio-cultural influences. The incongruence in gender may be physical and/ or psychosocial, and can disrupt the well-being of the affected person and the family. Transgender persons face discrimination and disparity in their needs like education, shelter and even food, that adds to their mental health problems.

Transgender remains an ostracized identity in Indian culture, where the reputation of the family is put at stake, with the fear of losing the affected child to eunuch groups. The child may be born with a medical problem like disorders of sexual differentiation (DSD), or may only demonstrate emotional and psychosocial non-congruence to the 'assigned gender at birth'. The gender of rearing is often decided by the parents after birth. In India, most parents of babies with DSD opine that male gender of rearing is easier to assign than female gender. However, this may become an unethical decision and may not be in agreement with the gender role and identity that the child assumes later in life. In addition to the psychosocial concerns, medical problems, need for hormonal replacement therapy, cost of and access to surgical reconstructive options and managing associated complications are other concerns for transgender persons. The health care providers for transgender and gender 'nonconforming people, need to be aware of the local legal situation, family dynamics, the patients' and their families' attitudes, and accordingly provide the services. Thus, in addition to medical knowhow, the practicing physicians should be familiar with the legal aspects pertaining to this field so as to appropriately assess and help these patients.

The medical and social concerns related to transgenders have received greater recognition in the past decade. A few global associations highlighted transgender rights and took initiatives to promote healthcare and advocacy, and prohibit discrimination to ensure the wellbeing of transgender people. Therefore, with increasing awareness and greater media coverage regarding the barriers and difficulties faced by transgender population, and in relation to the rights of the LGBT community, the Government of India has passed "The Transgender Persons (Protection of Rights) Act" in December 2019, formulated by the Ministry of Law and Justice, to address various issues faced by transgenders. This Act deals with discrimination in society, recognition of identity, welfare measures, educational disparity, social security, access to health care and offences & penalties *[Available at URL: https://thc.nic.in/Central%20Governmental%20Rules/Transgender%20Persons%20(Protection%20of%20Rights)%20Rules,%202020.pdf]*

A transgender person is defined as 'a person whose gender does not match with the gender assigned to that person at birth and includes trans-man or trans-woman (whether or not such person has undergone Sex Reassignment Surgery or hormone therapy or laser therapy or such other therapy), person with intersex variations, genderqueer and person having such socio-cultural identities as *kinner, hijra, aravani* and *jogta*' (Transgender Act, 2019).

The different chapters under the Gazette cover the following points:

- Preliminary including definitions
- Prohibition against discrimination
- Recognition of identity of transgender persons
- Welfare measures by government
- Obligation of establishments and other persons

- Education, social security and health of transgender persons
- National council for transgender persons
- Offences and penalties
- Miscellaneous.

The following are a few salient features under the Act:

- Discrimination against a transgender is strictly prohibited with regard to educational institutes, employment and social rights.
- Transgenders to be recognized as their self-perceived gender identity and can get a certificate issued by District Magistrate with identity as transgender.
- Welfare schemes are to be made available by the Government that are transgender sensitive, non-stigmatising and non-discriminatory.
- Educational and healthcare facilities should be made available for transgender care with provision for coverage of medical expenses for surgical and medical therapy.
- A National Council for transgender persons is to be set up for advising, monitoring and coordinating activities related to transgender health.
- Any threat to life, safety or wellbeing, including abuse towards transgenders, shall be punishable with imprisonment for a term which shall not be less than six months but which may extend to two years and with fine.

Minireview
Management of childhood adrenocortical carcinoma

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Introduction: Adrenocortical carcinoma is rare, accounting for 0.2% of all childhood cancers. It has a bimodal distribution, affecting young children and adults. In children, it mostly presents before 4 years and after 12 years of age. Most are functional tumors (90%), mainly seen in young toddlers, while non-functional tumors are more common in adolescents.

Adrenocortical adenoma vs. carcinoma: It is very difficult to distinguish adrenocortical adenoma from carcinoma on clinical and histopathological basis. High risk criteria have been defined by the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) group as presence of one of the following features: age at diagnosis, tumor volume more than 200 cm^3, presence of Cushing syndrome, initial biopsy (open or Tru-cut), surgical excision with microscopic residuals or spillage (R1) or macroscopic residuals (R2), regional lymph nodes involvement, histologic vascular invasion, and distant metastases at diagnosis.[1]

Thus, initial investigations planned, along with histological criteria, are necessary for prognostication and further management. [2]

Table 1: Recommended list of investigations

For early tumor evaluation	USG Pelvis and abdomen/ CT scan Pelvis and abdomen	
When clinical and radiological suspicion of malignant ACC is high	Abdominal magnetic resonance imaging (MRI) /whole-body MRI, Positron emission tomography (PET) scan or PET MRI	
When suspicion of lung, bone, brain metastases	Chest CT, Bone CT, Brain MRI	If not undergoing whole body MRI/PET scanBrain MRI if suspicious/ proven Li–Fraumeni syndrome

Hormonal assessment	Glucocorticoid excess: dexamethasone suppression test, 24-hours urinary free cortisol, basal ACTH, salivary cortisol	In all patients at diagnosis, and a regular monitoring of hormonal levels is recommended during the follow-up
	Sex steroid excess: DHEAS, 17OH-progesterone, androstenedione, testosterone, 17-beta-estradiol, 11-deoxycortisol, estrone and estradiol Mineralocorticoid excess: aldosterone, Serum potassium, aldosterone/renin ratio, Urinary catecholamines and metanephrine levels	
Genetic counselling		All patients

Histological Weineke criteria (Table 2) have been found to have a stronger prognostic predictive value as compared to criteria like Weiss criteria used in adults [2,3]. Ki-67 and P53 can be used as additional markers.

Table 2. Wieneke Index – Macroscopic and microscopic criteria for malignancy (Total 9 points- 1 point for each criterion)

1. Weight > 400 grams 2. Size > 10.5 cm 3. Extension into adjacent tissue and organs 4. Vena cava invasion	5. Venous invasion 6. Capsular invasion 7. More than 15 mitoses/20 HPF 8. Tumor necrosis 9. Atypical mitotic figures	Interpretation: ⩽ 2- Benign histology 3: Undetermined > 3: Malignant

Management:
Children's Oncology Group has given a grading system for adrenocortical tumors (table 3). [2,4]

Table 3. Children's Oncology Group (COG) staging system for adrenocortical tumours and proposed management *

Stage	Definition	Management
I	R0 (Complete histological resection) and small localised tumors (<100 gm or <200 cm^3), with normalisation of hormonal levels after surgery	Upfront surgery in case of resectable lesions
II	R0 and large localised tumors (⩾100 gm or ⩾200 cm^3), with normalisation of hormonal levels after surgery	Surgery + locoregional/ retroperitoneal lymph node dissection (RPLND). In case of unfavorable histology - consider mitotane
III	Unresectable tumors or gross/ macroscopic residual disease; tumor spillage (preop biopsy or intraoperatively); failure to normalize hormonal levels after exclusive surgery; retroperitoneal lymph nodes involvement	In case of unresectable localised tumor, neoadjuvant chemotherapy and mitotane to reduce volume and invasion may be attempted.In other cases, six courses of adjuvant chemotherapy, supplemented by mitotane, can be proposed by multidisciplinary team. Or surgery + RPLND + CED chemotherapy for eight cycles and mitotane for 8 months
IV	Distant metastases	If surgery is not possible, upfront 2-4 cycles of multiagent chemotherapy + mitotane is recommended, with regular monitoring according to Response Evaluation Criteria In Solid Tumors (RECIST criteria). Once volume reduction occurs, delayed tumor and metastases surgery to be considered. If no volume reduction- consider other new targeted therapies

Adapted from Adrenocortical tumors in children and adolescents: the EXPeRT/ PARTNER diagnostic and therapeutic recommendations

*- Management needs to be individualised in consultation with a multidisciplinary team.

Surgery: In case of localised disease, the primary treatment modality is open surgery, as an initial open or Tru-cut biopsy should be avoided to prevent spillage, especially in a functional tumor. Upfront en-bloc resection of the primary tumor with dissection of regional lymph nodes (if suspicious or enlarged) should be done. In case of known metastatic disease, surgery should be done only in patients who are in good clinical condition, when a reasonable clearance of metastatic sites looks ultimately feasible. [4,5]

Chemotherapy: For grade 2 onwards, the first line recommended regimen is CED (cisplatin, etoposide and doxorubicin) as per the ARAR0332 protocol or NN1/NN2 (vincristine, ifosfamide and doxorubicin/ carboplatin and etoposide) according to the GPOH strategy. Neoadjuvant chemotherapy should be considered in unresectable, recurrent and metastatic tumors. Mitotane has been FDA approved for treatment of such adrenocortical carcinomas with or without chemotherapy. It is also used off-label in the treatment of Cushing syndrome. [2,4,5]

A note on mitotane [6-9]:

- Mitotane is a derivative of the insecticide DDT and an isomer of p,p'-DDD (4,4' dichlorodiphenyldichloroethane). It is also known as 2,4'-(dichlorodiphenyl)-2,2-dichloroethane (o,p'-DDD). Mitotane is able to interfere with the mitochondrial respiratory chain function and to induce morphologic fragmentation of the mitochondrial membranes that are required for respiratory chain activity and presumably steroidogenesis. It has also been found to block sterol-O-acyl transferase 1, which results in disturbed steroidogenesis and lipid-induced endoplasmic reticulum stress, thus causing cytotoxic atrophy of the both normal and neoplastic adrenal cells. Benefit depends on maintenance of adequate plasma drug levels > 14µg/ml and toxicity occurs at > 20µg/ml. The relationship between steady state plasma level and dose administered is variable, with significant (5-10 fold) inter-patient variation. It has a very long elimination half-life due to strong drug diffusion in the adipose tissues and organs, metabolite DDE as well as interaction with metabolizing enzymes. Also, it has a narrow therapeutic index. Thus, individualised treatment is needed with frequent therapeutic drug monitoring.
- Mitotane is available as a 500 mg oral preparation. The dose is started with 500 mg and gradually built up every 4-7 days, escalating to reach a maximum of 4g/m2 within a period of 2-4 weeks. It has to be administered in three divided doses, along with fat-rich snacks or meals. In the low dose regimen, monitoring should start after 4-8 weeks of start of treatment, and done every 2-3 monthly, though mostly targets are reached after 3 months even in a high dose regimen. Before starting therapy, proper examination of the central nervous system, evaluation of complete blood count, LFT, KFT, lipid profile, thyroid function tests and baseline ACTH and PRA assays should be done.
- Treatment leads to adrenal insufficiency in most patients, and increases the metabolic clearance of glucocorticoids by CYP3A4 induction. Thus, oral glucocorticoid replacement (at least double the required replacement dose, as mitotane inactivates 50% of administered hydrocortisone) ± mineralocorticoid (fludrocortisone) must be given. Most patients will ultimately require high dose glucocorticoid replacement. Stress dose advice should be given. Proper monitoring by ACTH and PRA assays should be done.
- Other adverse effects are:
    - Gastrointestinal (most common) - anorexia, nausea, vomiting and diarrhoea.
    - CNS - ataxia, vertigo, lethargy, somnolence, epilepsy, encephalopathy.
    - Hormonal- prepubertal gynaecomastia, adrenal insufficiency, hypothyroidism, male hypogonadism.
    - Skin - transient skin rash.

  Some infrequent genitourinary, cardiac and visual side effects are also seen. In case of any adverse effect, the drug should be temporarily stopped, and restarted after a period of 2-4 weeks at a lower dose, and built up subsequently. The duration of treatment and end point are not defined as of yet.

Other novel therapies: Many targeted therapies like IGF2, multikinase inhibitors, EGF receptor and VEGF inhibitors, mTOR inhibitors, Wnt signaling inhibitors and inverse agonist of steroidogenic factor 1 are being studied in adults at present.

