# CAPE NEWS

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

***www.ispae.org.in***

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Contents

**From the Editor's desk**

Dear members,

With rampant inadvertent use of steroids, exogenous Cushing syndrome (CS) tops among the causes of CS in children and often leads to life threatening complications, particularly when exogenous steroids are stopped abruptly without appropriate glucocorticoid replacement. Although endogenous CS is rare in children, localisation of the source of hypercortisolism and management is of great interest and is extremely challenging. In this issue of CAPENEWS, we have included various aspects of exogenous and endogenous CS in children which will be useful not only to pediatric endocrinologists and also for general pediatricians.

I thank all my team members Dr Rajni Sharma, Dr Sachin Mittal Dr Ravindra Kumar, and Dr Reetha Gopinath for their active participation in designing this issue and for their valuable contributions. My special thanks to Dr Anju Virmani, for her whole hearted efforts to make this issue a fantastic one.

**Editor, CAPENEWS**

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

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

## Mid-Term ISPAE Meet: Nashik, Maharashtra, 15-16 Oct 2016,

**in association with International Society for Pediatric and Adolescent Diabetes (ISPAD)**

The theme of this meeting is **"Sugars & Beyond".**

**Organizing Chair: Dr. Sudha Rao,**
**Organising Secretary: Dr. Tushar Godbole**
**Scientific Chair: Dr. Preeti Dabadghao**
For registrations, please contact:
**Dr. Tushar Godbole [+91-7774082834], Email: ispae2016@gmail.com**

**Secretary's Report**

Dear ISPAE members,

Congratulations to Dr Vijayasarathi and his team for coming up with another fantastic edition of CAPE news.

The first quarter of a new ISPAE year is over. Congratulations to our Fellows who attended the APPES Fellows' School and came out with flying colors! ISPAE managed to support their travel with a generous educational grant committed by Novo Nordisk. We have also given the 'ISPAE Observership Award' money to the winner Dr Abraham Paulose, MOSC Medical College, Malankara, Kerala.

The ISPAE website (www.ispae.org.in) has new resources in Hindi, English and Malayalam, for our members to use for their patients of Turner syndrome, childhood diabetes, congenital hypothyroidism, PCO, stress advice for patients on steroids and of diabetes insipidus, among others. The Global Consensus Recommendations on Prevention and Management of Nutritional Rickets, in which ISPAE was represented, is now available online in JCEM, Hormone Research in Pediatrics, and in the ISPAE website. Do check out the site, and do feel free to contribute (please contact the Executive or Dr Ravikumar, Webmaster).

Now we are eagerly waiting for the mid-term ISPAE 2016 meet at Nashik , Maharastra, "Sugars and Beyond" on 15-16$^{th}$ October 2016, in association with ISPAD. Special kudos to Dr Tushar Godbole for coming out with a beautiful brochure. We hope you have already registered for it! With prominent speakers from our own country and abroad, I am sure that this midterm meet will be an academic feast. The scientific program will include a "PET" like interactive workshop of 5 hours, for dieticians, educators, pediatricians, social workers, and others involved with handling the "Nuts and Bolts of Diabetes Management in Children".

News from our international pediatric endocrine sister societies' consortium includes the award of the year 2021 Joint Meeting to SLEP (South American Pediatric Endocrine Society). The important international meetings this year include the 55$^{th}$ Annual Meeting of ESPE in France, Paris, 10-12$^{th}$ September, the 42$^{nd}$ Annual Conference of ISPAD at Valencia, Spain, 26-29$^{th}$ October, and the 9$^{th}$ biannual meeting of APPES, jointly with JSPE, 17-20$^{th}$ November. In addition, the 46$^{th}$ Annual Conference of the Endocrine Society of India will be held in New Delhi: 21-23$^{rd}$ October *2016*.

**The most exciting news for ISPAE is that the APPES Fellows' School 2017 has been awarded to ISPAE following a bid submitted by Dr Anju Seth and Dr Ganesh Jewalikar on behalf of ISPAE.**

With best wishes

Dr M. Vijayakumar, Secretary, ISPAE

# Hearty Welcome to New ISPAE Members

1. Thakur Vikrant Anand, Bijnore, UP
2. Sathyakala Vijayanand, Coimbatore, TN
3. Shankar Kanumakala, UK

# Monitoring steroid therapy

**Dr Bhanu K Bhakhri, Joint Secretary, ISPAE; Associate Professor of Pediatrics, SSPH & PGTI, Noida, U.P**

Corticosteroids (CS) are among commonly prescribed medications, used on long term basis, among children and adolescents. Exploratory research has generated a quantum of evidence indicating potential usefulness of CS in various chronic conditions in children. Hence, the usages of CS for pediatric patients keep rising, both as unscrupulous use as a 'magic drug' by some practitioners, and as evidence based therapy.

It is difficult to forget the comprehensive list of potential adverse effects of long term CS use mentioned in pharmacology, since possibly no other medication seem to match the evil spectrum. Children and adolescents have additional disadvantages due to differences in growth, development, and metabolism, so a double-edged-sword-like situation develops where therapeutic options available are limited, and the adverse effects are inevitable. Unfortunately, awareness about monitoring potential adverse effects of long term CS use is not yet widespread among practitioners. In addition, information regarding appropriate ways of monitoring is limited, so this important aspect is overlooked more often than not. The following is a compilation of some relevant information useful for monitoring of children and adolescents on long term CS.

**Why monitor?**

At present CS are crucial in the therapy of some common childhood illnesses: bronchial asthma and allergies, nephrotic syndrome, immune thrombocytopenic purpura, and in pediatric rheumatology, neurology, dermatology and oncology. Corticosteroids are synthetic analogues of the natural steroid hormones, having primarily glucocorticoid (GC) and minimal mineralocorticoid properties, given in pharmacologic doses to suppress inflammation. The systemic side effects of CS are primarily those related to glucocorticoid excess, and include growth retardation, abnormal glucose and lipid metabolism (anti-insulin, diabetogenic), hypertension, musculoskeletal problems (osteoporosis, osteonecrosis, myopathy), eye disorders (cataract, glaucoma), skin changes (striae, acne), gastrointestinal problems (ulcers, bleeds), immunosuppression, and neuro-psychiatric manifestations. Suppression of the hypothalamo-pituitary-adrenal (HPA) axis can result in an adrenal crisis on withdrawal of medication, especially if it done abruptly. The risk of adverse effects is affected by factors like potency, dose, duration, regimen, route of administration and concomitant use of other toxic medications.

**Whom to monitor?**

**Dose & duration of therapy:** Children receiving physiological replacement doses (equivalent to 10-12 mg/m$^2$/day) for primary or secondary adrenal insufficiency are not at risk of adverse effects, even during long term therapy, provided they are regularly followed up for dose modification and compliance. The consensus is that children receiving supraphysiological doses, for either 2 consecutive weeks or 3 cumulative weeks over duration of 6 months require monitoring for HPA axis suppression.

**Route of administration:** This guideline for dose and duration of therapy applies to oral and parenteral use of systemic CS. There is no universal consensus on monitoring while on long term inhaled, topical, intranasal and intra-articular CS. A Cochrane Review (2014) found no risk of growth retardation with long term use of inhaled steroids, but periodic evaluation of adrenal reserve and bone mineral density is advised. Similarly, long term use of intranasal CS appears to have no significant effect on final height; however, it is advisable to monitor growth, adrenal reserve and bone mineral parameters, especially when they are used concomitantly with inhaled steroids. Further, once daily dosing is recommended for long term intranasal use. Studies have established the safety of topical and intra-articular steroids, but caution that long term (unspecified) use of potent (unspecified) CS requires monitoring.

**Table 1:** Summary of monitoring recommendations for adverse effects while on long term corticosteroid treatment

| **Potential adverse effect** | **What to monitor?** | **How to monitor?** | **When to monitor?** | **Remarks** |
|---|---|---|---|---|
| Growth retardation | Growth,<br><br>Skeletal maturity | Weight, height, BMI charting<br>Bone age | 3-6 monthly<br>12 monthly | Also consider nutritional factors and adrenal suppression |
| Adrenal suppression | Adrenal reserve | Morning cortisol<br>ACTH stimulated cortisol | 3 monthly | Vague symptoms<br>Stress advice if stimulated cortisol abnormal |
| Cushing syndrome | Clinical features<br>Metabolic derangements | Weight, BMI, BP<br>Fasting plasma glucose, OGTT, electrolytes | 3-6 monthly | - |
| Iatrogenic diabetes | Glucose tolerance | Fasting plasma glucose, OGTT | Annual | Frequent if obese or family history of type 2 diabetes |
| Ophthalmo-logical effects | Cataract<br>Glaucoma | Assessment by ophthalmologist | Annual | Frequent if family history or connective tissue disorder, diabetes |
| Bone health | BMD<br>Pathological fractures<br>Avascular necrosis | DEXA<br>Lateral spine X-ray<br><br>Bone scan/MRI on case to case basis | First after 3 months of therapy, then annually | Emphasis on calcium and vitamin D intake, exercise.<br>High risk if concomitant growth deceleration, Cushingoid features |

**What, how and when to monitor?**

**At beginning of therapy:** The baseline record should include detailed history with emphasis on past/family history of metabolic, neuropsychiatric, gastrointestinal disorders, osteoporosis and infections (tuberculosis, vericella, hepatitis, HIV, fungal etc). It is important to probe for concomitant use of other medications and to rule out pregnancy in adolescent girls. Examination should include anthropometric parameters, blood pressure, pubertal and nutritional status. Baseline fasting plasma glucose, lipid profile and blood counts need recording and tuberculosis should be ruled out. The summary of monitoring recommendations for individual adverse effects is provided in table 1.

**At the end of therapy:** It is important to have a high index of suspicion for adverse effects while on long term CS, and after the cessation of therapy, since adverse effects may take variable time to disappear. Adrenal suppression might take several months to recover. In order to minimize the risk of adverse effects, dosing should be kept as low as possible, preferably as single daily (early morning) dosing, if possible on alternate days, and adding/ substituting steroid-sparing agents.

Additional advice: providing a steroid information card, avoiding contact with infections and adopting a healthy diet and lifestyle, are helpful.

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# Guidelines for Steroid Withdrawal

**Dr Tushar Godbole, Consultant Pediatric Endocrinologist, Nashik; EBM, ISPAE**

Besides various metabolic, immune-suppressive, ophthalmic and skeletal ill-effects of chronic glucocorticoid (GC) therapy, hypothalamo-pituitary-adrenal axis (HPAA) suppression is an important and potentially life-threatening side effect. The HPAA gets suppressed after prolonged GC administration and happens at multiple levels including reduced CRH and ACTH drive, atrophy of the adrenal cortex and reduction of GC receptors at the tissue level. The adrenal cortex takes weeks to months to recover completely from this suppression. Sudden withdrawal of GC after prolonged administration can lead to adrenal insufficiency. This brief document gives practical guidelines for steroid withdrawal.