Conclusion: Locally advanced or metastatic childhood ACT have a very poor prognosis even after surgery and intensive chemotherapy. Rational early investigations, Children's Oncology Group staging, judicious use of mitotane is useful with in the management of ACC.

Reference:

- *Cecchetto G, Ganarin A, Bien E, Vorwerk P, Bisogno G, Godzinski J, Dall'Igna P, Reguerre Y, Schneider D, Brugières L, Leblond P, Ferrari A, Brecht I, De Paoli A, Orbach D. Outcome and prognostic factors in high-risk childhood adrenocortical carcinomas: A report from the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT). Pediatr Blood Cancer. 2017 Jun;64(6). doi: 10.1002/pbc.26368.*
- *Virgone C, Roganovic J, Vorwerk P, et al. Adrenocortical tumours in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations. Pediatr Blood Cancer. 2021;68:e29025.*
- *Das S, Sengupta M, Islam N, Roy P, Datta C, Mishra PK, Banerjee S, Chaudhuri MK, Chatterjee U. Weineke criteria, Ki-67 index and p53 status to study pediatric adrenocortical tumors: Is there a correlation? J Pediatr Surg. 2016 Nov;51(11):1795-1800. doi: 10.1016/j.jpedsurg.2016.07.014.*
- *Gupta N, Rivera M, Novotny P, Rodriguez V, Bancos I, Lteif A. Adrenocortical Carcinoma in Children: A Clinicopathological Analysis of 41 Patients at the Mayo Clinic from 1950 to 2017. Horm Res Paediatr. 2018;90(1):8-18. doi: 10.1159/000488855.*
- *Ardicli B, User IR, Ciftci AO, Akyuz C, Kutluk MT, Yalcin B, Gonc N, Ozon ZA, Alikasifoglu A, Oguz B, Haliloglu M, Orhan D, Tanyel FC, Karnak I, Ekinci S. Adrenocortical tumours in children: a review of surgical management at a tertiary care centre. ANZ J Surg. 2021 May;91(5):992-9. doi: 10.1111/ans.16542.*
- *Redlich A, Boxberger N, Strugala D, Frühwald MC, Leuschner I, Kropf S, Bucsky P, Vorwerk P. Systemic treatment of adrenocortical carcinoma in children: data from the German GPOH-MET 97 trial. Klin Padiatr. 2012 Oct;224(6):366-71. doi: 10.1055/s-0032-1327579.*
- *Oddie PD, Albert BB, Hofman PL, Jefferies C, Laughton S, Carter PJ. Mitotane in the treatment of childhood adrenocortical carcinoma: a potent endocrine disruptor. Endocrinol Diabetes Metab Case Rep. 2018 Aug 23;2018:18-0059. doi: 10.1530/EDM-18-0059.*
- *Franczyk B, Rysz J, Gluba-Brzózka A. Pharmacogenetics of Drugs Used in the Treatment of Cancers. Genes (Basel). 2022 Feb;13(2):311. doi:10.3390/genes13020311*
- *Garg MB, Sakoff JA, Ackland SP. A simple HPLC method for plasma level monitoring of mitotane and its two main metabolites in adrenocortical cancer patients. J Chromatogr B Analyt Technol Biomed Life Sci. 2011 Aug 1;879(23):2201-5. doi: 10.1016/j.jchromb.2011.06.001.*
- *Puglisi S, Calabrese A, Basile V, Pia A, Reimondo G, Perotti P, Terzolo M. New perspectives for mitotane treatment of adrenocortical carcinoma. Best Pract Res Clin Endocrinol Metab. 2020 May;34(3):101415. doi: 10.1016/j.beem.2020.101415.*

The following two interesting case reports submitted by ISPAE members highlight the need for an individualised approach in every case of ACC.

Hirsutism in a girl: what was unearthed

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The authors report a case of a 5-year-old girl who presented with complaints of left flank discomfort, along with increased hair growth over the upper lip, lower part of the body and legs for the last 5 months, with deepening of the voice over the last 4 months. There was no history suggestive of cortisol excess.

Clinical assessment showed features of virilisation with muscular build, hirsutism and clitoromegaly (Fig 1). Blood pressure was 100/70 mmHg (95th centile for age).

Endocrine assessment revealed: elevated fasting serum testosterone of 1012 ng/dL (N < 20 ng/dL) and DHEAS > 1000 mcg/dL (N < 0.1mcg/dL). The overnight 1 mg dexamethasone suppression test gave a serum cortisol of < 1 mcg/dl the next morning. CECT whole abdomen with chest cuts done subsequently showed a 75x72x65 mm large enhancing mass of soft tissue density, with a lobulated outline, in the left suprarenal region, pushing the upper pole of the left kidney, with no vena caval invasion or periadrenal extension, and no evidence of hepatic or lung metastasis (Fig 2). The 24 hr urine levels of fractionated metanephrines and normetanephrines were normal. A diagnosis of left adrenal mass, possibly androgen secreting ACC without any evidence of cortisol excess, was made.

After anaesthesia clearance, she underwent laparoscopic left adrenalectomy under GA, with adequate perioperative steroid coverage. Intraoperative findings showed a 7x6 cm bosselated ovoid adrenal SOL not fixed to the surrounding structures, with no enlarged lymph nodes. Histopathological examination of the mass, weighing almost 200 gm, showed on microscopy, nests of large polygonal cells with granular eosinophilic cytoplasm, vesicular nucleus and prominent nucleoli. The cells showed nuclear anisonucleosis; high nuclear grade,

mitotic figures including atypical mitosis were identified. Clear cells comprised approximately 10%, with focal areas of necrosis and hemorrhage. The overall features were diagnostic of ACC, with no capsular or lymphovascular invasion. Hormonal evaluation one month after the surgery revealed morning cortisol of 9.89 mcg/dl, serum DHEAS < 15 mcg/dl, fasting morning serum testosterone < 20 ng/dl, serum androstenedione < 0.3 ng/ml. The patient remains on follow up; except the clitoromegaly, all features of hyperandrogenism have started regressing.

Our diagnosis was ACC (ENSAT stage II, T2N0M0) in a 5-year-old girl, presenting with features of virilisation, subjected to adrenalectomy, leading to remission of symptoms on follow up. The key principles highlighted in this case include: early and expedited diagnosis, complete resection in limited disease, favorable histology and regular follow-up for disease recurrence. The index case was fortunate to have scored positively on all these aspects till the authors last saw her.

References:

1. Rittmaster RS. Hirsutism [review] Lancet. 1997; 349:191–5.

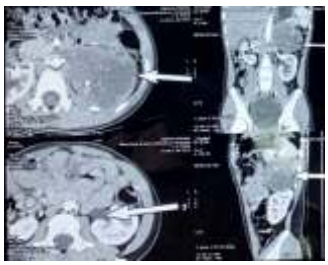
2. Rosenfield RL. Clinical practice. Hirsutism. N Engl J Med. 2005; 353:2578–88

3. Grisanti S, Cosentini D, Laganà M, Turla A, Berruti A. Different management of adrenocortical carcinoma in children compared to adults: is it time to share guidelines.Endocrine. 2021 Dec;74(3):475-477.

4. Gupta N, Rivera M, Novotny P, Rodriguez V, Bancos I, Lteif A. Adrenocortical Carcinoma in Children: A Clinicopathological Analysis of 41 Patients at the Mayo Clinic from 1950 to 2017. Horm Res Paediatr. 2018;90(1):8-18.

Fig 1:
Clitoromegaly in the index case

Fig 2:
CECT abdomen showing large left adrenal mass with calcification



(Authors have obtained permission to present these image)

Functional Adrenocortical Oncocytoma: Challenges with the pathological classification!

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A 5 month old infant presented with cushingoid features, normal development, and sudden weight gain, predominantly around the face, and excessive body hair. Physical examination revealed increased vellus hair over the face, trunk, and extremities. Genital examination was normal, growth was normal, but BP was elevated (140/80 mmHg - above the 95th percentile). 2D ECHO showed reported features of hypertrophic cardiomyopathy with systolic anterior motion of mitral leaflet. Biochemical testing showed serum cortisol (random) 50 mcg/dl, testosterone > 2160 ng/dl, DHEAS > 1000 ug/dl, ACTH <5 pg/ml, low serum potassium (2.5 mmol/L) and elevated serum bicarbonate (38 mmol/L). CT abdomen revealed a 3.5x3.2x2.6 cm (CC xTRxAP) left adrenal mass with pre-contrast attenuation of 50HU and heterogeneously enhancing on contrast, with absolute washout of 78% and relative washout of 58%. The opposite adrenal was normal on imaging. Plasma metanephrines and nor-metanephrines were normal. Pre-operative work up was consistent with an androgen-cortisol co-secreting adrenocortical tumor. The child was started on potassium replacement, spironolactone and propranolol; and underwent successful open left adrenalectomy. The gross specimen was a brownish encapsulated tumor, weighing 17 gm, and measuring 3.8x2.9x2.8 cm. The tumor was composed of eosinophilic/ oncocytic cells with areas of focal confluent necrosis, and areas of sinusoidal invasion, but no definitive evidence of capsular invasion (Figure 1a-c).

Mitotic figures were < 5/50 HPF, with no atypical mitosis. On immunohistochemistry, the tumor showed Inhibin, Melan-A positivity, p53 wild type, Beta catenin positivity and a MiB-1(Ki-67 receptor) of 10-15%, ATRX retained, Reticulin maintained (Figure 2a-e).

Applying the Wienkie criteria for adrenocortical neoplasms, the tumor was classified as a benign adrenocortical tumor (as described in the Mini Review above). However, using the Lin-Weiss-Bisceglia criteria, a diagnosis of adrenal oncocytoma with uncertain malignant potential was made. (Major criteria of the Lin Weiss Bisceglia criteria include: >5 mitosis/50 HPF, atypical mitoses and venous invasion; minor include: large size > 10 cm or > 200 gm, necrosis, capsular invasion and sinusoidal invasion. Presence of one major indicates malignant neoplasm, 1 or more minor criteria indicates uncertain potential and none indicates benign nature).

Post-operative labs revealed random cortisol <1 mcg/dl, DHEAS 3.22 mcg/dl, testosterone <10 ng/dl. The child was started on a replacement dose of hydrocortisone in the dose of 25mg/sq.m; after six months of therapy, has now been weaned off steroids. Repeat hormone parameters measured showed normalization post operatively. Repeat ECG and ECHO showed resolution of the hypertrophic cardiomyopathy.

Adrenal oncocytic tumors are extremely rare; most of them are benign and non-functional [1]. Functional tumors are associated with clinical manifestations of hormonal excess such as Cushing syndrome, virilization, and Sexual precocity [1,2]. Adrenal oncocytic tumors can be of three categories namely adenomas, tumors of undetermined malignant potential, and malignant tumors (oncocytic adrenocortical carcinomas). Out them, tumors of undetermined malignant potential and oncocytic adrenal cortical carcinomas are aggressive in nature, and are associated with poor clinical outcomes. [3] About 10 cases of pediatric adrenal oncocytic tumors has been reported till date.

Histologically oncocytic tumors are characterized by oncocytes with eosinophilic granular cytoplasm and ultra-structurally with numerous closely packed mitochondria. [4] Apart from that, they stain frequently with vimentin and keratin. [5] In most adrenal tumors, the size and CT/ MRI appearance helps in assessing the malignant potential. However, oncocytic tumors are of large volume, and malignant potential is not solely determined by the size of the tumor. [6] On immunohistochemistry functional tumor in the index case was positive for Inhibin, Melan-A reiterating adrenocortical origin. Germline p53 mutation, mostly related to the Li-Fraumein syndrome, are seen in 80% of pediatric adrenocortical cancers (ACC). Our case showed wild type staining pattern for p53 (non-mutation type). Global loss of ATXR is noted in a small subset of ACC. Our case has retained expression of ATRX. Beta catenin which was positive in our case showed nuclear and cytoplasmic positivity in the tumor cells highlighting a wnt activated pathway. It is seen in both adenomas and carcinomas; positivity indicates poor prognosis. MIB1 labeling index has been a useful adjunct in addition to established criteria for clinical decisions in difficult cases. Pediatric adrenocortical tumors show higher labeling indices than adult counterparts. Most adrenocortical adenomas show <10% MIB1 index. a cut-off threshold at 15% is more specific in predicting behavior as ACC. Our case had borderline value between 10-15% on MIB1. Mitotic count and MIB1 labeling index, considered primarily important in most criteria, are significantly influenced by tissue fixation, which further adds to challenges in categorization in predictive criteria. Reticulin staining pattern has been used in classifying adrenal tumors when one of the other worrisome features is also present (altered reticulin with any one of the following features like mitotic count >5 per 50 high power field, tumor necrosis, or vascular invasion indicate malignancy). Our case had maintained peri-cellular reticulin network with no areas of loss. [7]

Classification of pediatric adrenocortical tumors is difficult compared to the adult counterparts according to Weiss criteria, as it leads to over-diagnosis of tumors with benign behavior. Criteria proposed by Wienkie et al. in 2003 are currently preferred for pediatric ACC (described in the Mini Review). This has a total score of 9 points. Score of >/= 4 indicate the tumor is malignant or associated with poor outcome. A score of 3 indicates tumor is of uncertain malignant potential, </= 2 indicate a benign tumor. In our case, the tumor is categorized as benign variant (score 1) according to Wienkie's criteria. [5]

In 2004, Bisceglia et al proposed a new criteria modified from Weiss and Vargas, to discriminate adrenocortical adenomas from oncocytic adrenocortical tumors (described above). A tumor is considered malignant if it exhibits

any of the major criteria; it is considered of uncertain malignant potential (borderline) if 1 or more minor criteria are established; and benign if none of the above-listed features are present. [8] According to the Lin-Weiss-Bisceglia criteria, our tumor is categorized as adrenal oncocytic tumor with undetermined malignant potential.

The treatment of functional tumors is complete surgical excision. irrespective of size. [9] Our patient thus had a functional adrenal oncocytoma with undetermined malignant potential, doing well after complete resection, with resolution of hormone hypersecretion and recovery of the hypothalamo-pituitary-adrenal axis. Ours is a rare case of a pure oncocytic adrenocortical tumor in the pediatric age group presenting with both cushingoid and virilization features, unusual for a adrenocortical adenoma. Though not meeting the "defined" criteria to qualify for an ACC, worrisome features including necrosis, sinusoidal invasion and an elevated MIB1 labeling index, the child merits close follow up.

References:

1. Michalkiewicz E, Sandrini R, Figueiredo B, Miranda EC, Caran E, Oliveira-Filho AG, Marques R, Pianovski MA, Lacerda L, Cristofani LM, Jenkins J, Rodriguez-Galindo C, Ri-beiro RC. Clinical and outcome characteristics of children with adrenocortical tumours: a re-port from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol. 2004 Mar 1;22(5):838-45. doi: 10.1200/JCO.2004.08.085. PMID: 14990639.

2. Lim YJ, Lee SM, Shin JH, Koh HC, Lee YH. Virilizing adrenocortical oncocytoma in a child: a case report. J Korean Med Sci. 2010 Jul;25(7):1077-9. doi: 10.3346/jkms.2010.25.7.1077.

3. Sharma D, Sharma S, Jhobta A, Sood RG. Virilizing adrenal oncocytoma. J Clin Imaging Sci. 2012;2:76. doi: 10.4103/2156-7514.104309. Epub 2012 Dec 4.

4. Narayanan N, Kamalanathan S, Sahoo J, Naik D, Kumaravel S, Ganesh RN. Pediatric Adrenocortical Oncocytoma presenting as Cushing's Syndrome and Peripheral Precocious Puberty: A Case Report and Review of Literature. J ASEAN Fed Endocr Soc. 2021;36(2):205-208. doi: 10.15605/jafes.036.02.17.

5. Wieneke JA, Thompson LD, Heffess CS. Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. Am J Surg Pathol. 2003 Jul;27(7):867-81doi10.1097/00000478-200307000-00001.

6. Yordanova G, Iotova V, Kalchev K, Ivanov K, Balev B, Kolev N, Tonev A, Oosterhuis W. Virilizing adrenal oncocytoma in a 9-year-old girl: rare neoplasm with an intriguing post-operative course. J Pediatr Endocrinol Metab. 2015 May;28(5-6):685-90. doi: 10.1515/jpem-2014-0308.

7. Overview of the 2022 WHO Classification of Adrenal Cortical Tumors. Endocr Pathol. 2022 Mar;33(1):155-196. doi: 10.1007/s12022-022-09710-8. Epub 2022 Mar 14. PMID: 35288842;

8. Bisceglia M, Ludovico O, Di Mattia A, Ben-Dor D, Sandbank J, Pasquinelli G, Lau SK, Weiss LM. Adrenocortical oncocytic tumours: report of 10 cases and review of the literature. Int J Surg Pathol. 2004 Jul;12(3):231-43. doi: 10.1177/106689690401200304

9.Subbiah, S., Nahar, U., Samujh, R., & Bhansali, A. (2013). Heterosexual precocity: rare manifestation of virilizing adrenocortical oncocytoma. Annals of Saudi medicine, 33(3),294–297. https://doi.org/10.5144/0256-4947.2013.294

Figure 1: (a) H&E stain of the tumour showing Oncocytic cells (Magnification 40X) with areas of necrosis (b) and sinusoidal invasion (c) (Magnification 4X)

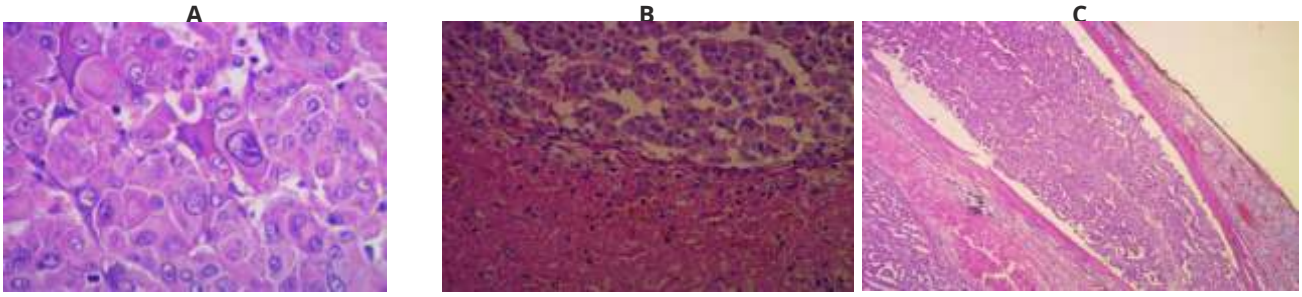
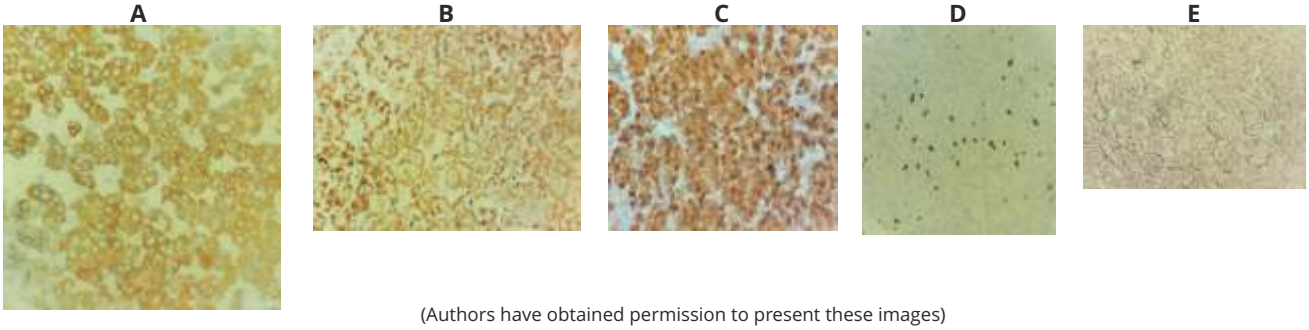


Figure 2: Immunohistochemistry showing Inhibin positivity (a), Melan a positivity (b) and Beta-Catenin positivity. (c) The MIB-1 positivity ranged from 10-15% (d) and Reticulin stain was retained reticulin network (e)



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CAPE News | ISPAE

Reports of ISPAE activities: Training the trainers (TOT) in Pediatric Endocrinology in PEDICON 2022, Noida

Dr M Vijayakumar
National Coordinator CIAP TOT in Pediatric Endocrinology

The National TOT in pediatric endocrinology was conducted during Pedicon 2022, at the venue in Noida on 19th March 2022. Dr PSN Menon and Dr Shaila Bhatacharya (national convenors of the TOT) led the scientific sessions. Dr Hemchand Prasad, Dr Sirisha Kusuma, Dr Amarnath Kulkarni, Dr Diksha Shirodkar, Dr Dhivyalakshmi, Dr Aashima Dabas, Dr Pavithra Nagaraj, Dr Vani H N and Dr Parvathy L were the speakers. Dr Anurag Bajpai, Dr Anju Seth, Dr Riaz I, Dr Vijayakumar M and Dr Tushar Godbole moderated the sessions. The course module was released by the Hon National IAP President Dr Remesh Kumar. The TOT was attended by about 50 delegates from all over India. This event was the inaugural TOT of training programs in Endocrinology being conducted by CIAP all over India.

ISPAE WEBSITE – a REPORT

Dr Sirisha Kusuma
Rainbow Children's Hospital, Hyderabad

As the webmaster, I take pleasure in reporting that in the last 18 months, the ISPAE website has been revamped to improve its appearance as well as the functionality and ease of navigation. Dr Aayush Gupta and Dr Chetan Dave have been tremendously helpful in bringing about these changes.

1. We gave the website a new look that is more vibrant, informative, and appealing.
2. We created a secure ISPAE member online database and activated a member search function where an existing ISPAE member can search (after login) for other registered ISPAE members according to their city of practice and their email addresses (displayed with their permission). This will help pediatric endocrinologists and endocrinologists find their colleagues practicing in other places to refer a patient.
3. A large number of diabetes educators working in different regions of India are also now becoming ISPAE members, and it will be easy to locate them when needed, from the member database.
4. The membership application process has been made completely online.
5. The Observership application has also been made online.
6. The Patient Resource page has been updated and made more user-friendly. New information is being continually added, like "List of NGOs helping T1Ds", a link to "ISPAD-LFAC carb counting book for Indian foods (Co-authored by Ms Sheryl Salis)", "Diabetes Care Guides in regional languages", etc.
7. A Guideline section has been added, with separate pages for "ISPAE guidelines" and others. Links to the upcoming ISPAD Guidelines 2022 will also be provided.
8. A separate page has been created for Covid-19 related information for patients as well as physicians.
9. New pages for the ISPAE's flagship course "IDEAL" and for the abbreviated course "BEST" have been added, with relevant information and application details.
10. ISPAE's official journal JPED: 'Journal of Pediatric Endocrinology and Diabetes' website is linked to the ISPAE website.
11. The homepage links to the ISPAE Facebook page and ISPAE YouTube channel are activated.
12. Pictures from ISPAE-PUNE 2021 are uploaded to the gallery.

We are in the process of working with our vendors to continue to improve functions like search engine optimization and adaptability to mobile devices. We welcome feedback, suggestions and active involvement.