**What are the symptoms of adrenal insufficiency?**

Anorexia, weight loss, fever, flu like symptoms, vomiting, and abdominal pain are the usual symptoms. Rarely children can present with hypotension, shock or convulsions.

**Who needs steroid withdrawal?**

Any child who has received systemic steroids in supraphysiologic doses (>10 mg/$m^2$/day of hydrocortisone equivalent) for more than 2 consecutive or 3 cumulative weeks over 6 months, is potentially at risk for adrenal suppression. Such a child deserves evaluation for HPAA and steroid tapering. Any child who has Cushingoid features while on steroids, will have adrenal suppression and will definitely need tapering. In children on steroids for chronic disorders, the disease activity majorly dictates steroid dose and side-effects suggest tapering. Children on inhaled steroids may have adrenal suppression, but sudden withdrawal is generally not the issue, because the underlying disease demands slow tapering. The guidelines for steroid withdrawal are not based on any randomized controlled trials.

**Steps for tapering steroids:**

1. In a child without underlying active disease, the steroids can be tapered to physiologic doses. This can be achieved quickly by reducing 20-25% every 3-4 days till 30 mg/$m^2$/day. After that, the tapering can be slower, at 10-20% every 4-7 days.
2. Switch from high/intermediate steroids to low potency steroids. Prednisolone can have cross-reactivity with cortisol assay.
3. Once physiologic doses are reached, switch to single early morning dose.
4. Test HPAA recovery.

**How to test HPAA recovery?**

HPAA can be tested on physiologic doses, by collecting the 8:00 am serum cortisol sample before giving the single morning dose. This value, if suppressed, confirms the diagnosis of HPAA suppression; and one needs to continue steroid replacement at a physiologic dose. A normal value alone, however, does not confirm complete recovery. In the absence of symptoms of adrenal insufficiency, one needs to check the adrenal reserve by doing ACTH stimulation testing, in order to know the adrenal reserve.

**When to stop steroids completely?**

On physiologic doses, if the 8:00 am serum cortisol is < 6 µg/dl, one needs to continue steroid replacement in physiologic doses. If the level has reached the normal value of 18-20 µg/dl, the steroids can be safely discontinued. In reality, it may take months to reach this level. More often, one gets values between 6-20 µg/dl. With this, the stress reserve of adrenal needs to be assessed with the short ACTH stimulation test. A cortisol value > 20 µg/dl indicates good recovery, and that it is safe to discontinue steroid replacement. Values < 20 µg/dl even on ACTH stimulation requires stress dosing during periods of stress. The conventional 250 µg Synacthen test may have false-negative results. The low-dose 1 µg intravenous ACTH test is supposedly better in picking-up milder adrenal insufficiency.

**How is stress dosing given?**

Children with adrenal suppression require stress dosing in addition to physiologic replacement. Children with recovered basal secretion but impaired stress response need only stress dosing during periods of stress. The general idea is to replace with 3-10 times the physiologic doses till the time stress is present. Patients with planned surgery, who are kept nil-by-mouth, need intravenous replacement. Although not a recommendation, it is a good idea to split the dose into continuous infusion and 8 hourly IV/IM boluses, to ensure constant delivery even when infusion is stopped inadvertently (e.g. power failure) or a single bolus dose is missed. Once oral intake resumes, the dose can be switched to oral hydrocortisone and tapered as the stress (fever/infection) goes away.

| **Stress steroids during periods of physiological stress** | |
|---|---|
| *Adrenal crisis/critical illness:* | Hydrocortisone injection 100 mg/$m^2$ (max. 100 mg) IV/IM stat with saline volume expansion, followed by 25 mg/$m^2$ q 6 hours (max. 25 mg q 6 hours); call endocrinologist. |
| *Surgery:* | Hydrocortisone injection 50–100 mg/$m^2$ IV (max 100 mg) pre-operatively, then 25 mg/$m^2$ q 6 hours (max 25 mg q 6 hours); call endocrinologist. |
| *Illness or fever:* | 20 mg/$m^2$/day hydrocortisone equivalent, in 2-3 divided doses/day |
| *Fever >38.5°C or vomiting:* | 30 mg/$m^2$/day hydrocortisone equivalent, in 3 divided doses |
| *Unable to tolerate orally:* | Hydrocortisone must be administered parenterally, 25 mg/$m^2$/dose q 6 hours IV or q 8 hours IM |
| Ref: Allergy Asthma Clin Immunol. 2011; 7(1): 13 | |

**Do children on inhaled / topical steroids need tapering / stress dosing?**

There have been numerous reports of children suffering with adrenal insufficiency with inhaled steroids in doses above 500 µg/day of fluticasone (1000 µg of budesonide). They need stress dosing. Topical steroids can cause Cushing syndrome and adrenal suppression. Any child who was on any steroid form/preparation and developing symptoms of adrenal insufficiency needs evaluation and replacement with glucocorticoids.

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# An Approach to a Child with Cushing Syndrome

**Prachi A Bansal, Senior resident, Nalini S Shah, Professor and Head**

**Department of Endocrinology, KEM Hospital, Mumbai**

Cushing Syndrome (CS) is a generic term used to describe a morbid clinical state caused by prolonged glucocorticoid excess. The term "Cushing disease" (CD) is reserved for endogenous hypercortisolism caused by an adrenocorticotropic hormone (ACTH) producing pituitary adenoma. The classical presentation of prolonged hypercortisolism in children is growth failure coupled with weight gain. Catabolic manifestations of hypercortisolism (e.g. thin skin, dark livid striae, easy bruising, muscle weakness, and osteoporosis), although of high discriminatory value, are less common in children. Thus, a high index of suspicion is required to diagnose this rare entity (10-20% of 2-3 CD cases/million population/year). Delayed puberty as well as sexual precocity and signs of hyperandrogenism (e.g., hirsutism and acne) are well described manifestations in children. In rare cases, CD can present as polycystic ovary syndrome, type 2 diabetes mellitus, hypertension, obsessive compulsive disorder, or osteoporosis. The spectrum of clinical manifestations at a given level of hypercortisolism is also variable. However, it is a progressive disorder, and appearance of new features over time increases the probability of disease. Delay in diagnosis in a child not only affects growth, puberty and general wellbeing, but also leads to increased mortality.

**Practical Approach to Diagnosis:**

The diagnostic work up of a patient with suspected CD is challenging for several reasons. First, the spectrum of clinical presentation is broad, and it can be difficult to clinically detect milder cases. Second, the performance and interpretation of the battery of tests employed to establish endogenous hypercortisolism requires considerable expertise. Some patients with CS, especially those with mild or cyclical disease, may have normal results. In addition, patients who do not have CS, but have rather common conditions such as obesity, metabolic syndrome, stress etc., can have abnormal results. When ACTH dependent hypercortisolism is conclusively established but pituitary imaging is negative, the next challenge is to differentiate an inapparent pituitary adenoma from ectopic ACTH producing tumor. This requires CRH stimulated bilateral inferior petrosal sinus sampling (IPSS). Even after confirming a pituitary source, performing adenomectomy may not be the lasting solution, as CD tends to persist or recur in a significant number of cases.

**Table 1: Classification of Cushing Syndrome**

| |
|---|
| **ACTH-dependent CS** |
| Cushing disease (ACTH secreting pituitary adenoma) |
| Ectopic ACTH syndrome |
| Ectopic CRH-secreting tumor |
| **ACTH-independent CS** |
| Exogenous glucocorticoid administration |
| Adrenocortical tumor (adenoma/carcinoma) |
| Primary adrenocortical hyperplasia |
| *Primary pigmented nodular adrenocortical disease (PPNAD)* |
| *Primary bilateral macronodular adrenal hyperplasia (PBMAH)* |
| *McCune-Albright syndrome (MAH)* |

**Proving Endogenous Hypercortisolism**

The first step in the evaluation of a child with suspected CS is to exclude exogenous steroid exposure through a proper drug history. A further diagnostic step is to establish the biochemical hypercortisolism and then identify its source (Table 1). It is important to note that isolated cortisol and ACTH measurements are not of value in diagnosis, given the circadian nature of cortisol and ACTH secretion.

Endogenous hypercortisolism can be proven by one of the tests mentioned in Table 2. Initial evaluation requires determination of urinary-free cortisol (UFC), late night salivary cortisol, overnight dexamethasone suppression (ODS) test, or standard two day low dose dexamethasone suppression (LDDS) tests.

In patients with a high index of clinical suspicion and equivocal, discordant, or negative initial test results, subsequent evaluation with either midnight serum cortisol level or LDDS-corticotropin-releasing hormone (LDDS-CRH) test may be required. Hypercortisolism, unassociated with CS, has been observed in individuals with metabolic syndrome, stress, and a state of corticosteroid-binding globulin excess. The lowering of diagnostic cut-off levels over time had increased the sensitivity of these tests at the cost of their specificity.

**Table 2: Tests for endogenous hypercortisolism**

| |
|---|
| **(1) Quantitative estimation of cortisol production** |
| Urinary free cortisol (UFC) estimation |
| **(2) Circadian rhythm** |
| Late-night salivary cortisol |
| Midnight serum cortisol |
| **(3) Dexamethasone suppression tests** |
| Overnight dexamethasone suppression (ODS) test |
| Standard 2-day low-dose dexamethasone suppression (LDDS) test |

**UFC Measurement**

Twenty four hour urinary free-cortisol excretion is an integrated measure of serum free-cortisol concentration. A minimum of two UFC collections must be obtained. Samples must be refrigerated until analyzed. A level above the upper limit of normal for a given assay is used as a criterion for a positive test. Antibody-based assays yield higher levels compared

with liquid chromatography-mass spectrometry (LC-MS/MS). Sensitivity in children is reported to be nearly 89%. False positive test results can occur with the concomitant use of drugs such as carbamazepine and fenofibrate. False-negative results have been seen in individuals with renal impairment and mild CS.

**Late night salivary cortisol**

Loss of circadian rhythm is one of the earliest abnormalities in CS. Late night salivary cortisol sampling is a good surrogate for midnight serum cortisol. It can be measured by enzyme linked immunosorbent assay (ELISA) and LC-MS/MS. Samples are collected on two separate evenings either by passive drooling or by placing a salivette in the mouth and chewing for 1 to 2 minutes. At a cut off of 1.45 ng/ml, the late night salivary cortisol has good sensitivity and specificity (100% and 95% respectively) for diagnosing CS.

**Midnight Serum Cortisol**

Evaluation of the sleeping midnight serum cortisol level (>1.8 mcg/dl) has been reported to have high sensitivity (100%) but poor specificity (20%). Obtaining a midnight serum cortisol sample necessitates hospitalization. Collection is typically performed 24h after admission in an attempt to alleviate stress. Blood from a pre-cannulated venous access port is collected within 5 minutes after the individual is awakened.

**Dexamethasone Suppression Test**

Variability in the absorption and metabolism of dexamethasone can influence these tests. Drugs that accelerate dexamethasone metabolism may give falsely high levels of serum cortisol, and vice versa.