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The IDEAL program – ISPAE Diabetes Education And Learning

Dr Preeti Singh, Associate Professor, Department of Pediatrics
Lady Hardinge Medical College, New Delhi

THE IDEAL JOURNEY...
(The Ispae Diabetes Education And Learning program)

"Some people want it to happen; some wish it would happen; others make it happen." said Michael Jordan. The hard work and determination of the IDEAL Core Committee and the team effort of 47 experienced IDEAL Faculty have translated the dream of "creating a Pediatric Diabetes Educator (PDE) course in India" into reality. Having spent hours collaboratively developing modules to cover every aspect of pediatric diabetes care as delivered in the best centers in the world, combined with what is practical in various socioeconomic settings in our own country, they continue to spend many more hours voluntarily working tirelessly, with great zeal and enthusiasm, to conduct the program in the most effective way possible. No wonder the program is proving to be a grand success.

The aim of IDEAL is to deliver structured, intensive, virtual PDE training which is affordable and accessible for the trainees. The two courses conducted so far were from Oct-Dec 2021 and Feb-April 2022; the third group is now underway. Small batches of trainees - comprising nurses, dieticians, admins of online T1D groups and others who were already involved to varying extents in providing care to children, adolescents and young adults with diabetes and now doctors – are selected, after an entrance MCQ exam, to maximize socio-cultural, linguistic and geographical (urban and semi-urban areas, across India) diversity. Each batch is taught over 12 weeks: 2 sessions per week, of little over 2 hours each, followed by submissions from the trainees.

The comprehensive curriculum, delivered completely virtually, comprise of 17 modules, designed to cover basic and advanced skills needed for ambulatory management of pediatric diabetes. Three-member faculty teams for each of the 17 sessions have prepared a handout and two talks, case scenarios for discussion, and MCQs for pre- and post-testing. Each session therefore has the online pre-test, the two formal presentations covering the topic, followed by intensively interactive case-based discussions, which is aimed at involving all trainees, several poll questions to ensure their constant attention and engagement, and the post-test. The handouts are retained by the trainees, who can also revise by listening to recording of each session, uploaded on Google Classroom. At the end of each session, compulsory assignments are given, to assess the understanding and practical application of the concepts. These consist of 5-8 min videos related to the topic taught, which the trainees are expected to prepare and upload on Google Classroom within a week. The faculty for each session assess their submissions for clarity, delivery, and other aspects, and also analyze the post-test performance to understand which areas have lacunae and need further clarity.

Five feedback sessions are scheduled, interspersed throughout the course. During these sessions, the faculty discuss the assignments and the post-test performance, providing constructive feedback to each trainee. At the end, an Exit Exam consisting of an online timed MCQ exam and individual vivas by a team of one internal and two external experts is conducted to assess the trainees' learning. The program is very rigorous and time-consuming. The 80% mandatory attendance of sessions (including answering of poll questions) and need for timely submission of the assignments for the trainees to be eligible to appear in the Exit Exam ensures that all sessions are taken seriously, in spite of the trainees' busy professional and personal schedules. Fortunately, this "boot camp" atmosphere is well taken, even appreciated by the trainees, as it helps them comprehend the concepts taught and their practical application in real settings. Certification is based on their overall performance, including the assignments and the Exit Exam. An online certification ceremony is held for each batch: for the first two batches, on the auspicious days of 26th January (Republic Day) and 16th May (Buddha Poornima) respectively.

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So far, the journey of team IDEAL has been both challenging and rewarding. The platform for teaching, learning, interaction and continued networking has faced several challenges in the form of trainees having variable baseline knowledge, language barriers, technology support, social strata, and motivation levels, so our own learning curve was rather steep. Nevertheless, the team is striving to reach out to health care providers in inaccessible and remote areas to provide evidence-based, high quality, individualized care to children, adolescents and young adults with diabetes, while sensitizing physicians less familiar with pediatric diabetes to provide optimal care. Team IDEAL takes pride in the successful training of these two batches of competent and confident pediatric diabetes educators, from whom and about whom glowing feedback has been received.

What of the future? The trainees who received certification after the demanding course and rigorous exam, have also taken ISPAE membership. The growing IDEALITES family (trained diabetes educators, IDEAL faculty and core committee) is gaining strength steadily not only as a sub-group, but also making the parent body more vibrant and inclusive. The ISPAE website now has much more to offer physicians, educators, and families. IDEALITES stay connected, network, discuss cases, and share information and resources through a WhatApp group, the ISPAE website and CAPE News, the quarterly ISPAE newsletter. The current IDEAL batch, exclusively physicians, is being trained from June to August 2022. We hope to sustain this effort with three courses per year: two for non-physicians and one for physicians; to produce all handouts in Hindi also, and to gradually develop other resources needed to improve pediatric diabetes care in our country and our region.

Pediatric Endocrinology in PEDICON 2022

Dr Sirisha Kusuma
Rainbow Children's Hospital, Hyderabad

Pediatric endocrinology had a substantial representation as a subspecialty field in the annual conference of the Indian Academy of Pediatrics - PEDICON 2022, held in Noida from 19th -23rd March 2022.

The academic feast started with the TOT- "Training of Trainers"- meeting on the 19th of March, when the coordinators, contributors, and writing committee members from ISPAE met with the prospective trainers from the general pediatric community and presented and discussed the teaching modules on various pediatric endocrinology topics.

The pediatric endocrinology symposium was held on the third day of PEDICON along with other subspecialty symposia. During the two-hour session chaired by ISPAE president Dr Shaila Bhattacharyya, Dr Rakesh Kumar presented "Update in the management of Type 1 Diabetes" and Dr Sirisha Kusuma B spoke regarding the "Management of Non-nutritional Rickets". This was followed by a case-based panel discussion on "Thyroid disorders in children", moderated by Dr Vijayakumar. Panelists Dr Mahesh Maheshwari, Dr Pavithra Nagaraj, Dr Ravindra Kumar, and Dr Bhanukiran Bakri discussed the crucial aspects of recognizing and evaluating common thyroid disorders at various stages of infancy and childhood. The essential nature of universal newborn screening for congenital hypothyroidism was highlighted by all the faculty members. The session was attended by a good number of pediatric colleagues and was quite informative, and interactive.

During the 3rd and 4th days of the conference, various other endocrinology topics were discussed in different forums. Dr Parvathy L elaborated "How to plot growth charts?". Panel discussions were held on "Disorders of Sex Differentiation" (Moderator: Dr Anurag Bajpai, Panelists: Dr Ganesh Jevalikar, Dr Mahesh Maheshwari), "Lab maladies in endocrinology" (Moderator: Dr Shaila Bhattacharyya, Panelists: Dr Zalak Shah Upadhyay, Dr Vijay Jaiswal, Dr. Riaz I, and Dr Vikas Mehrotra), and "Pubertal Disorders in Office Practice" (Moderator: Dr Sharmila Kulkarni, Panelists: Dr Tushar Godbole, Dr Shalini Agarwal, Dr Anjali Sachdeva, Dr Nirupama Mishra, and Dr Umang Arora). A "pediatric endocrinology rapid-fire" session was conducted by Dr Anju Virmani and made vibrant by the participating faculty, Dr Vijaykumar, Dr IPS Kochar, and Dr Mohan Shenoy.

Overall, it was a productive and inclusive PEDICON for pediatric endocrinology.

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Learning pearls from PEDICON

Prof. Mahesh Maheshwari[1], Dr Zalak Upadhyay[2], Prof. Vijay Jaiswal[3], Dr Parvathy Lalitha[4], Dr Pavithra Nagaraj[5]

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Thyroid disorders in children

Congenital Hypothyroidism (CH)

- Newborn screening by testing cord blood or heel prick dried blood spot (DBS) in each and every baby is the best way to identify CH as clinical features are subtle or absent in the neonatal period.
- TSH >20 mIU/L (serum units) is the cut-off for recall if screening sample is taken from cord blood or after 48 hrs of age or between.
- TSH (>34 mIU/L) is the cut-off for recall if sampling done between 24-48 h of age.
- Screening can be done with cord blood/ DBS or venous sample for TSH at 48-72 hours of life. Abnormal values must be confirmed with a fresh venous sample. Thyroxine is started if in the confirmatory sample also there is:-
  - Persistent TSH elevation > 10 mIU/L beyond 3 weeks regardless of T4/ Ft4, or
  - Low FT4 < 1.1ng/dl or T4 < 8 mcg/dl (irrespective of TSH), or
  - FT4 < 1.17 ng/dl or T4 < 10 mcg/dl with elevated TSH > 20 in <2 weeks of age or >10 beyond 2 weeks of age)
- Initial screening may miss 2% of cases with CH, especially if with TSH alone. The reasons could be secondary or tertiary hypothyroidism, or slowly evolving hypothyroidism (e.g. ectopic gland/ hemiagenesis). So, even if screening was normal at birth, if clinically hypothyroidism is suspected later, thyroid function should be tested.
- If the baby was not screened at birth, pediatricians should remember to check thyroid function whenever the baby is first seen.
- Once replacement is started, adherence and technique should be checked at every visit. Poor compliance may be suspected in a child with high TSH, especially if T4 is normal/ high: after missing, the parents may have given more tablets lately to try to compensate). Also, check if any iron/ calcium supplements being taken with or soon after the thyroxine tablet (iron/ calcium/ soy must be given at least few hours after thyroxine ingestion).
- Standard dose of Levothyroxine (10-15 µg/kg/day) normalizes FT4/ T4 within 2 weeks and TSH within 1 month. Sometimes, TSH may take longer to settle. The dose should be titrated to maintain the T4/ FT4 values in the upper half of the normal range and TSH between 1-3, during regular follow up.
- Babies with the possibility of transient CH should be re-evaluated at the age of 3 years, for permanence of CH and the need for lifelong therapy.
- Hearing test and clinical evaluation for other congenital malformations should be performed in all babies with CH.

Thyroid function tests

- Common indications - short stature, weight gain, constipation, dry skin, cold intolerance, neck swelling, pubertal and menstrual disorders.
- Less common indications - Down syndrome, children on anti-epileptics, post brain surgery, irradiation, trauma, nephrotic syndrome, severe LV dysfunction, severe dyslipidemia, carpel tunnel syndrome, sleep apnea.
- Pituitary enlargement with hyperprolactinemia can be associated with hypothyroidism.
- Obese children may have mildly raised TSH (with normal T4), which is the effect of obesity, and not the cause. This is due to increased leptin-mediated production of prothyrotropin-releasing hormone (pro-TRH), impaired feedback due to a lowered number of T3 receptors in the hypothalamus. This mildly raised TSH will not need thyroxine administration.

- In a child with nephrotic syndrome (NS), due to excessive loss of urinary protein leading to loss of albumin, TBG (thyroxine binding globulin) and TBPA (Thyroxin binding pre- albumin), the total T3 and T4 can be altered. In NS or any other cause of hypoproteinemia, it is better to look at Free T4 levels and confirm the diagnosis.

Anti-thyroid antibody tests

- Routine measurement is not recommended.
- Primary hypothyroidism with autoimmune thyroiditis – 85-90% children have positive serum TPO Ab titres, while 30-50% have positive TgAb titers.
- Subclinical hypothyroidism - Useful to predict the likelihood of progression to permanent overt hypothyroidism.

Graves' disease

- Methimazole (MMI) is the preferred treatment choice of anti-thyroid drug (ATD).
- Remission rate is low, especially in a young child, with a large thyroid gland (> 2.5 normal size for age), high initial serum TRAb levels, or very high FT4.
- Surgery or Radioactive Iodine (RAI) therapy are the other options, if no remission after 2 years of drug therapy.
- RAI therapy is indicated in children more than 5 years when serious or persistent side effects of ATD occur, or the child relapses after ATD treatment.
- If hyperthyroidism still persists at 12 months after RAI, a second course can be considered.
- Thyroid Surgery is indicated in children < 5 years with obstructive symptoms from a large goiter, i.e. > 80 gm.

Goiter

- May be physiological during puberty.
- Single, solid mass with irregular edges, calcification or hypo-echogenicity suggest malignancy on ultrasound.

Disorders of Sexual Development

- Genetics, acts of omission, acts of commission and hormones plays an important role in the sex development of the male and female child.
- Basic requirements of work up: History of delayed puberty, microphallus, maternal virilization; Clinical examination for presence of gonads, hypertension, features of salt wasting; and Ultrasound for identification of Mullerian structures.
- Atypical genitalia, bilateral cryptorchidism, penoscrotal hypospadias with microphallus suggest XY DSD.
- Inguinal, labial gonads, labial fusion with AG ratio above 0.5 and clitoromegaly above 0.9 cm are indicator of XX DSD.
- Isolated penile hypospadias, prominent clitoris, labial adhesion, and microphallus in an obese child do not need evaluation.
- 17-OHP, DHEAS, DOC levels help in the diagnosis of XX DSD.
- Bilateral cryptorchidism with presence of Mullerian structures and very high 17-OHP suggest 21-OHD.
- Bilateral cryptorchidism with presence of Mullerian structures, high 17-OHP and history of maternal virilization suggest aromatase deficiency.
- DHEAS, androstenedione, testosterone, DHT are investigations of choice in XY DSD.
- Salt wasting and high 17-OHP suggest 3β-HSD in XY DSD.
- High AMH suggests resistance; low AMH indicates dysgenesis in Ovotesticular DSD.
- Delayed puberty with primary amenorrhea and hypertension in XY DSD suggests 17- OHD defect.
- DSD with hematuria and hypertension in XX DSD suggest 11-OHD defect.
- Primary amenorrhea without pubarche in XX child with testo/ DHT ratio < 10, indicates androgen insensitivity and causes feminization during puberty.
- Clitoral enlargement with absent uterus and testo/ DHT ratio > 10 indicate 5ARD2 defect, the child should be advised rearing as male.

- Work up is a must in: Isolated peno-scrotal/ Perineal Hypospadias
  Bilateral undescended testes
  Isolated micropenis and Isolated clitoromegaly.

Type 1 Diabetes Mellitus

- CSII (insulin pump) is the most physiological method of insulin administration: sensor augmented insulin pump therapy should be the 1st option.
- MDI with insulin analogs is the 2nd best option.
- Premixed insulin has no place in the treatment of T1DM.
- DSME is the most important factor to improve outcomes in T1DM.
- Technology is evolving fast toward "artificial pancreas".
- Diabetic ketoacidosis (DKA) is a serious but preventable complication of pediatric diabetes, with a mortality rate of 0.3-0.5% in developed countries and 10% in developing countries. New onset diabetes (type 1 and sometimes type 2 diabetes) quite commonly presents with DKA in children and adolescents. Diagnosis requires a high index of suspicion.
- ISPAD (International Society of Pediatric and Adolescent Diabetes) Clinical Practice Consensus Guidelines 2018 provide a comprehensive review of the updates in the management of pediatric DKA. The 2022 Guidelines will soon be released. The BSPED interim guidelines for management of DKA in children & young people less than 18 years is also broadly similar to ISPAD. Treatment may need modification to suit the individual patient, which necessitates frequent clinical and biochemical assessment and tailored specific treatment.
- Increased leukocyte count in DKA is not necessarily suggestive of infection, and all children need not be given antibiotics. Increased leukocyte in DKA can be due to various factors such as:
  Lack of insulin
  Inflammatory processes activity
  Secretion of adrenaline and cortisol
  Infection
- Insulin therapy is started at least 1 hour after starting fluid replacement therapy.
- Intramuscular Regular insulin given 4 hourly/ rapid acting insulin analogues given 2 hourly are an alternative for the treatment of uncomplicated mild to moderate DKA.
- Potassium replacement is essential in all cases of DKA, except if the patient is hyperkalemic; if so, potassium is deferred till urine output is documented.
- Warning signs and symptoms of cerebral edema include onset of headache after treatment initiation or worsening of headache, slowing of heart rate, change in neurological status, neurological signs like cranial nerve palsies, rising blood pressure, and decreased oxygen saturation.
- In children with multiple risk factors for cerebral edema, mannitol/ hypertonic saline should be available at the bedside, with the dose calculated, for administration if there is an acute worsening of neurological status.
- Hypoglycemia management- give 15 gm simple carbs, and wait for 15 min to see response:
  15 gm glucose in the form of glucose tablets
  15 gm (3 teaspoon) sugar dissolved in water
  15ml (1 tablespoon) honey
  150 ml juice.

Rickets

- Vitamin D deficiency is still the number one cause of rickets: consider other forms only if absence of response to vitamin D in 3-4 months of treatment.
- PTH is the cornerstone of investigation. The sample must be handled immediately after collection.
- Normal calcium does not rule out calcipenia. Calcipenic rickets can have low phosphate.
- Phosphopenic Rickets is not just XLHR.
- Rule out RTA to distinguished from HHRH. Distal RTA is calcipenic whereas proximal RTA is phosphopenic.

Doses for management of Vitamin D deficiency or Nutritional rickets in children:

Age	Daily dose for 12 weeks (IU)	Alternative intermittent dose regimen	Maintenance dose (daily) (IU)
< 6 months	2,000	NA	400
6-12 months	2,000	Equivalent of 2,000 IU can be given on a monthly or weekly basis	400
>12 months	3,000	60,000 IU fortnightly (every 2 weeks) - 5 doses	600

- A daily regimen is preferred over intermittent dosing. Reassess response after 12 weeks. Ensure daily calcium intake of 50-75 mg/ kg/ day, not exceeding 500 mg /day. Optimum duration of maintenance vitamin D therapy is not known at present.
- Sun Exposure - Recommendation during the period of 11am-3pm of bare skin exposure of over 12-18% of body surface area for 15-30 min in infants and 30-45 min in older children, at least 5 days a week, without barriers like glass or sunscreens.

Growth

- Growth speaks of health and disease in a child. Regular growth monitoring is essential to identify pathological states at the right time and initiate treatment.
- The new IAP pediatrician-friendly growth charts provide MPH percentile correction tool to assess family growth potential easily and a BMI assessment tool for quick recognition of overweight and obesity in children.
- BMI charts are available for detailed assessment.
- Compromised weight age suggests possibility of chronic illness and nutritional causes. Compromised height age is more in favor of endocrine causes or skeletal dysplasia.
- Children thought to have constitutional delay of growth and puberty or familial short stature merit close clinical, laboratory and anthropometric follow up to rule out pathology.
- In familial short stature, height centile corresponds to MPH centile, growth velocity is normal, bone age corresponds to chronological age.
- Girls with unexplained short stature and delayed puberty needs karyotype analysis to rule out Turner syndrome (TS).
- Early initiation of growth hormone and induction of puberty are prudent for optimal growth in TS.
- Growth failure is an important parameter in differentiating pathological obesity from simple obesity.

Miscellaneous

- Height acceleration, bone age advancement and appearance of breast buds (girls)/ increase in testicular volume (boys) is indicative of CPP (central precocious puberty).
- USG of Pelvis (pubertal cut-off can be taken as ovarian volume > 1ml, uterine volume > 2 ml, and endometrial thickness > 3 mm) and GnRHa stimulation test (baseline LH > 0.5 IU/L and stimulated LH > 5 IU/L, LH/ FSH ratio > 1) also give valuable information.
- MRI brain is indicated in CPP especially in boys, and in girls with onset less than 6 years of age.
- Liraglutide (GLP-1 analog) in high doses has been approved by FDA for obesity in children ⩾ 12 years. The main side effects are hypoglycemia and nausea.

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Report and Learning Pearls from ISPAE ACES Meets - March and April 2022

Dr Hari Mangtani, Consultant Paediatric Endocrinologist
Pearl Endocrine Clinic, Nagpur

March ISPAE-ACES

Dr Reshma (postgraduate, Dept of Pediatrics, Sri Ramachandra Institute of Higher Education and Research, Chennai), presented an interesting case of Turner syndrome (TS), moderated by Dr Kavitha Bhat (Senior Consultant Pediatric Endocrinologist, Aster CMI Hospital, Bengaluru); followed by an expert talk focusing on updates in the management of TS in children by Dr Shanlee Davis (Asst Prof., University of Colorado & Director, eXtraOrdinary Kids TS Clinic, Children's Hospital, Colorado). The other case on short stature was presented by Dr Suraksha RS (Dept of Pediatrics, Topiwala National Medical College & Nair Hospital, Mumbai), and moderated by Dr IPS Kochar (Consultant Pediatric Endocrinologist, Indraprastha Apollo Hospital, Delhi). The second expert talk highlighting updates in the diagnosis and continuum of care of Growth hormone deficiency in children was by Prof. Martin Oswald Savage (Professor Emeritus of Pediatric Endocrinology, Dept of Endocrinology, William Harvey Research Institute, Barts & the Royal London School of Medicine and Dentistry, University of London).

Turner syndrome: PEARLS

- TS can be due to complete or partial absence of the second sex chromosome in females, which could be a non-disjunction event during meiosis (45X0 & mosaicism) or due to a chromosomal breakage (isochromosome, rings, translocation).
- The prevalence of TS is 1/2,500 liveborn females despite the majority (99%) of monosomy fetuses aborting spontaneously.
- Any female with growth failure, pubertal delay, characteristic facial features, left-sided cardiac anomalies, premature ovarian insufficiency, and infertility should be checked for the presence of TS, with a karyotype (KT).
- Patients with mosaicism have a milder phenotype. If a standard KT is reported normal in suspected cases, mosaicism should be looked for by extended cell count (50 cells) or FISH (200 cells) studies. Also, a second tissue is checked despite normal blood KT if the clinical suspicion is strong.
- Different KTs can manifest as TS, with genotype-phenotype correlation. However, the same management guidelines apply to all TS patients, irrespective of the type of TS KT.
- In Monosomy X, one may do a buccal FISH/ Blood FISH to rule out low-level Y chromosomal mosaicism. Those with Y-material have a high risk for gonadoblastoma (10%), so gonadectomy is recommended.
- Short stature is the most prominent feature of TS (95-100%). TS has a slow growth velocity (GV) during childhood and lacks the pubertal growth spurt, resulting in significantly lower final height (FH) in untreated TS.
- Mosaicism (presence), parental height (taller), Y-material (presence), puberty (spontaneous), and chronic untreated underlying systemic disorder (absence) are the factors that determine the FH (taller).
- A multidisciplinary team is required for screening and follow-up of the cardiometabolic risk, skeletal health, endocrinopathies, and autoimmune conditions.
- Treatment with GH should be started at 4-6 years of age and continued till the desired height is achieved or growth potential ends (BA ~14 years). Oxandrolone, a non-aromatizable androgen known to improve GV without affecting BA, can be started at a dose of 0.03-0.05mg/kg/day in children above 10 years to improve FH. However, virilization and hepatotoxicity limit its use.
- Most TS patients require estrogen (E2) replacement, which is started at about 11-12 years of age with a very low dose, and gradually built up to the adult dose over 2-3 years' time. Progesterone is added after breakthrough bleeding occurs, or after 2 years of unopposed E2 therapy.
- Congenital/ Acquired aortopathy/ heart disease is present in almost 50% of TS patients and also is the leading cause of premature mortality, stressing the lifelong cardiovascular surveillance.
- Ovarian tissue cryopreservation is still at an experimental stage.