**ODS Test**

Dexamethasone (1 mg) is usually given at 2300 hours on an outpatient basis and serum cortisol measured at 0800 hours the next morning. To enhance its sensitivity, a lower cut off of <1.8 mcg/dl is advocated (sensitivity of 95% and specificity of 80%). However, data regarding performance and interpretation of this test in children is lacking.

**Standard Two-Day LDDS Test**

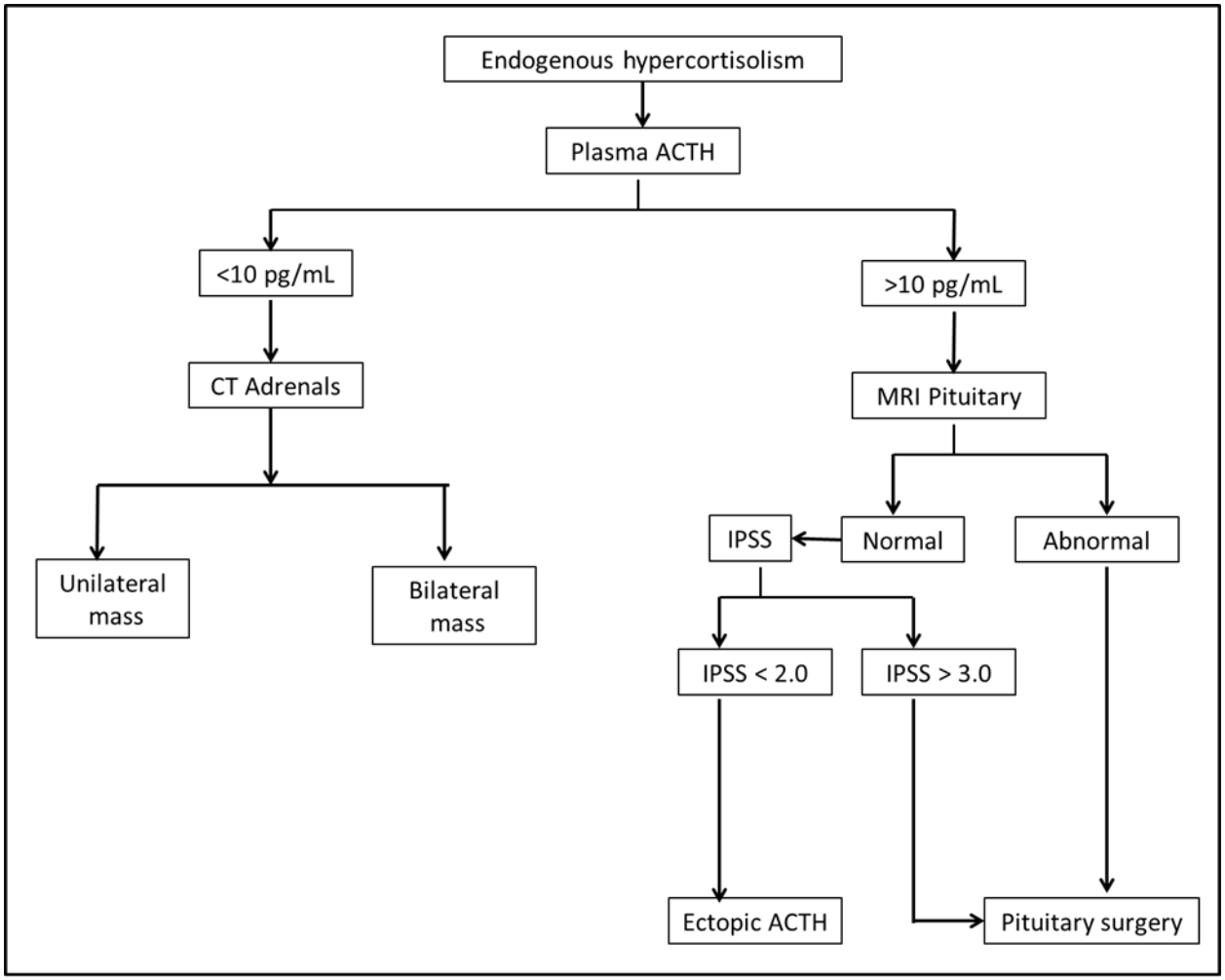
For pediatric patients weighing >40 kg, an adult dose schedule is used (0.5 mg dexamethasone every 6h for 2 consecutive days), and serum cortisol estimated 6h after the last dose of dexamethasone. For patients weighing <40 kg, the recommended dose of dexamethasone is 30 mcg/kg/d. Serum cortisol values <1.8 mcg/dl exclude CS with 97% sensitivity.

**LDDS-CRH Test**

Few patients with CD show suppression after LDDS test. CRH administration increases the levels of ACTH and cortisol. The test is performed by administration of intravenous (IV) CRH (1 µg/kg) 2h after the last dose of dexamethasone. Serum cortisol values >1.4 µg/dL measured 15 minutes after CRH administration indicate CD (sensitivity 98%, specificity 60%). A recent study has reported that severe obesity confounds the interpretation of the dexamethasone-CRH test. The authors have suggested that definite height gain on follow up is a simple, yet useful, way to help distinguish children with pseudo-Cushing's syndrome from those with CS.

**Determining the Source of Endogenous Hypercortisolism**

Plasma ACTH, imaging studies and bilateral inferior petrosal sinus sampling (IPSS) are used to identify the source of endogenous hypercortisolism. A schematic diagram for localization of the source in a proven case of endogenous CS is provided in Figure 1.




**Plasma ACTH**

Plasma ACTH estimation with two-site immunometric assay provides a useful parameter for the diagnosis of adrenal CS in a manner similar to suppressed TSH in Graves' disease. Patients with suppressed morning plasma ACTH (< 10 pg/mL) need adrenal imaging, whereas those with normal or elevated ACTH (> 10 pg/mL) require pituitary imaging. Stratakis et al reported that morning plasma ACTH > 29 pg/mL has a specificity of 100% and sensitivity of 70% for diagnosis of ACTH-dependent CS.

**Magnetic Resonance Imaging of Pituitary Gland**

Post-contrast (gadolinium) spoiled gradient-recalled acquisition is superior to conventional dynamic contrast spin echo magnetic resonance imaging (MRI) in children and adolescents with CD. The reported rate of visualization of pituitary micro-adenomas on MRI varies from 50 to 70%.

**IPSS**

In the absence of localization of an adenoma by MRI, a more invasive test such as IPSS is needed in individuals with suspected ACTH-dependent CS. A pituitary to peripheral ACTH ratio >2 in basal- and >3 in CRH-stimulated IPSS has a sensitivity of 100% in diagnosing CD. False-negative results on IPSS have been attributed to anatomical problems like anomalous venous drainage. Lateralization of the tumor with IPSS is possible in 60-70% patients. The reported complication rate is < 1% in the hands of an experienced interventional radiologist.

**Computerized Tomography of Adrenal Glands**

In the case of ACTH-independent CS, CT of the adrenal glands is the next investigation of choice. Adrenocortical adenomas and carcinomas are easily identified by CT images. PPNAD is more difficult to diagnose radiologically, but the absence of an obvious adrenal lesion in a case of ACTH-independent CS points toward this etiology.

**Summary:**

CD is a rare disorder associated with severe morbidity affecting the child's growth, puberty, and generalized wellbeing. Conducting tests for a clinically florid CS case to establish endogenous hypercortisolism is easy. The real challenge lies in dealing with the subtle cases where even experienced endocrinologists may find it difficult to interpret test results and may have to resort to a wait-and-watch policy. The basic dictum which still serves as a golden rule is not to proceed further, until there is convincing evidence of biochemical hypercortisolism. While localizing the source, suppressed levels of plasma ACTH and positive adrenal imaging provide an easy path. In case of ACTH-dependent CS, an MRI showing a clearly defined pituitary adenoma is rewarding. Equivocal or negative findings on an MRI scan mandate CRH-stimulated IPSS. Thus, a systematic approach to the diagnosis and differential diagnosis of CS avoids errors and helps to define the appropriate treatment strategy.

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# Management of Adrenal Cushing syndrome in children

**Leena Priyambada, Assistant Professor, Department of Pediatrics, Christian Medical College, Vellore, TN**

ACTH-independent Cushing syndrome (CS), accounts for approximately 15% of all childhood CS. It is more frequent in younger children (<7 years of age). The various primary adrenal causes of CS are:

- Adrenal tumors (adenoma/carcinoma)
- Primary adrenocortical hyperplasia
    - Primary Pigmentary Nodular Adrenocortical Disease (PPNAD)
    - Mc Cune Albright Syndrome (MAS)
    - ACTH-independent macronodular adrenal hyperplasia (AIMAH)

**Evaluation**

Biochemical approach to a child with adrenal CS is described in the article (An Approach to Diagnosis of Childhood Cushing Disease). Once the ACTH independent endogenous CS is confirmed, next step is to perform **CT** imaging of adrenals. Large size, irregular margins, heterogeneous density, calcification, high vascularity, and <50% contrast washout after 10 min favour malignancy (adrenocortical carcinoma). Smaller tumors (<4cm), low unenhanced CT attenuation values (<10HU) and rapid contrast medium washout favour adrenocortical adenomas. Isointensity with liver on both T1 and T2 weighted images and chemical shift evidence of lipid on MRI also favour adenoma. Massive enlargement of both adrenal glands suggests AIMAH whereas normal- or small-sized adrenal glands, nodules with atrophic cortex suggest PPNAD. MRI is also useful for detection of local invasion and involvement of the vena cava in suspected ACC. FDG uptake is seen in FDG PET scan in malignant tumors and not usually in benign adenomas. "Fused" PET-CT imaging improves the sensitivity specificity and predictive values of PET. FNAC cannot differentiate between a benign and malignant lesion.

**Treatment**

**Surgery:**

The treatment of choice for adrenal causes of CS is surgical resection. In bilateral micronodular or macronodular adrenal disease, such as PPNAD and AIMAH, bilateral total adrenalectomy is usually the treatment of choice. In some cases of asymmetrical involvement and doubtful diagnosis of a bilateral disease process, a unilateral adrenalectomy may be done initially. Unilateral adrenalectomy leads to significant clinical and biochemical improvement but the patient should be closely followed up for the need to remove the second gland. ACC are also surgically removed, unless at advanced stages. In case a solitary metastasis exists, it should be removed but requires extensive surgery.

**Medical management:** There is not much data available regarding medical management of adrenal causes of CS in children. Pharmacotherapy may be used in cases of:

1. Interim management while waiting/preparing for surgery

2. Acute control severe hypercortisolism if life-threatening complications of CS such as infection, pulmonary thromboembolism, cardiovascular complications, and acute psychosis are present.
3. Inoperable tumors or as adjuvant therapy in ACC.
4. Cyclic CS may be managed with drugs.

The choice of medical therapy should be guided by efficacy, individual patient factors, and cost. The goal is normalization of clinical features and cortisol levels. Adrenal enzyme inhibitors are most commonly used, but adrenolytic agents and glucocorticoid-receptor antagonists also have been used. Drugs used to control hypercortisolism are:

***Adrenal enzyme inhibitors***: Ketoconazole, metyrapone, etomidate.
Ketoconazole is the most commonly used drug for interim management. It inhibits the first step in cortisol biosynthesis, C17-20 desmolase, decreasing androgen production; and conversion of 11-deoxycortisol to cortisol. Hepatitis needs to be watched for. Metyrapone is mainly an inhibitor of CYP11B1 (11-beta-hydroxylase). It can worsen salt retention and hypertension and cause androgenic side effects in the long term. Etomidate has been proved to be a useful medication to control symptoms acutely within a few hours when infused intravenously in a low, non-hypnotic dose of 0.3 mg/kg per hour. It blocks 11-beta-hydroxylation of deoxycortisol to produce cortisol.
***Glucocorticoid receptor antagonist***: Mifepristone is a glucocorticoid and progesterone receptor antagonist, which can provide rapid improvement in glycemic control, insulin resistance, and hypertension. It has been used for cortisol-induced psychosis.
***Adrenolytic agents:*** Mitotane is an adrenocorticolytic drug that is used primarily for the treatment of adrenal carcinoma. It has a cytotoxic effect on adrenal tissue in humans in both normal adrenals and in adrenocortical tumors. It also inhibits CYP11B1 (11-beta-hydroxylase) and cholesterol side-chain cleavage (CYP11A1) enzymes. Steroid replacements may be needed if mitotane or etomidate are used long term.
**Other drugs** used for inoperable tumors or as adjuvant therapy in ACC are cisplatin, 5-flourouracil, suramin, doxorubicin, and etoposide. Targeted therapies like Figitumumab, an anti-IGF 1R monoclonal antibody, Multikinase inhibitors like sorafenib and sunitinib, Epidermal growth factor receptor and vascular endothelial growth factor inhibitors, rapamycin signaling (mTOR) inhibitors, everolimus and temsirolimus, Wnt signaling inhibitors and inverse agonist of steroidogenic factor 1 are being tried for ACC. Radiotherapy can also be used in the case of metastases. Management of associated morbidities of poor growth, obesity, insulin resistance, hypertension, dyslipidemia, hypercoagulability, impaired bone mineral density, and psychiatric disorders plays an important role. Following bilateral adrenalectomy, patients require lifetime replacement with both glucocorticoids and mineralocorticoids.

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# Management of Cushing's Disease in Children

**Anish Kolly, Senior resident, Vijaya Sarathi, Associate Professor, Vydehi Institute of Medical Sciences and Research Center, Bengaluru**

Endogenous Cushing Syndrome (CS) is a rare disease in children. In preschool children, primary adrenal causes are responsible for most cases of CS, while ACTH dependent causes are responsible for 75-80% cases in children above 5 years. Almost all cases of ACTH dependent CS are due to an ACTH secreting pituitary adenoma; ectopic ACTH secretion (EAS) is extremely rare in children.

Transsphenoidal surgery (TSS) is the optimal treatment for Cushing disease (CD). The challenges of performing a TSS in children include the relatively smaller size of adenomas, and the absence of aeration in the sphenoidal bone in children. Postopertaive serum 8:00 am cortisol is the most commonly used test to define cure in CD and suppressed values suggest remission/cure. However, currently there is no consensus on its cut-off. Using various cutoffs and end points, the success rate of TSS in children ranges from 45-95%. In an Indian study, the remission rate was 56% in the hands of an experienced surgeon. Initial remission rates were higher amongst children in whom the adenoma was clearly identifiable during surgery. Younger age, smaller size of adenoma, and undetectable post-op day 1 basal serum cortisol levels have been associated with high long term remission rates. Macroadenomas or tumors invading the cavernous sinus are associated with poorer outcomes. Elevated cortisol levels in the immediate post-operative period do not necessarily indicate failure, and evaluation should be repeated after 6 weeks of TSS to look for continued partial improvement in cortisol levels.

Successful TSS usually induces a state of transient ACTH deficiency, during which steroid coverage is necessary. If evaluation in the immediate postoperative period suggests ACTH deficiency, glucocorticoid replacement should be done followed by periodical assessment to guide weaning of steroids. Permanent ACTH deficiency has also been reported in 3-24% patients. Post-operative assessment should also include electrolytes and other pituitary hormones. The spectrum of hypopituitarism is variable, with frequent growth hormone deficiency (GHD) reported (8-78% patients in some studies). Other anterior pituitary hormones such as TSH (5-33%) and gonadotropins (0-44%) can also be involved. Diabetes insipidus has also been reported in 3-11% of patients in the postoperative period.

The options for second-line therapy in failed surgeries include repeat TSS, pituitary radiotherapy (RT), medical therapy, and bilateral adrenalectomy.

Pituitary RT was the treatment of choice for CD in children before TSS became widely available. RT is known to be effective in children with CD, with a more rapid mode of action than in adults: most children show a response within 9-12 months of RT. The success rates in children range from 50-92%. More focused RT can be achieved by linear particle accelerator, photon beam therapy or stereotactic radiosurgery (SRS) using a gamma knife. Benefits of SRS include reduced number of sittings and lower rates of side-effects, but it is not available in many centers and experience in pediatric CD is limited. Hypopituitarism is a

frequently encountered complication associated with pituitary RT. Immediate GHD is commonly seen post RT with reports of 86% (6/7) - 91% (5/6). However GH was seen to normalize over time, as assessed in the long term follow up in these studies. The gonadotropin deficiency is also common and seen in 12.5-62.5% cases.

Medical options for CD include pituitary directed modalities and adrenal directed modalities. Pituitary directed modalities at present include the dopamine agonist cabergoline and the somatostatin receptor antagonist paseriotide. Newer drugs on the horizon include EGFR antagonist gefitinib, HSP90 antagonist silibinin and selective V2b receptor antagonists. Adrenal directed therapies include the adrenolytic agent mitotane, and steroidogenesis inhibitors ketoconazole, metyrapone, and osilodrostat. Glucocorticoid antagonists such as mifeprestone have also been tried, with monitoring of efficacy by clinical features. In some cases of refractory and aggressive CD, chemotherapeutic agents such as temozolamide have also been tried. However at present the use of medical therapy is not approved in children in view of lack of evidence.

Bilateral adrenalectomy is usually considered as a last resort when rapid control of cortisol levels is required and the tumor is not localized. The incidence of Nelson Syndrome (NS) post- adrenalectomy is seen to be higher in children than adults, with rates as high as 25-50%. Since children are more prone to NS, regular surveillance should be done and RT or pituitary directed medical therapy considered in such cases. In severe cases pituitary surgery may be required.

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## Pre-and Post-operative Management of Cushing Syndrome


**Dr. Rajni Sharma, Assistant Professor, Division of Pediatric Endocrinology, AIIMS, New Delhi**


*An 11-year old boy with Cushing syndrome due to left adrenal adenoma is posted for laparoscopic left adrenalectomy. You are consulted for preoperative stabilization and advice regarding steroid replacement in the post-operative period. What are the important management points you will consider?*

Pre-operatively, it is essential to clinically stabilize the patient. Most have arterial hypertension with fluid retention that needs to be controlled with antihypertensive therapy.

The choice of drugs includes spironolactone, ACE inhibitors or calcium channel antagonists. Electrolyte abnormalities like hypokalemia, which can pose a risk of life threatening cardiac arrhythmia, also need to be corrected preoperatively.

Impaired glucose tolerance or frank diabetes mellitus are frequently present, due to gluconeogenesis, decreased peripheral utilization of glucose and anti-insulin activity of glucocorticoids. The patient should be screened for diabetes with blood sugar (fasting and postprandial), A1C, and if necessary, an oral glucose tolerance test. Control of glycemia can be achieved by oral anti-diabetic drugs (metformin) or insulin.

There may be difficulties in the pre- and intra-operative period due to obesity, including placement of intravenous lines, intubation and positioning during laparascopy. Great care should be taken during positioning due to the possibility of underlying osteoporosis and a propensity for fractures.

The post-operative period may be complicated by delayed recovery due to the prolonged effect of lipophilic anesthetic agents deposited in the body fat, and difficulty in extubation. Prophylactic antibiotics are advised due to poor immunity and high risk of infection. There is also a tendency to poor wound healing, gastroesophageal reflux and thromboembolism.

***How would you plan his steroid replacement post-operatively?***

The removal of the source of excess cortisol (adenoma/ tumor) in patients with ACTH-independent CS causes a sudden decrease in cortisol production. Moreover, endogenous ACTH production is already low in these patients and the other adrenal gland is atrophic leading to a high risk of adrenal crisis in the post-operative period. Similarly, removal of pituitary adenoma in Cushing's disease can lead to low ACTH and therefore low cortisol levels in the post-operative period. Therefore, intravenous supplementation of hydrocortisone in stress dosages (100 mg/$m^2$/day) should be initiated in the intra-operative or immediate post-operative period. This dose is slowly tapered in the next few days to physiological doses (12-18 mg/ $m^2$/day), given orally.

In patients with ACTH-dependent CS, 8 am serum cortisol level should be repeated on post-operative day 4-5, after withholding hydrocortisone for 24 hours. A low serum cortisol level (< 2 μg/dL) is highly indicative of surgical success and clinical remission.

Hydrocortisone is continued in physiological doses, with supplementary dosing during periods of stress or illness (double dose for mild illness, triple dose for moderate illness). An 8 am serum cortisol is repeated after 3-6 months (again after withholding hydrocortisone for 24 hours). A cortisol value >10 μg/dL indicates normal basal production of cortisol, at which point physiological hydrocortisone replacement can be tapered off and stopped. An ACTH (Synacten/ Acthar gel) stimulation test is done to assess the recovery of the hypothalamic-pituitary-adrenal (HPA) axis. A cortisol value <18 μg/dL indicates incomplete recovery and the need to supplement hydrocortisone during periods of stress, whereas a value >18 μg/dL indicates complete HPA axis recovery. Generally, complete HPA axis recovery takes place in 6-12 months.

## A Case of Pediatric Cushing Syndrome due to ectopic ACTH secretion

**Dr T Karthikraj, Dr V Kumaravel, Dr RV Jeyabalaji, Dr Sivan Arul Selvan, Alpha Hospital & Research Centre, Madurai**

**Case summary:**

A 12yo girl was hospitalized with complaints of facial puffiness, generalized swelling of the body, recent increase in weight and easy fatigability, for the past one month. She also had a history of dark discoloration of the lips and oral mucosa for the past one week. On examination her height (132cm) was below the 3$^{rd}$ centile and weight (32kg) was below the 10$^{th}$ centile. She had hyperpigmentation of her lips, oral mucosa, bilateral pitting pedal edema, truncal obesity, hypertrichosis over forehead and acne-form eruptions over face (fig 1A). Her blood pressure (120/80) was between 95$^{th}$ and 99$^{th}$ centile for age, sex and height. Her systemic examination was normal. There was no history previous hospitalization or drug intake (steroids).