Growth hormone deficiency: Pearls

- Growth disorders can be Primary (disorders intrinsic to the growth plate) or Secondary (affect the function of the growth plate - include the endocrine system, nutrition, etc.) or Idiopathic e.g. ISS, SGA.
- GHD is a broad-spectrum condition ranging from mild to extreme deficiency of GH. In 70% patients, GHD is idiopathic, and is usually mild to moderately severe. Other patients may have congenital or acquired Hypothalamic-Pituitary defects, and mostly have moderate to severe GHD.
- Provocative GH testing is required only when history and examination suggest underlying GHD, or the patient demonstrates low GV or low IGF-1 levels. It is not required if the short child has normal GV, normal BA, and age appropriate IGF-1 levels.
- All children with GHD must have an MRI of the hypothalamic-pituitary region.
- GH therapy aims to induce catch-up growth, maintain growth within the normal range, and achieve a FH close to the target height.
- Monitor adherence to therapy as poor adherence is associated with poor response to GH therapy. One should also monitor for side effects, and IGF-1 levels (maintain within the age and sex-appropriate range).
- After the completion of the linear growth, retest for persistent GHD. If GHD present, the patients need to be transitioned to the adult endocrinologist and continued on low-dose GH therapy for its metabolic benefits.

April ISPAE-ACES

Dr Jyotsna Venkatamathi P (Clinical Fellow, Pediatric and Adolescent Endocrinology, Manipal Hospital, Bengaluru) presented an interesting case of adrenal insufficiency (AI) moderated by Dr Riaz I (Associate Professor, Pediatrics, In-charge, Pediatric Endocrine Clinic, Dept of Pediatrics, Govt Medical College, Thiruvanathapuram), followed by an expert talk on AI in children: causes, consequences, and care by Dr V Sri Nagesh (Sri Nagesh Diabetes, Thyroid and Endocrine Clinic, Hyderabad). A case of CAH was presented by Dr Chirantap Oza (Clinical and Research Fellow, Pediatric Endocrinology, Hirabai Cowasji Jehangir Medical Research Institute, Pune), moderated by Dr Dhivyalakshmi J (Associate Professor & Consultant Pediatric Endocrinologist, Sri Ramachandra Medical College, Chennai). The 2nd expert talk on Recent updates in diagnosis and management of Congenital Adrenal Hyperplasia (CAH) was by Prof. Anna Nordenström (Senior Consultant, Astrid Lindgren Children's Hospital, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden).

Adrenal insufficiency: Pearls

- CAH is the commonest cause of primary AI (PAI). Genetic causes of PAI, although rare, should be kept in mind, particularly when the presentation is very early after birth and associated with other organ system involvement.
- An ACTH stimulation test with a 60-min stimulated values is a standard method to assess adrenal function.
- If the ACTH levels are > 300 pg/mL there is no need for a stimulation test.
- Morning cortisol < 5ug/dL with an ACTH level > 2-fold the reference range can be taken as a surrogate of AI if an ACTH stimulation test is not available.
- Plasma renin and aldosterone levels should be measured wherever possible in PAI.
- Hydrocortisone replacement needs the highest dose to be in the morning and lower doses in the evening. Prednisolone can be used in selected cases where compliance or cost is an issue. Dexamethasone should not be used as HRT.
- For adrenal crisis, the choice of therapy is IV hydrocortisone, ideally as a continuous infusion. Parents must be given injection hydrocortisone, and taught how and when to use it.
- Acton Prolangatum can be used where ACTH is not available for adrenal stimulation; a dose of 25 IU of AP is equivalent to 250ug of synecten.

CAH: Pearls

- Deficiency of 21-αHydroxylase, an enzyme encoded by CYP21A2, is the commonest cause of CAH. The clinical presentation, depending to the degree of virilization and severity of salt-wasting, in turn depends on the underlying genetic defect.

- 17-hydroxy progesterone (17OHP), the intermediate product in the steroid synthesis pathway accumulates in classical CAH, and through a series of metabolic steps is converted to Dihydrotestosterone (DHT) which is responsible for the virilization of the female fetus.
- 17OHP also gets converted to 21-deoxycortisol, pathognomonic of 21OHD, which through multiple enzymatic steps gets converted to 11-ketotestosterone (11-KT) and 11 ketodihydrotestosterone (11-DHT), which are also responsible for the virilization in 21-OHD.
- 17OHP levels are used for neonatal screening or early diagnosis of CAH. They correlate very well with the genotype.
- Hydrocortisone and fludrocortisone, along with salt solution in early infancy, are the mainstay of therapy.
- Overtreatment can lead to growth failure. Undertreatment is associated with the advancement of bone age which can result in reduced final height.
- Hydrocortisone replacement doses increase significantly during puberty due to the decreased activity of the hepatic 11-beta-hydroxysteroid dehydrogenase-1 (11B-HSD1).
- The adrenal medulla which produces adrenaline/epinephrine under the influence of cortisol (produced in the adrenal cortex) also gets affected in CAH. The resultant adrenalin deficiency can increase the risk of hypoglycemia and stress vulnerability.
- Newer treatment modalities include modified-release hydrocortisone which has diurnal drug absorption, but is not available for children see Pedendoscan above. The other drug is the corticotropin-releasing factor receptor -1 antagonist (undergoing clinical trial). Another drug undergoing pediatric trials, an inhibitor of the CYP17A1 enzyme, is expected to reduce androgen production and thus help reduce the glucocorticoid dose.
- The development of TART is a common complication, particularly in males with poorly controlled CAH. TART can lead to subfertility/infertility thus stressing the importance of strict adherence to the treatment and regular clinical and radiological monitoring.
- Androstenedione to testosterone ratio (A/T ratio) of >1 suggests testosterone is mainly of adrenal origin. In addition, LH and FSH levels are also useful to differentiate between testicular and adrenal androgen production in males with CAH and to diagnose gonadal dysfunction.

ISPAE ACES series- May 2022- Bone disorders

Dr Swathi P, Fellow, Division of Pediatric and Adolescent Endocrinology
IGICH, Bangalore

The first case was presented by me: a boy with short stature – "thinking beyond rickets"; and moderated by Dr Ganesh Jevalikar (Principal Consultant, Max Healthcare, Saket, Delhi and Gurgaon). The second one was an interesting case of rickets presented by Dr Bhogavalli Lakshmi Harshitha (Post Graduate, SRMC, Chennai), and moderated by Dr Sirisha Kusuma (Consultant Pediatric and Adolescent Endocrinologist, Rainbow Children's Hospital, Hyderabad). The expert talks were on Skeletal Dysplasias by Dr Akhil Kulkarni (Professor of Radiology, SSIMS & RI, Davangere) and Nutritional Rickets by Dr Zulf Mughal (Consultant, Pediatric Bone Disease, Royal Manchester Children's Hospital & Clinical Professor, Child Health, University Of Manchester).

Learning Pearls:

- The incidence of skeletal dysplasia (SD) is 1:5000 live births.
- Most SDs are disproportionate, except Osteogenesis Imperfecta and some sclerosing bone dysplasias.
- Complete genetic skeletal survey remains the mainstay in the diagnosis of SD; it is not necessary in proportionate short stature.
- Skeletal survey is highly recommended in prepubertal children (immature skeleton) and includes skull & spine (AP, lateral), chest (AP), pelvis (AP), long bones (AP) and hand and wrist (PA).
- Radiologically, SD can be classified based on bone mineralization, axial skeletal involvement, appendicular skeletal involvement, growth delay and other abnormalities.

- Accurate molecular diagnosis of SD is more important in this era for genetic counselling; for prenatal, preimplantation genetic diagnosis and molecularly targeted therapeutics in the future.
- Dyggve – Melchior – Clausen syndrome is an osteochondrodysplasia which belongs to the subgroup spondylo-epimetaphyseal dysplasias (SEMDs) which includes a number of conditions with combinations of specific vertebral, epiphyseal, and metaphyseal anomalies.
- It is a progressive SEMD, belonging to group 13 of 2019 International Skeletal Dysplasia Nosology, inherited autosomal recessively and produced by mutations in the Dymeclin gene mapped in 18q12-21.1 chromosomal region.
- Clinical features include short trunk dwarfism, limb deformities, pectus carinum (protruding sternum), scoliosis, stiff joints, rhizomelic limb shortening, microcephaly, coarse face and variable degrees of mental retardation (progressive).
- Orthopedic complications expected in this condition are atlanto-axial instability, lumbar lordosis, scoliosis, thoracic kyphosis, subluxation of the hips, genu valgum and restricted joint mobility.
- The specific radiological features seen this condition are markedly flattened vertebral bodies (platyspondyly), double-humped appearance of the vertebra, misaligned spine, metaphyseal irregularities, laterally displaced capital femoral epiphyses, small pelvis with thickened and lacy iliac crests, cupped metaphyses and cone shaped epiphyses seen in the hands and feet.
- Radiological findings become evident by 3-4 years of age and persist in adulthood.
- Microcephaly and statural delay become evident and increase during childhood.
- Smith-McCort dysplasia is a close variant of DMC, with all features resembling the latter, including the radiological findings, except that there is no evidence of mental retardation in the former.
- The highlights of nosology and classification of skeletal disorders 2019 (revised) – ** follow genotype first and phenotype later approach; ** group 18 is now bent bone dysplasia instead of campomelic dysplasia; ** group 19 is called primordial dwarfism; ** slender bone group and new entities have been added to the SEMD group.
- IAP revised guidelines on prevention and treatment of Vitamin D deficiency (VDD) and rickets (2022):
  - Definition of VDD:
    - >100 ng/ml – toxicity
    - >20 ng/ml – sufficient
    - 12-20 ng/ml – insufficient
    - <12 ng/ml – deficiency
  - Children are at risk of VDD during periods of rapid growth, secondary systemic illnesses and when on drugs like antiepileptics, antifungals and steroids.
  - Optimum duration of vitamin D therapy is not known at present.
  - STOSS therapy is not recommended.
  - Monitoring of treatment can be done by repeating X-rays at 4 weeks and 12 weeks of therapy; biochemical parameters can be repeated after 12 weeks of therapy; it is important to normalize PTH.
  - If the response by 12 weeks is poor, think of non-nutritional causes of rickets.
  - If 25-OHD > 100 ng/ml, monitor for hypercalcemia and hypercalciuria.
- The correction of deficiency occurs as follows:
  - S. Phosphorus normalizes by 96 hours
  - S. Calcium by 1 week
  - ALP and radiological by 1 month
  - Physical deformities: months to years
  - Motor milestone improves by 2-3 weeks
  - Most deformities correct with growth.
- Prolonged monitoring of children with nutritional rickets is necessary.
- All infants (premature and on EBF) should receive preventive dosage of Vitamin D.
- The breast milk calcium in mothers with nutritional rickets is found to be 10% lower than normal mothers.

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- Non-osseous features of nutritional rickets: hypocalcemic tetany and seizures, hypercalcemic dilated cardiomyopathy, pain and pathological fractures, delayed motor milestones, raised intracranial pressure, craniosynostosis, and muscle weakness.
- Severity of reactive hyperparathyroidism indicates the severity of calcium deficiency in the body.
- Never make a diagnosis of pseudohypoparathyroidism without ruling out vitamin D deficiency.
- If there are rickety changes in X-rays without osteopenia, think of hypophosphatemic rickets and X-linked hypophosphatemia (XLH).
- Older adolescents with nutritional rickets can have pseudo-fractures in the inner aspect of proximal femur/ pelvis and present with severe pain.

Diabetes Educators' corner: Eternal gratitude and best care to children and families with Type 1 Diabetes: Sharing lessons learnt with Health Care Professional colleagues



Ms Geetha S Rao[1], Dr Reshma Harsha Vijay[2] and Ms Madhumati S Vaishnav[3]
Diabetes Collaborative Study Group, Samatvam: Science and Research for Human Welfare Trust, Jnana Sanjeevini Diabetes Hospital and Medical Center and Samatvam Endocrinology Diabetes Center, Bangalore.

The authors dedicate this write up of their inspiring work to doyens in the care of Type 1 DM - **Padma Shri late Professor Dr Man Mohan Singh Ahuja,** and **Professor Dr Graham Ogle (founder of Life For a Child with Diabetes).**
The authors share a few nuggets from the "half century" of continued learning of their Samatvam Team and their journey in the care of individuals with T1DM. These might be helpful to youngsters planning a career in T1DM care.