Table 1: Initial evaluation for suspected Cushing syndrome

| | | | |
|---|---|---|---|
| Serum potassium | 1.3 meq/L | Serum 8:00 am cortisol | 32.44 µg/dl |
| Free T3 | 3.57ng/ml | Plasma 8:00 am ACTH | 230 pg/ml |
| Free T4 | 1.37ng/ml | Serum DHEAS | 282.8 µg/L |
| TSH | 1.85 µIU/ml | ONDST cortisol | 30.2 µg/dl |
| Fasting plasma glucose | 124 mg/dl | Postprandial plasma glucose | 166 mg/dl |

The child was suspected to have Cushing syndrome (CS): evaluation was suggestive of ACTH dependent CS (table 1) with severe hypokalemia and very high ACTH levels. MRI pituitary revealed mild pituitary enlargement with convex upper surface but no definitive hypodense lesion suggestive of pituitary adenoma (fig 2A and 2B). CT abdomen and chest revealed bilateral adrenal enlargement suggestive of adrenal hyperplasia (fig 2D) and a heterogeneously enhancing mixed density lesion with faint calcification noted on the left side of the anterior mediastinum, measuring 3.8 X 3.5 cm, suggestive of thymoma or mixed germ cell tumor (fig 2E). A CT guided trucut biopsy of the anterior mediastinal mass showed a uniform type of small round tumor cells with eosinophilic cytoplasm arranged in trabecular pattern and diffuse sheets with focal calcification, suggestive of a thymoma or dysgerminoma. Preoperatively, hypokalemia was corrected with oral potassium chloride supplementation and hyperglycemia was managed with insulin. Subsequently, the child underwent VATS, with excision of the anterior mediastinal tumor. Immunohistochemistry was positive for cytokeratin and chromogranin, and negative for S100, suggesting Grade II thymic neuroendocrine tumor (carcinoid). She was discharged on replacement doses of

hydrocortisone. A week later, her 8:00 am serum cortisol was 0.8 µg/dl, and plasma ACTH level 31.6 pg/ml.

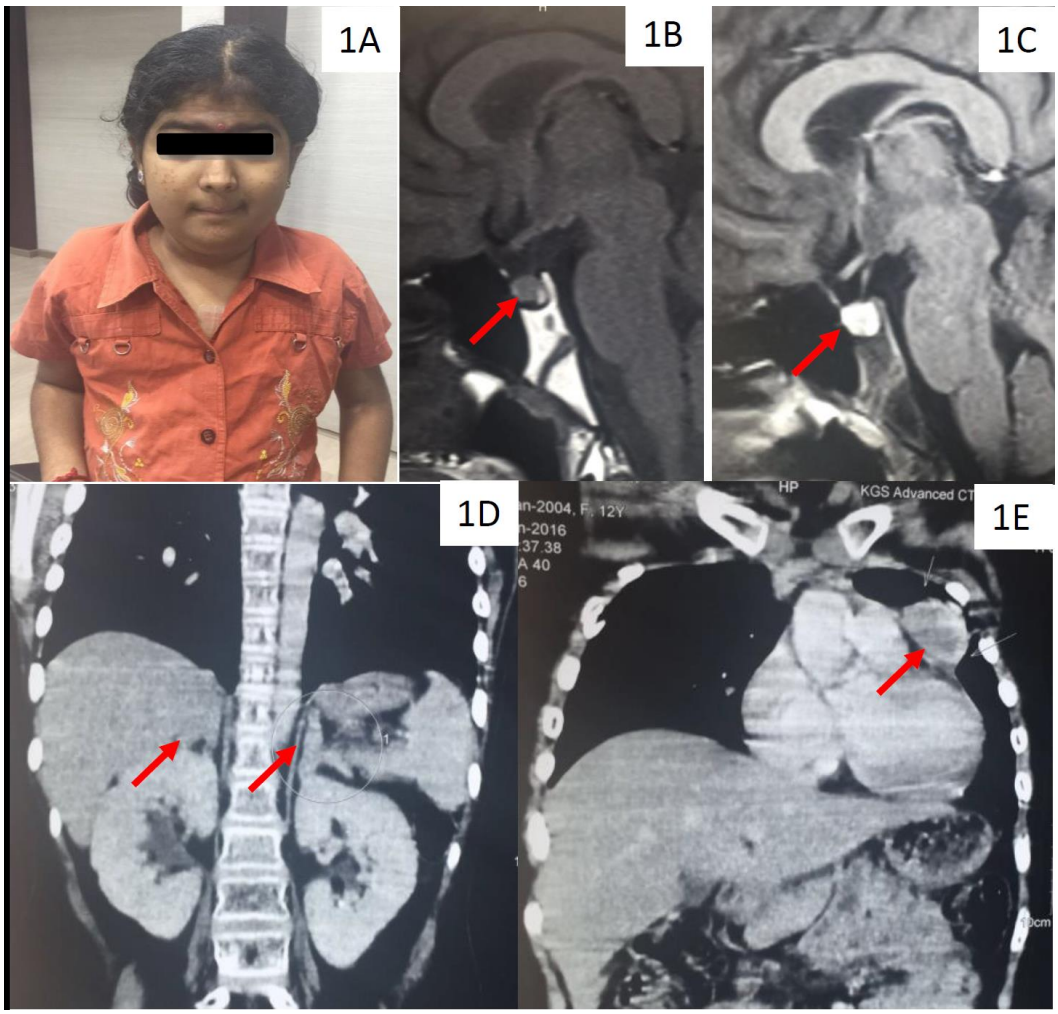


Fig 1: Clinical photograph of the child (fig 1A), MRI of pituitary showing mild pituitary enlargement with convex upper surface (fig 1B) with intense homogenous enhancement (fig 1C), heterogeneously enhancing mixed density lesion with faint calcification noted on left side anterior mediastinum measuring 3.8x 3.5 cm (fig 1D) and diffuse hyperplasia of both adrenal glands (fig 1E).

**Discussion**

The incidence of endogenous CS is 2-5 new cases per million general population per year; it is rare in childhood and adolescence. Cushing's disease (CD), caused by an ACTH secreting pituitary adenoma, is the commonest cause of CS in children over 5 years of age (nearly 80%). A small proportion of ACTH-dependent CS cases are due to ectopic ACTH-secreting tumors, mainly reported in adult patients.

Ectopic ACTH secretion (EAS) often presents with severe hypercortisolemia not only in adults but also in children. It is associated with severe hypokalemia and associated metabolic alkalosis, severe muscle weakness and hyperpigmentation. Other features like hypertension, dysglycemia, and acne, are also more common, whereas weight gain is a less

common feature of EAS. However, there is a significant overlap and no feature has a strong discriminative power to differentiate EAS from CD. In our patient, severe hypokalemia (1.3 mg/dl), very high ACTH (230 pg/ml) level and marked hyperpigmentation favored EAS.

Since ACTH secreting pituitary adenoma is the most common cause of ACTH dependent CS, our initial investigation was an MRI of the pituitary. Since this did not show have a definitive adenoma, we looked for an ectopic source. Pituitary hyperplasia often coexists in CRH co-secreting tumors, and can misdirect localization to the pituitary, leading to inadvertent pituitary surgery.

Unlike in adults, in whom EAS is often due to small cell cancer of lung, in children and adolescents bronchial carcinoids, thymic carcinoids, and pancreatic neuroendocrine tumors are the common causes. CS is seen in approximately 20% of patients with thymic carcinoids. Despite aggressive treatment, thymic carcinoid tumors have poor prognosis.

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## Hypertensive encephalopathy: an unusual presentation of pediatric Cushing syndrome


**Dr Sandeep Julka, Dr Ashish Jaiswal, Dr Rajneesh Kutumbale, Dr Manish Patel, Dr Divya Kutumbale, Dr Jayesh Jajodia. Radiance -The Hormone Health Clinic, Indore, MP**


**Case Report:**

A 4yo boy presented to us in the emergency department with complaints of abnormal behavior, speech and vision along with paucity of movements on the right side for the past 12-24 hours. The boy was the first child of a non-consanguineous couple. The perinatal period was uneventful; the mother did not know the birth weight of the child, but said he was not obese. Milestones were normal. The mother noticed excess weight gain since the age of 6 months, which was gradually progressing, with history of polyphagia and sleep disturbances. There was no history of intake of exogenous steroid.

Anthropometric measurements showed he was 25 kg (> 97$^{th}$ percentile), 106 cm (25$^{th}$ percentile), with BMI > 95$^{th}$ percentile. On examination he was markedly obese, with predominantly truncal obesity and a plethoric moon face (fig 1A). Abdominal cutaneous striae were very few and not pathognomonic of Cushing Syndrome (CS). His blood pressure

was 170/120 mmHg. Neurological examination revealed right sided hemiparesis with minimal speech, and minimal interest in the surroundings. He had no signs of meningitis, altered sensorium, or restricted visual acuity; fundus examination was normal. Laboratory investigations revealed leukocytosis and normal serum electrolytes, normal renal function tests, and normal fasting and postprandial glucose levels. Chest X-ray was normal. Ultrasonography of abdomen showed heterogeneous hypoechoic mass (4.6 X 5.0 cm) in the right suprarenal area (adrenal mass). CS was suspected and further endocrine tests were performed to determine the etiology. Serum 8:00 am cortisol was > 60 µg/dl; overnight dexamethasone suppression test, low dose dexamethasone suppression test, and high dose dexamethasone suppression test were all unsuppressed. Diurnal variation of plasma cortisol was not observed. Plasma ACTH level was 8.8 pg/ml. Thyroid function tests were normal. A 24-hour urinary VMA done to rule out pheochromocytoma, was normal. MRI abdomen was suggestive of lipid poor right adrenal adenoma (4.1X5.5X4.8cm) (Fig 2A and 2B). Left adrenal was normal. MRI brain showed generalized cerebral and cerebellar atrophy. Pituitary gland was normal.

The child was stabilized with medical management prior to surgery with anti-hypertensive, anti-epileptics, and antibiotics. On exploratory laparotomy, done through the right supra umbilical transverse incision, a non-adherent, right adrenal mass measuring 5 X 4.5 X 3 cm was found and was excised. Cut section of the specimen was solid, greyish white to yellow in color (fig 2C). Histopathology revealed a capsulated tumor with high vascularity and foci of calcification. No atypical mitosis or necrosis and capsular invasion were seen. Ki 67 proliferation index was 2-4%. There was compressed adrenal parenchyma at the periphery (Fig 2D). Immunohistochemistry was positive for synaptophysin and inhibin, weakly positive for melan A and negative for chromogranin and calretinine. Features were suggestive of adrenocortical adenoma.