A pictorial depiction of the inspiring journey is depicted in Figure 1.

Figure 1: Esprit de corps: (a) Professor MMS Ahuja with Type 1 Diabetes children and health care volunteers at the first 'Camp Man Mohan', Shimla, India, 1987. (b) Professor Graham Ogle with Samatvam team representatives at World Diabetes Conference, Abu Dhabi, 2017. (c) 'Camp Man Mohan', Visit to Chitradurga Fort, Sanehalli, India, 2019. (d) Health Care Professionals: Samatvam Jnana Sanjeevini Medical Center and Diabetes Hospital, Bangalore, India.

Theme 1: Insulin, love and care and Type 4 Diabetes

Professionals caring for individuals with T1DM will agree that "perfect" physiological insulin replacement and "intensive" and sustained psychosocial support are mandatory for holistic and complete Type 1 Diabetes care.

Literature uses the term "Type 3 DM" in situations such as: (a) family members and other care givers of people with diabetes, who also "suffer" during their short- and long-term care for their loved ones; (b) pathogenetic overlap or coexistence of type 2 Diabetes and Alzheimer's disease; and (c) secondary diabetes associated with exocrine pancreatic disease [1-5]. Authors use the term "Type 4 DM" to describe Health Care Professionals (HCPs) who try to understand and give their best continuously over years and decades to each and every T1D child to youth to adult who reposes faith in them.

Empathy is the ability to share the feelings of others. Altruism can be defined as caring about other people and acting in someone else's interest. The genuinely experienced joy on seeing T1D youngsters with "normal" HbA1c, optimal blood glucose time in range, normal growth and development, normal BP, negative urine albumin excretion, normal glomerular filtration rate, normal lipid profile and normal retinal examination, etc. contributes to an altruistic emotion and empathy towards them. A genuine constant striving of the health care team towards achieving this goal also may contribute to the same.

Theme 2: Patients are our best teachers – The "outside" and "inside" of Diabetes

Ms Shobha Setia, India's first Specialist Nurse Counsellor (herself a T1D), once remarked that doctors only know the outside (textbook) of diabetes, whereas those with diabetes know the inside. Hence, there is a need to understand those with T1D better to help them. HCPs like Ms Shobha Setia know both the inside and outside of T1D, and are true role model assets for any T1D health care team (sufferers are often the best healers) [6].

Prof Jean Pirart's aphorisms for looking after people with diabetes: Prof Pirart, the celebrated Belgian diabetologist (after having personally taken care of 4000 plus patients with diabetes in Europe, over 25 years, with the world's longest systematic follow-up, at that time) had given the following advice to young physicians [7,8].

"Do not trust schemes and classifications too much. After all, a patient has a right to be himself regardless of the pattern he should fit in accordance with your theories."

"Be ambitious and always try to give the best of yourself for the cause of your patients, but remain realistic. Do not try to normalize all parameters."

"Do not talk in a scholarly way; high blood sugar or low blood pressure are as good as hyperglycaemia or hypotension. Speak to be understood, not to be admired."

"Be cautious in taking any decision to change something that is running well, however odd a treatment it seems to be."

"Listen to your patients. The key to a problem is more often found in their talk than in a laboratory test."

"Do not evade any question; if not appropriate for the time being put the question aside and answer it in due time some weeks later."

Professor Michael McDermott and **Endocrine Secrets (4th Edition 2004. Elsevier Mosby. ISBN: 9781560536116): here is his advice to all clinicians caring for individuals with T1D:**

"A book can provide us with many facts. Better still, for those who are willing, it can make us think, reason and question. These are the basic tools we need to be good, competent health care providers. But our greatest teachers are our patients. They show us the face, the heart, and the soul of disease and of recovery. It is the truly great providers who understand the enrichment, humility and wisdom that come from this source. I encourage the readers of this book to study it, and many others as well, to equip them with the basic information to make responsible and, when possible, data-based decisions regarding the evaluation and management of their patients. However, I urge them to learn mostly from their patients, to spend time with them, to show them sincere compassion, and most of all, to show them respect. We should never fail them in this. They deserve no less than the best of our humanity, and regardless of the outcome, this is what they will best remember and appreciate."

Theme 3: Economics and Affordability

Equitable access to various essential components of T1D care, remains a social and political challenge world over.

Discipline compensation for poverty: Focusing on the economically poor, over decades the DISHA Free Diabetes Clinic has been caring for the underprivileged in Bengaluru[9]. Even in the face of severe resource constraints, a subset of low SES T1D youngsters achieve good glycemic control and pursue healthy, productive and contented lives by practising intense discipline and rigid life adjustment (sacrificing flexibility and enjoyment). At DISHA, a few good Samaritan individuals and institutions also provide financial and motivational support for T1D children to pursue formal school and college education and facilitate employment opportunities. Incidentally, in two surveys, nearly 80% of the DISHA children aspired to become doctors, and a few "Diabetes doctors" [9].

Theme 4: The importance of team work in T1D care

Team work is pivotal for a chronic, lifelong disease like T1D, where self-management is crucial on an hour-to-hour and day-to-day basis. Dr Stephen Swensen (Senior Fellow, Mayo Clinic, USA), emphasises "esprit de corps" which symbolises the connectedness, the trust, the camaraderie, the fulfilment, the passion, and the loyalty of the team to each other and to their mission. Esprit de corps is a French phrase that translates into 'group spirit'. This team spirit is also mandatory for best T1D care, with the person with diabetes being the Captain, as well as the prime beneficiary of the team [10].

"God, grant me the serenity to accept the things I cannot change, courage to change the things I can, and wisdom to know the difference." - American theologian Mr Reinhold Niebuhr (1892–1971) [11].

Thus, empathy and altruism, improving affordability, patient-centric approach, team work are the pillars of principles to be adopted by youngsters planning to take up a career in management of T1D.

References:

1. Feeley CA, Sereika SM, Chasens ER, Siminerio L, Charron-Prochownik D, Muzumdar RH, Viswanathan P. Sleep in Parental Caregivers and Children with Type 1 Diabetes. J Sch Nurs 2021 Aug;37(4):259-269 doi: 101177/1059840519865942 Epub 2019 Jul 31. doi:10.1177/1059840519865942

2. Bhattamisra SK Siang TC, Rong CY, Annan NC, Sean EHY, Xi LW, Lyn OS, Shan LH, Choudhury H, Pandey M, Gorain B. Type-3c Diabetes Mellitus, Diabetes of Exocrine Pancreas - An Update. Curr Diabetes Rev 2019;15(5):382-394. Published online 2019. doi:10.2174/1573399815666190115145702.

3. de La Monte SM, Wands JR. Alzheimer's Disease Is Type 3 Diabetes-Evidence Reviewed. Vol 2.; 2008. doi:10.1177/193229680800200619.

4. Jorwal P, Verma R, Balhara Y. Psychological health of caregivers of individuals with type 2 diabetes mellitus: A cross-sectional comparative study. Journal of Social Health and Diabetes. 2015;03(02):095-101. doi:10.4103/2321-0656.152806

5. Anaforoğlu I, Ramazanoğullari I, Algün E, Kutanis R. Depression, anxiety and quality of life of family caregivers of patients with type 2 diabetes. Medical Principles and Practice. 2012;21(4):360-365. doi:10.1159/000334622

6. S. Manjunath, R. Krishna, U. Dayashankar, For Diabetes Collaborative Study Group, Jnana Sanjeevini Medical Center, Endocrinology and Diabetology, Bangalore, India. "Sufferers" as great "Healers": Experiences with people with T1DM as health care providers ["Inside" and "Outside" of diabetes] D-0702.World Diabetes Congress, International Diabetes Federation at Dubai- 4-8 December 2011.

7. J Pirart. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl)]. Diabete Metab 1977;3(4):245-256. 1977;3(4):245-256.

8. Robert Tattersall. Why is diabetology such a good speciality. Diabetes Digest Volume 2 Number 1 2003. 2003;2:8-8.

9. "Rationed SHBGM" – Limited Self Home Blood Glucose Monitoring in Improving Metabolic Control in Economically Disadvantaged Children with Type 1 Diabetes in India: Discipline "Compensation" For Poverty. S Geetha Rao, Prathima Krishnamurthy, Usha Rangaraj, Bina Naik, SS Srikanta, Tejeswini Deepak and A Sharda, for the Diabetes Collaborative Study Group. 36th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes ISPAD, Buenos Aires, Argentina, 2010. ISPAD 2010 Poster 158.

10. Swensen SJ. Esprit de Corps and Quality Making the Case for Eradicating Burnout. J Healthc Manag. J Healthc Manag 2018;63(1):7-11. doi:10.1097/JHM-D-17-00197

11. https://en.wikipedia.org/wiki/Serenity_Prayer

ACTIVITIES BY ISPAE members:

Academic meetings

Pediatric Endocrinology CME in New Delhi by Dr Ravindra Kumar

A Pediatric Endocrinology module was organized by Dr Ravindra Kumar at Dr BR Ambedkar Medical College, Delhi on 29/05/22 from 9am to 5pm under the Presidential Action Plan of IAP and IAP North Delhi. It was attended by > 60 participants including pediatricians, and postgraduate students. Drs IPS Kochar, Aashima Dabas and Richa Arora spoke on growth disorders; Dr Vijay Jaiswal on obesity and Dr Manish Gupta on Vit D disorders. Dr Ravindra Kumar discussed precocious puberty and congenital hypothyroidism; Dr Anju Virmani dealt with Type 1 DM and Dr Ganesh Jevalikar with DSD. The workshop was very interactive, with important practical points on how to deal with all these common pediatric endocrine disorders in office practice.

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Continuing Medical Education programs under the flagship of the Pediatric Endocrinology Association of Karnataka (PEAK)

1. Pediatric Endocrinology CME at Bagalkot

Our first CME under President Dr Shaila Bhattacharyya was conducted on 13.3.2022 at S. Nijalingappa Medical College and Hangal Shree Kumareshwar Hospital. The program was attended by 67 participants from in and around Bagalkot, including pediatricians, general practitioners and postgraduates. Dr Bhattacharyya discussed plotting of growth charts; it was a very interactive session where the audience were made to use the growth charts. This was followed by a case presentation on short stature by a postgraduate. Dr Pavithra Nagaraj spoke on approach to short stature: also an interactive session with practical points on how to check anthropometric measurements, and the usual mistakes encountered, along with an overview on growth hormone therapy. Dr Pachapure spoke on the much needed topic Management of type 1 Diabetes with education on the types of insulin, storage, complications etc. Dr Bhattacharyya was felicitated by the IAP Bagalkot branch for her contribution in the field of pediatric and adolescent endocrinology.

2. Pediatric endocrinology CME at Tumkur

With over 40 participants (general practitioners, pediatricians and postgraduates from 3 medical colleges and private and government institutions in and around Tumkur), this pediatric endocrinology CME at the Urban Resort, Tumkur on 17.04.2022 was a success. We started with a postgraduate presentation of a case of short stature, followed by a talk on growth charts and approach to short stature by Dr Pavithra Nagaraj. Dr Mounica Reddy spoke on Ambulatory management of T1D. Later, Dr Pavithra and Dr Mounica had a panel discussion on obesity and congenital hypothyroidism.

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3. Pediatric Endocrinology CME at Davangere

PEAK conducted a successful 4 hour CME at Bapuji Child Health Hospital and JJM Medical College, Davangere on 07.04.2022, attended by over 50 delegates. The team included Dr Shaila Bhattacharyya (President, ISPAE & Chairperson, PEAK), Dr Pavithra Nagaraj (Joint secretary-cum-treasurer, PEAK) and Dr Diksha Shirodkar (Executive member, PEAK). The welcome speech was given by Dr Muganagowda Patil, Head, Dept of Pediatrics. The inaugural ceremony was conducted in the presence of all esteemed dignitaries by watering a plant. The topics discussed were approach to CAH and precocious puberty, and management of DKA. A panel discussion was moderated by Dr Nagamani Agarwal (senior pediatrician) on common pediatric endocrine queries by practicing pediatricians.

4. Pediatric Endocrinology CME at Mangalore

"The Harmony of hormones", a pediatric endocrinology CME conducted by PEAK and IAP Dakshina Kannada group on 12.06.2022 at Moti Mahal convention hall, Mangalore, Dakshina Kannada, received an overwhelming response by more than 75 participants (pediatricians affiliated to medical colleges, postgraduates and private practitioners). The program started with a talk by Dr Diksha Shirodkar on Congenital Hypothyroidism - a pediatrician's perspective. The second talk on plotting of growth charts and approach to short stature by Dr Shaila Bhattacharyya included a hands-on practical exercise of plotting growth charts. This was followed by the inaugural function, with the office bearers of IAP DK, former IAP President Dr Santhosh Soans and Dr Shaila Bhattacharyya lighting the lamp. The post tea session had a talk on overview of DSD and approach to CAH by Dr Koushik Urala (pediatric endocrinologist, Kasturba Medical College, Manipal University, Udupi). The vote of thanks was given by IAP DK President Dr Shreekrishna GN.

Patient meetings

PRADER WILLI SYNDROME- MULTIDISCIPLINARY CLINIC

Dr Kavitha Bhat (Senior Consultant Pediatric Endocrinologist) & Dr Namratha Upadhya (Specialist Pediatric Endocrinologist), Aster Hospitals, Bangalore

A special clinic was conducted by Aster Hospitals, Bangalore on 21/5/22 to consolidate specialist appointments in a single day for a multidisciplinary screening of children with Prader Willi Syndrome (PWS) and facilitate interaction among their families. Thirteen children with PWS (9mo-16y) and their families participated in the event, including 2 virtual consultations.

A pre-clinic problem list was created for each child, followed by comprehensive evaluation by pediatric endocrinologists, pulmonologist, orthopedician, ophthalmologist, dentist, nutritionist, psychologist, physiotherapist, and psychiatrist. Patients were given a handout with anticipatory guidance in PWS and tips to tackle common problems. All specialist inputs were collated, and a composite plan made for each child. The event was acknowledged by the Indian PWS Association on their social media handle. It was followed up by a virtual Facebook live session on 27/5/22, by a multidisciplinary team to answer common queries in PWS.

Carbohydrate Counting & Insulin Pump Workshop, Kurukshetra, Haryana

A Carbohydrate Counting and Insulin Pump Workshop was organized at Shree Guru Kripa Endocrine Clinic, Kurukshetra, by Dr Mudita Dhingra, for families and children with T1D. The objective of the event was to sensitize patients about the importance of carbohydrate (carb) counting and benefit of calculating carb exchanges in day-to-day practice. Around 15 patients attended the workshop and learnt about weighing kitchen items on a food weighing scale and its implications in carb counting. They were also given handouts of carb exchange list for easy utility at home. Families were counselled about the benefits of CSII over MDI, and 1 patient was initiated on Medtronic 780G insulin pump. Children were given prizes for the best HbA1c report and winning a quiz on carb counting. In addition, all children were offered free blood glucose testing and POC HbA1c reports. A nutritionist and representative from Medtronic also guided children during the session.

Achievements of ISPAE members:

Dr Shaila Bhattacharyya and Dr Mahesh Maheshwari have been awarded Fellowship of Indian Academy of Pediatrics (FIAP) in the 59th IAP Pedicon at Noida on 21/3/2021, for their contribution to the welfare of children at large for several years.

A thesis research work done by Dr Swati Dokania (mentored by Dr Mahesh Maheshwari), AIIMS Bhopal, was awarded the prestigious DK Shrivastava Gold medal in the annual MP State Pediatric Conference at Chhindwara. The topic was "An Exploratory Study To Understand The Effect Of Educational Intervention In The Parents Of Children Diagnosed With Type 1 Diabetes".

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Dr Anjali, Associate Professor Pediatrics, Pt. BD Sharma PGIMS, Rohtak, received the second prize for Best Research Paper on COVID-19 Pandemic (Clinical) for her paper titled 'Effect of COVID-19 second wave on children with Type 1 Diabetes Mellitus in India' by Directorate of Medical Education and Research, Government of Haryana. She was awarded a cash prize of Rs 25000. The Govt of Haryana has given this award by selecting papers on COVID 19 (2nd wave) from all Govt Medical Colleges of the state, in order to promote research work in Govt Medical Colleges through an incentive-based scheme.

Miscellaneous useful information

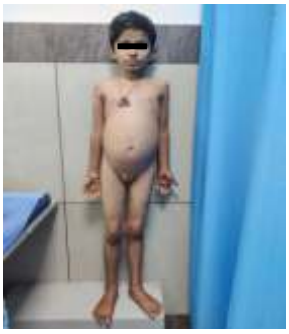
UPCOMING MEETINGS IN PEDIATRIC ENDOCRINOLOGY – PLEASE BLOCK YOUR DATES

- ISPAE 2022 Chandigarh, November 19th – 20th, 2022
- ISPAE 2023 Bengaluru, November 2023 (dates to be finalized)
- ISPAD 2022 – 48th Annual meeting of ISPAD in Abu Dhabi (UAE) – October 13th to 16th. https://2022.ispad.org/
- 30th International Pediatric Congress and 60th Annual conference of Indian Academy of Indian Academy of Pediatrics, 19th – 23rd February 2023, Gandhi Nagar, Gujarat

Pictorial case based questions-Part 2

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

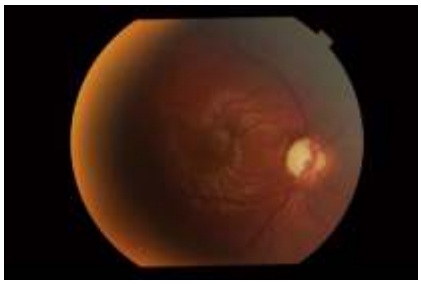
A 10 year old girl presented with hyperglycemia of 7y duration, HbA1c 16.9 %, short stature, mild diabetic ketoacidosis, multiple areas of lumpy-bumpy deposits over the arms, abdominal distension and hepatomegaly. The clinical pictures are below.



Written informed consent taken from the guardian/ patient for the above clinical pictures

a. Diagnose the condition
Mauriac Syndrome
b. If at all for academic purposes, a liver biopsy was performed, what histopathology picture would you expect to see?
Glycogenosis (glycogen deposition) and fatty liver

A 15 year old boy presented with long standing polyuria, polyphagia and visual difficulty. His fundus image was as follows



a. What is the condition and gene involved?
Wolfram syndrome (DIDMOAD) gene- WFS1 and CIDS2 genes

b. Any other evolving impairment you would expect over time?
Hearing impairment

Hearty congratulations to Dr Aaradhana Singh for the correct answers

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Trainees' Section
The Adrenal Quiz

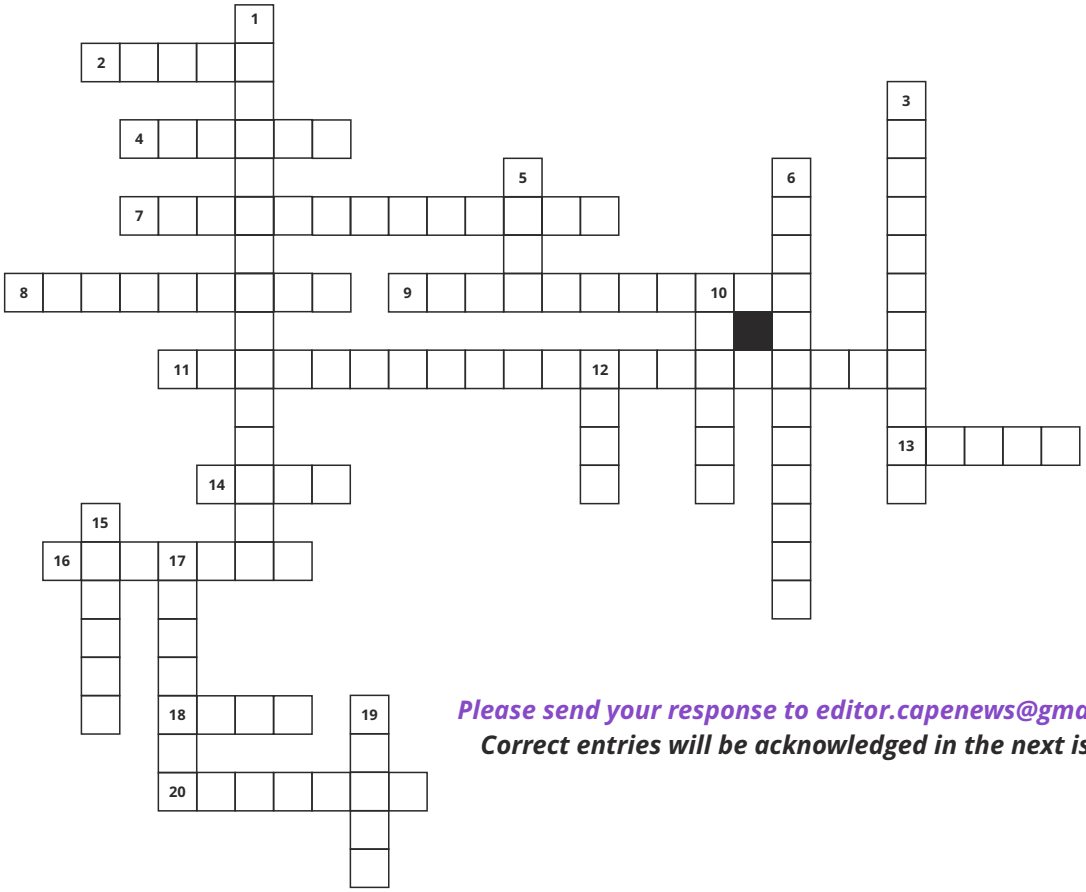
Here is yet another exciting quiz on the adrenal gland. Solve this crossword with the help of the clues given below.

Across

2. The new-born adrenal gland weighs _____ to the adult adrenal gland.
4. 80% of patients with triple A syndrome have a mutation in the gene AAAS coding for _____ protein.
7. An effective secretory protein used as a tumor marker helping correlate the malignant potential and size of pheochromocytoma.
8. The 11βOH steroid dehydrogenase 2 is responsible for converting _____to cortisone.
9. The condition with craniosynostosis caused due to P450 oxidoreductase deficiency is called...
11. What is M in IMAGe syndrome?
13. Syndrome with central adrenal insufficiency and common variable immunodeficiency
14. Defects in _____ synthesis or processing leads to red hair, obesity, secondary adrenal insufficiency and pale skin.
16. 17αHydroxylase deficiency presents with_____ puberty
18. The mutation in this gene causes the malignant type of familial paraganglioma syndrome 4.
20. What does N stand in PPNAD?

Down

1. Drug of choice for mineralocorticoid replacement in CAH
3. Intraabdominal paragangliomas, usually secretory in nature arise from the organ of _____
5. Methyl prednisolone is ———— times more potent with respect to the anti-inflammatory action compared to hydrocortisone
6. The most common cause for Cushing's disease is pituitary _____
10. Adrenal insufficiency causes due to mutation in the gene coding sTAR was formerly called _____ CAH
12. In the fetal adrenal gland what does the fetal zone produce?
15. Zellweger spectrum consists of Zellweger syndrome, neonatal adrenoleukodystrophy and infantile _____ syndrome
17. 21 Hydroxylase antibodies are seen in?
19. Type 11βHydroxysteroid dehydrogenase is produced by the _____.



Please send your response to editor.capenews@gmail.com
Correct entries will be acknowledged in the next issue.