Perioperatively, the child was supplemented with stress doses of parenteral hydrocortisone, followed by oral replacement doses, which continue till date. At last follow-up, ACTH stimulated cortisol was 7.5 µg/dl. Postoperatively, he gradually lost 4 kg weight with resolution of Cushingoid features (Fig 2). His antihypertensive drugs were tapered off over 6 months and at present he is normotensive off antihypertensive drugs.

**Discussion**

Hypertension has been reported in up to 60% of pediatric patients with CS. The prevalence of systolic hypertension has been reported to be higher in children with ACTH independent CS (74%) than those with Cushing disease (44%), with similar rates of diastolic hypertension (25%) in both groups. However, hypertensive encephalopathy is a rare manifestation of CS in children. Among a cohort of 113 pediatric CS, one child with bilateral

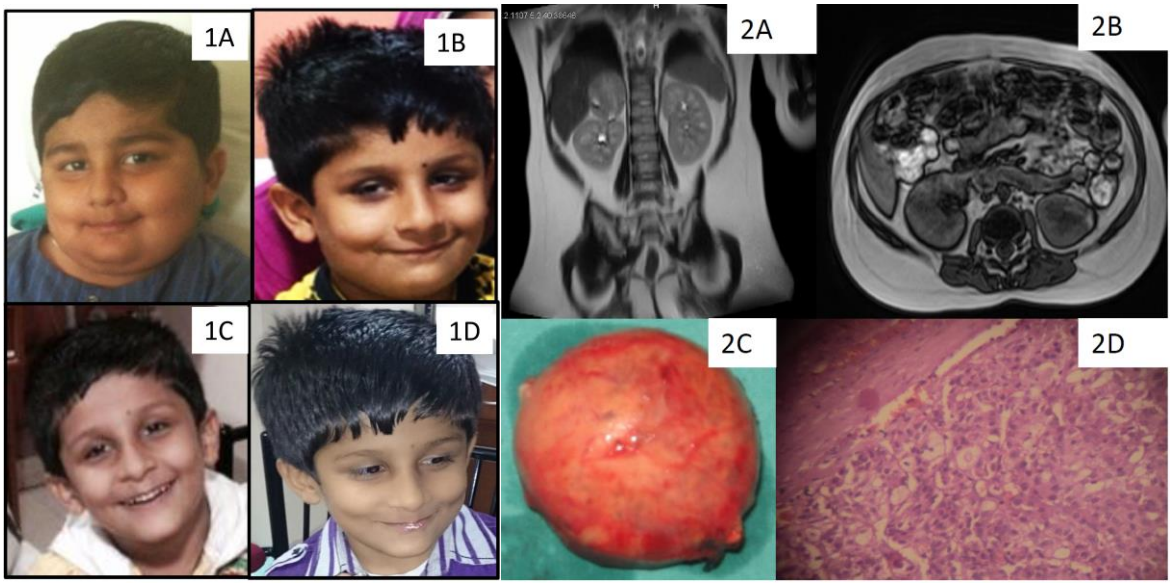


*Fig 1: Facial appearance of the child, with plethoric moon face at presentation (1A) with gradual resolution of Cushingoid facial features at 3 months (1B), 6 months (1C) and 1 year (1D) after excision of the tumor.*
*Fig 2: Longitudinal (2A) and transverse (2B) T1W images demonstrating lipid poor adenoma involving the right adrenal gland; Macroscopic (2C) and microscopic appearance on H & E staining (2D) of the mass suggestive adrenocortical adenoma.*

micronodular adrenal hyperplasia had reversible posterior (hypertensive) encephalopathy syndrome. This was the first pediatric CS case reported to have hypertensive encephalopathy. Another adolescent with ACTH independent CS presented with seizures and hypertension 2 years prior to her diagnosis of CS, but there was no documentation of hypercortisolism around the time of seizures. We report another rare case of pediatric CS presenting with hypertensive encephalopathy.

The pathogenesis of glucocorticoid-induced hypertension is not completely understood. It is thought to be related to both the mineralocorticoid activity of high cortisol levels (saturation of 11β-HSD II leading to impaired inactivation of cortisol to cortisone in renal tubules), as well as to effects of cortisol on the peripheral vasculature. Prompt initiation of antihypertensive therapy most often leads to reversal of hypertensive encephalopathy, as seen in our patient.

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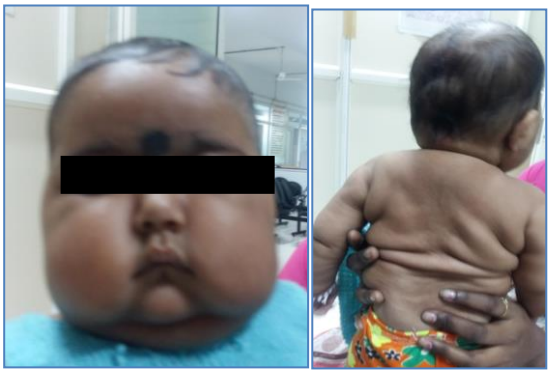
## Repercussions of overdosage of steroids: a short correspondence

**Dr Meghna Chawla, Clinical Fellow, Royal Manchester Children's Hospital, UK & Dr Tushar Deshpande, Assistant Professor, Dept of Paediatrics, Smt Kashibai Navale Medical College, Pune**

Corticosteroids are widely used for the treatment of various diseases. However, they are equally misused for a large number of unindicated conditions as a "quick relief" therapy as well. This may lead to growth arrest and Cushing syndrome with suppression of the hypothalamic pituitary adrenal (HPA) axis.

We report a case of Cushing Syndrome in an 8 month old boy (a rare presentation at this age), who was referred to the Endocrinology Clinic with complaints of excessive weight gain. He was born term with a birth weight of 2.5 kg and length of 50 cm. He was exclusively breast fed till 6 months and subsequently weaning started. At presentation, his weight was 8.5 kg (50$^{th}$centile), head circumference 43cm (3$^{rd}$centile) and length 65cm (< 3$^{rd}$centile). As is evident form his photograph, he had a moon face, hypertrichosis and prominent supraclavicular fat pads. Blood pressure was 112/70mmHg (95$^{th}$ percentile for age is 112/72 mmHg). Investigations showed a low serum 8:00 am cortisol (0.8 µg/dl), low plasma ACTH level (2.0 pg/ml), and random plasma glucose of 89 mg/dl. This was consistent with exogenous Cushing Syndrome. Subsequent detailed history revealed that 3 months back, he had suffered an episode of upper respiratory tract infection for which he was given betamethasone diproprionate drops, a high potency steroid, twice a day, by an unqualified practitioner. We stopped the offending drug, started oral replacement dose of hydrocortisone, and plan to continue monitoring serum cortisol levels until recovery of the HPA axis.

Irrational and inadvertent use of steroids should be curbed. Steroid containing preparations should not be sold over the counter without a proper prescription from a qualified pediatrician. This report also highlights the importance of providing crucial information to the caregivers regarding its potential side effects.

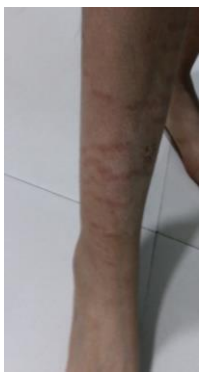


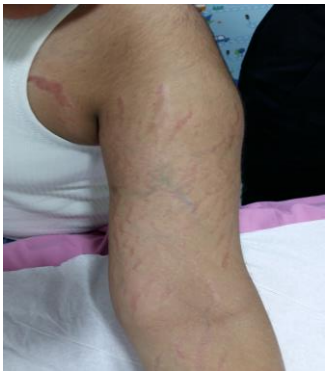
## A case of Cushing syndrome: "THINK ABOUT DRUG ADULTERATION"

**Dr OS Santhosh, Pediatric and Adolescent Endocrinologist, Karnataka Institute of Diabetology, White Lotus Healthcare & Cloud Nine KIDS Hospital, Bangalore**

An 11yo girl presented with concern of excess weight gain (7 kg over last 1y) and increased skin hair for past 3 months. The height velocity in the previous year was zero. On examination, extensive striae were seen over the abdomen, legs, arms, and chest. She was prepubertal, BP 120/80. She gave a history of asthma, being treated with a cocktail of

"Ayurvedic" medicines for the past 2y. There was no h/o abdominal pain, vision and headache.





In the 8:00 am fasting sample we found low serum cortisol (< 0.16 µg/dl), low plasma ACTH (< 1 pg/ml), low plasma glucose (64 mg/dl) and normal serum potassium (4.7 mEq/L). Toxicology analysis at AIMS (Kochi) showed presence of dexamethasone in one of the Ayurvedic medicines, but quantitative analysis could not be done.

The Ayurvedic medicines were stopped, and she was started on hydrocortisone, which gradually weaned to replacement doses over three weeks. Repeat 8:00 am test after 3 weeks revealed a cortisol of 2.62 µg/dl and ACTH of 19.9 pg/ml. Within 3 months of stopping the Ayurvedic medicines, weight reduction of 5 kg and height gain of 3 cm was noticed. This case is an example of an unacceptable practice putting a child's health at risk. We have to think about drug adulteration as a cause of unexplained symptoms.

# Pedendoscan

**Dr Sachin Mittal, Consultant Endocrinologist, Fortis Hospital, Chandigarh**

## Diabetes Mellitus

**A cross-sectional view of the current state of treatment of youth with type 2 diabetes in the USA: enrollment data from the Pediatric Diabetes Consortium Type 2 Diabetes Registry. Nambam B et al. Pediatr Diabetes. 2016 Mar 11**

Clinical characteristics, treatment approaches, clinical outcomes, and co-morbidities of 598 youth (<21 yr of age) with T2D, enrolled in the Pediatric Diabetes Consortium (PDC) T2D Registry from February 2012 to July 2015 at eight centers were studied. Those with increased disease duration had higher frequency of insulin therapy, and much lower rate of achieving target A1C level, highlighting the aggressive course of T2D in youth and adolescents. Additionally, co-morbidities are not being adequately treated.

**Glycemic control and complications in patients with type 1 diabetes - a registry-based longitudinal study of adolescents and young adults. Carlsen S et al. Pediatr Diabetes. 2016 Feb 15**

To assess longitudinal glycemic control and the prevalence of retinopathy and nephropathy in young people (age 14-30y) with T1D in Norway, data on 874 patients was obtained by linking two nationwide, population-based medical quality registries. Median A1C increased through adolescence to peak at age 17y for females and 19y for males; females had higher A1C than males. Subsequently, median A1C declined but was still >8% (>64 mmol/mol) for patients approaching 30y. Retinopathy was found in 16% and nephropathy in 13% of the group. Less than 40% of patients with albuminuria were treated with ACE inhibitors or angiotensin II receptor blockers. The authors concluded that the treatment of adolescents and young adults with T1D in Norway is not optimal, especially for patients in their late teens.

## Disorders of Sex Development

**Timing and outcome concerns regarding feminizing genitoplasty from the perspective of Egyptian families of girls with virilized external genitalia. Marei MM et al. Horm Res Paediatr. 2016;85(1):49-57.**

Thirty girls with virilization due to congenital adrenal hyperplasia, mostly Prader degrees III-IV, underwent single-stage feminizing genitoplasty, at a mean age of 22 months, between 2011 and 2014. The concerns and input of the mothers were prospectively studied. After comprehensive counselling, the mothers completed a questionnaire to clarify their priorities and concerns related to surgery. Egyptian families believe that early surgical reconstruction is in the best interest of their girls. They are marginally more concerned about functional outcomes and future child bearing than external appearance and cosmetic outcomes. The authors concluded that social difficulties add challenges to the management plan in conservative societies. Early genital reconstructive surgery, when reasonably indicated, needs to remain a viable option. Comprehensive psychosocial support is needed to defer feminizing genitoplasty in selected cases to adolescence.

## Growth and Puberty

**Assessment of estradiol response after depot triptorelin administration in girls with central precocious puberty. Freire AV et al. Horm Res Paediatr. 2016;85(1):58-64**

A prospective study was performed in 43 girls with central precocious puberty (CPP), to evaluate estradiol response to depot triptorelin. Estradiol (<14 pg/ml) assessment 24 h after depot triptorelin administration is a reliable and simple method to confirm ovarian suppression during treatment of CPP.

**High frequency of normal response during GH stimulation tests in patients with Ectopic Posterior Pituitary Gland: a source of false-negative diagnosis of pituitary insufficiency. Kochi C et al. Horm Res Paediatr. 2016;85(2):119-24**

Seventy five patients with ectopic posterior pituitary gland (EPP), short stature and reduced growth velocity, underwent GH stimulation (normal cut off - peak ≥5 ng/ml) after clonidine or insulin. Normal GH response was observed in 15 (20%) of them. Normal GH values after stimulation tests do not exclude EPP-associated GH deficiency (GHD). A simplified MRI included as part of the initial diagnostic evaluation can prevent misdiagnosis of GHD in patients with short stature.

**Growth and cardiovascular risk factors in prepubertal children born large or small for gestational age. Nordman H et al Horm Res Paediatr. 2016; 85(1):11 -17**

Both large and small birth sizes are associated with an increased risk of developing cardiovascular and metabolic problems later in life. A cohort of 49 large (LGA), 56 appropriate (AGA), and 23 small for gestational age (SGA)-born children (age 5-8y) were studied to determine whether such associations can be observed in the prepubertal phase. The children born LGA remained taller and heavier, and had a higher body mass index and body fat percentage than the AGA- and SGA-born children, with minimal differences in other cardiometabolic risk factors between the birth size groups.

## Bone & Mineral Metabolism

**Birth weight could influence Bone Mineral Content of 10-18 Year-Old Korean adolescents: Results from the Korea National Health and Nutrition Examination Survey (KNHANES) 2010. Cho WK et al. Horm Res Paediatr. 2016;85(2):125-30**

Data obtained from the KNHNES 2010 showed that the odds ratio (OR) of being in the highest BMC (bone mineral content) quartile, per 1-kg increase in birth weight (BW), was significantly increased after adjusting for age, height, smoking, drinking, metabolic equivalent of task, and gestational age, suggesting that BW might be one of the determinant factors of BMC in Korean adolescents.

## Obesity and Insulin Resistance

**Risk factors for childhood obesity in the first 1,000 days: a systematic review. Woo Baidal JA et al. Am J Prev Med. 2016 Feb 8**

A systematic review of existing evidence for modifiable childhood obesity risk factors present from conception to age 2 years was done using 282 studies. Higher maternal pre-pregnancy BMI, prenatal tobacco exposure, excess maternal gestational weight gain, high infant birth weight, and accelerated infant weight gain were consistently associated with later childhood obesity.

**Identification of genetic and environmental factors predicting metabolically healthy obesity in children: data from the BCAMS study. Li L et al. J Clin Endocrinol Metab. 2016 Feb 25**

To determine the prevalence of metabolically healthy obesity (MHO) in Chinese children, a cross-sectional study of 1,213 children ages 6-18y, with BMI ≥ 95th percentile, was conducted. Participants were classified as having MHO or metabolically unhealthy obesity (MUO) based on insulin resistance (IR) or cardio-metabolic risk (CR) factors (blood pressure, lipids and glucose). Waist circumference was an independent predictor of MHO. The authors concluded that approximate one-third of Chinese obese children can be classified as MHO. Both genetic predisposition and environment factors and their interaction contribute to the prediction of MHO status.

**Distinguishing characteristics of metabolically healthy versus metabolically unhealthy obese adolescent girls with polycystic ovary syndrome. Kim JY et al. Fertil Steril. 2016 Feb 24**

Seventy obese girls with PCOS were divided into 19 metabolically healthy obese (MHO) and 51 unhealthy obese (MUO) based on cutoff points for in vivo insulin sensitivity to investigate the key physical, metabolic, hormonal and cardiovascular characteristics of girls with polycystic ovary syndrome (PCOS). MUO-PCOS girls had higher waist circumference, visceral adipose tissue, leptin, and free testosterone, lower SHBG and E2, higher non-high-density lipoprotein (HDL) cholesterol and atherogenic lipoprotein particle concentrations, smaller HDL particle size, and higher high-sensitivity C-reactive protein compared with MHO-PCOS girls. MUO-PCOS girls had larger visceral adiposity, lower insulin sensitivity and β-cell function, worse hormonal profile, and severely atherogenic lipoprotein concentrations compared with MHO-PCOS girls.

# Photo Quiz

**Prachi A Bansal, Nalini S Shah, Department of Endocrinology, KEM Hospital, Mumbai**

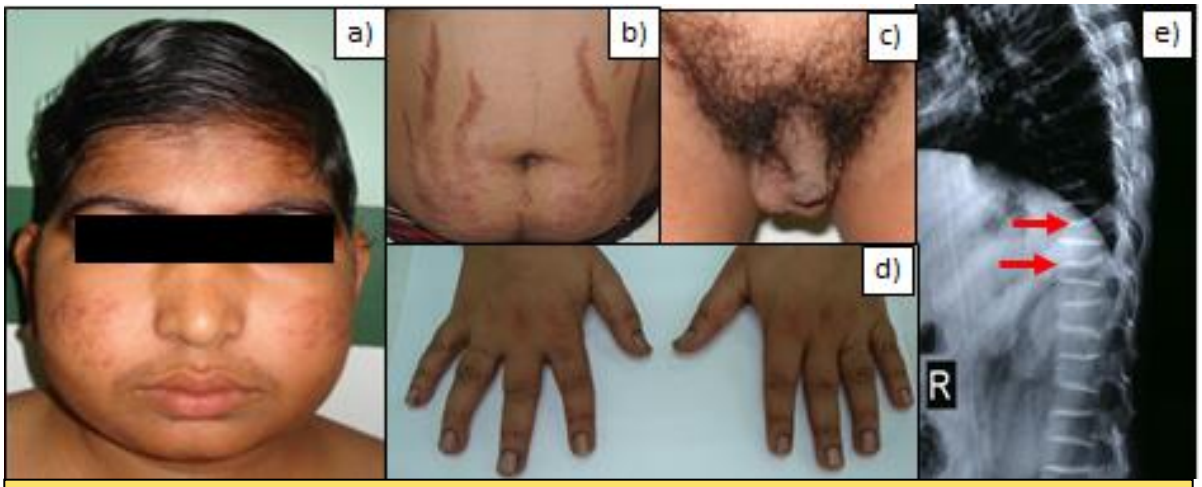



Photo quiz 1: Identify the findings in a 13 years old boy with Cushing syndrome. Which of the following is specific for ACTH dependent Cushing syndrome?

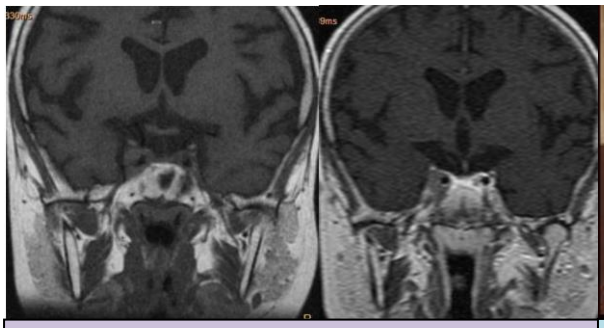


Photo quiz 2: Identify the imaging finding in an 8 years old boy with ACTH dependent Cushing syndrome.

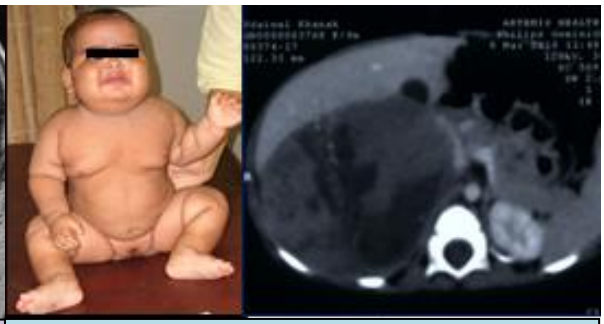


Photo quiz 3: A 9 months old girl with pubic hair, clitoromegaly, LDDS cortisol of 5.6µg/dl and plasma 8:00 am ACTH of < 10 pg/ml. What is the diagnosis?

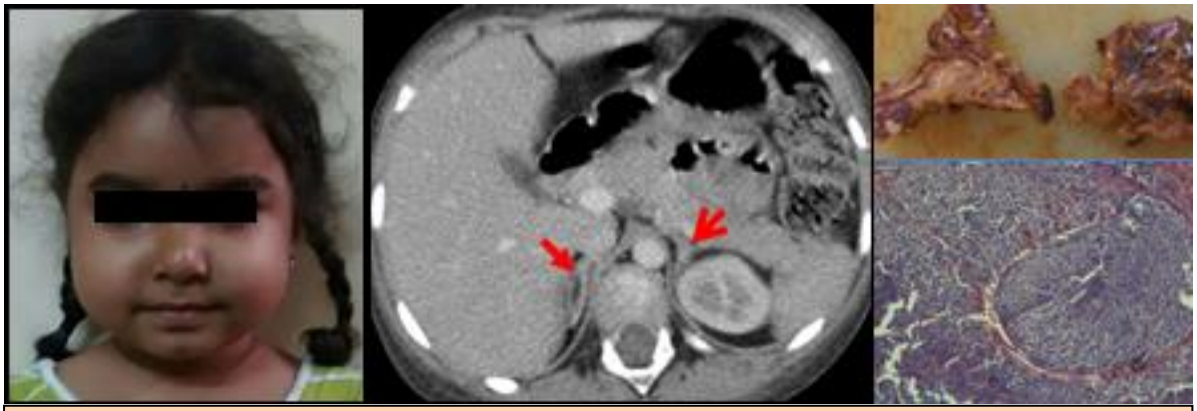


Photo quiz 4: A 6 years old girl with cyclical Cushing syndrome; serum 8:00 am cortisol of 18 µg/dl, plasma 8:00 am ACTH of 8.95 pg/ml, LDDS cortisol of 30.52 µg/dl and 24-h urinary free cortisol of 2029 µg. What is the diagnosis of this child? What are the clues towards the diagnosis?

# APPES FELLOW SCHOOL: A MEMORABLE EXPERIENCE

**Dr. Prashant Patil, Consultant Pediatric Endocrinologist at Rainbow Pediatric Multispeciality Centre, Ghatkopar Mumbai**

If anyone were to get wholesome international exposure at an early stage of one's career, I don't think one would ever complain!! With the help of ISPAE, four of us were able to attend the 17th APPES Fellows' School, held at Putrajaya, Malaysia, in November 2015. Putrajaya is a planned city which now also serves as the federal administrative centre of Malaysia. It was truly an amazing and thoroughly enriching experience. We cannot thank ISPAE enough for nominating and supporting us.

The APPES Fellows' School was wonderful, since it involved multilinguistic, multicultural, multi-ethnic participants staying under one roof with some of the stalwarts in the field of Pediatric Endocrinology from across the globe. Thirty seven young fellows from the Asia Pacific region participated. Credit should also go to the Malaysian Endocrine & Metabolic Society (MEMS) for arranging the event so meticulously that not once did we feel that we are away from our own country. The accommodation, Hotel Everly, was excellent with all necessary amenities available, and very helpful supporting staff. MEMS keenly encouraged interaction between participants from various regions, so not only did they make participants of different countries share rooms, they also shuffled the sitting arrangement every day, to make sure people of different cultures interacted comprehensively. We are so glad they did that; the results were truly visible at the lunch and dinner table. The camaradie and chemistry was truly infectious, and it got better every passing day.

The School was very intensive, with gruelling sessions covering different topics with the experts. In each session, three trainees briefly presented relevant cases, followed up a mentor building upon those cases to analyze and discuss the particular topic. Being case-based and largely interactive, they were very useful in clearing most of our doubts pertaining to practical aspects of the subject. The first day was dedicated to DSD, thyroid disorders, and endocrine emergencies. The second day covered disorders of growth, obesity and type 2 diabetes, and calcium and bone. Puberty, adrenal (and Cushing disease) and pituitary were covered on the third and final day.

Every session was followed by small group discussions (covering DSD, calcium disorders, diabetes), with different mentors every day. These discussions were really helpful as they involved a lot of reasoning and individual case-based approach. The intention was to generate interest in a particular case scenario and to logically discuss, with the help of mentors, the line of management, different protocols used in different centres, and the ideal approach to the case. The most notable thing was not a single session went over the time by even 5 minutes as everyone was very punctual.

As expected, the fellows had many questions on the confusing topic of DSD. Dr Reiko Horikawa (Japan) aptly cleared the majority of the doubts. The lecture on calcium disorders by Dr Rachel Gafni (USA) needs special mention. She simplified calcium metabolism so brilliantly and with such ease that I don't think there was any doubt in anyone's mind about this most difficult and complicated topic. Dr Paul Hofman's lecture on 'hypopituitarism' was very informative and reflected his vast experience on this subject. Similarly, the sessions by Dr Maria Craig on thyroid, Dr Nalini Shah on adrenal disorders and Cushing syndrome, and Dr Peter Simm on endocrine emergencies were equally enriching.

The School provided a platform for long term relationships with faculty and amongst participants. A little trans-Tasmanian rivalry created by Peter Simm & Paul Hofman was quite amusing, and even hilarious at times. I feel the most important part of this program was the active participation by the audience and one-on-one discussions with experts, who were so keen to teach everything they know.

The second day was truly special as MEMS and APPES had arranged a small trip in the evening. It involved a cruise along the picturesque and beautiful Putrajaya Lake, which is the largest manmade lake, around which the whole city is planned. At the end of the trip we took pictures of the group as well as with the experts, who happily obliged us. This was followed by a wonderful tropical sea food treat at a restaurant. We all created such a lot of noise that on a couple of occasions we were told to Shut UP!! We had a small quiz with topics related to Pediatric Endocrinology and general knowledge topics, which was

enjoyable. Finally the meeting was declared closed, leaving all of us a bit emotional and heavy hearted.

We met, we interacted, we chatted, and we played together. Lots of new friendships and promises to keep in touch were made.

Man is nothing but the memories he keeps, and I can truly say that the APPES Fellows' School 2015 was one memorable experience in my life!

Kudos to APPES, ISPAE& MEMS!!!

Thank you so much!!

# Pearls from APPES 2016

**Dr Aniket Kumbhojkar,** Assistant professor, Bharati vidyapeeth medical college, Sangli
**Dr Kartheek Nalluri,** Fellowin Pediatric Endocrinology, Manipal Hospital, Bengaluru
**Dr Prashant Patil,** Consultant Pediatric Endocrinologist at Rainbow Pediatric Multispeciality Centre, Ghatkopar Mumbai
**Dr Uppal Saurabh,** Consultant pediatric endocrinologist, Center for growth, diabetes and hormone disorders of children. Jalandhar

## Growth disorders

1. Sensitivity to diagnose GHD using one growth hormone stimulation test (GHST) is around 70%; however, it reaches 90-95% when 2 tests are used.
2. In countries like India, where procuring arginine is an issue, glucagon and clonidine are safe alternative agents for GHST.
3. The increase in height with GH therapy has no demonstrable effect on quality of life or psychosocial adjustment.
4. Routine use of GnRH agonist along with GH in peripubertal children with GH deficiency and short children born SGA cannot be suggested.
5. To date, the role of GH in treatment of idiopathic short stature (ISS) remains controversial. The discovery of a specific etiology, especially detecting new genes responsible for the short stature, can help clarify where use of GH would be beneficial.

## Bone and mineral metabolism

1. When calcium is low, PTH and $1,25(OH)_2D$ should be high
2. When PTH is high, phosphorus should be low
3. When phosphorus is low, $1,25(OH)_2D$ should be high
4. PTH increases calcium reabsorption in the distal tubule, but inhibits phosphorus absorption in the proximal tubule
5. Urine calcium is HIGH in BOTH Hypo and Hyperparathyroidism

6. HYPOCALCEMIA with
    - High PTH & Low phosphate: Calcipenic rickets (Calcium deficiency, Vitamin D deficiency).
    - Low PTH & High phosphorus: Hypoparathyroidism.
    - High PTH & High phosphorus: Pseudohypoparathyroidism, Renal insufficiency.
7. HYPOPHOSPHATEMIA with
    - High PTH & normal/low calcium: Calcipenic rickets with secondary hyperparathyroidism
    - High PTH & high calcium: Primary or tertiary hyperparathyroidism
    - Normal PTH, normal calcium & low/normal $1,25(OH)_2D$: FGF-23 mediated rickets
    - Associated with other renal losses: Fanconi syndrome
    - Low PTH, high $1,25(OH)_2D$ & hypercalciuria: HHRH
8. Hypercalcemia due to vitamin D toxicity will have normal $1,25(OH)_2D$ Vitamin D, in contrast to subcutaneous fat necrosis, in which it will be elevated.
9. Management of Hypercalcemia in hypervitaminosis D is done with extra fluids and/or diuretics. Prednisolone can also be used.
10. Mutations in CYP24A1 are associated with idiopathic hypercalcemia of infancy and vitamin D deficiency.
11. A patient with Vitamin D deficiency rickets will require intravenous calcium only if there are ongoing seizures due to hypocalcemia. Calcitriol may also be needed initially as 25OH vitamin D may take a few days to take effect.

**Central diabetes insipidus**

1. Early onset polyuria in postoperative cases of craniopharyngioma is due to intraoperative fluids or mannitol, not due to DI.
2. Central hypothyroidism and drugs like carbamazepine can lead to Partial DI-like picture in these cases.
3. The classic triphasic response described is not present in all cases; the duration of each phase can also be different in individual patients.
4. Information about urinary sodium and urine output are essential when we consider the diagnosis of SIADH.
5. B type natriuretic peptide action is to increase GFR, decrease sodium reabsorption, inhibit aldosterone and AD.

Childhood obesity

1. Risk of CHD events correlate positively with childhood BMI. The risk increases linearly with age, and across the entire BMI range; underscoring the importance of weight control early in life.
2. Suboptimal growth velocity, delayed puberty, developmental delay, vision and CNS problems are red flag signs, suggestive of pathological obesity.
3. No test is 100% sensitive or specific for Cushing syndrome. Clinical features may evolve over a period of time. Monitoring is very important in such cases.
4. Pseudohypoparathyroidism patients have ↓GSα activity and MC4R, TSH & GHRH resistance.

## Diabetes mellitus

1. Differentiation between type 1 and 2 diabetes may be difficult at presentation in some patients, due to overlapping clinical and biochemical features.
2. Presence of a strong family history, absence of severe obesity and absence of acanthosis nigricans are pointers to MODY.
3. MODY 2 (due to glucokinase deficiency) generally results in mild fasting hyperglycemia and does not require treatment.
4. 50% of babies with transient neonatal diabetes develop diabetes later in life.
5. Dyslipidemia screening should be done for type 2 DM at diagnosis and then 2 yearly. In type 1 DM, screening should be done > 12 years of age, or at puberty and then 5 yearly

## Hypothyroidism

1. Hypothyroidism is not associated with obesity. Mild weight gain may occur, with decreased appetite. BMI does not change when hypothyroidism is treated. Slowing of growth is a more consistent finding than weight gain. Growth slows abruptly only with severe hypothyroidism. Final height may be compromised if the replacement is started late and there was long-standing untreated disease.
2. Anti-thyroid antibodies are present in up to 10% of normal adolescents. Even in their presence, there is <20% chance of developing hypothyroidism. Therefore, most children do not need treatment. Monitor clinically and with TSH every 6-12 months.
3. In childhood, if TSH > 8 IU/L – it is better to treat.
4. Hypothyroidism is the only condition where a clinical presentation with signs of puberty is associated with delayed bone age (Von Wyk Grumbach syndrome).
5. In a case of autoimmune hypothyroidism, look for liver disease (incidence 1 in 150) in addition to other autoimmune problems.
6. The half-life of T4 is only 4-5 days in neonates.
7. Blood sample for TFT should be collected at least 4 hours after the last dose of levo-thyroxine
8. There insufficient evidence to support any specific timing of thyroxine dose. The recommendation is to give it at a convenient time and keep it same every day. Soy milk interferes markedly with its absorption.
9. When thyroxine replacement is started in longstanding cases of hypothyroidism, benign intracranial hypertension is a diagnosis of exclusion (after excluding brain tumor, encephalitis etc.).
10. In such a situation, thyroxine should be stopped for 1 week and restarted slowly. Acetazolamide and lumbar puncture are indicated if severe headache persists.

## Thyrotoxicosis

1. A tender goiter suggests the possibility of subacute thyroiditis in a thyrotoxic child.
2. In subacute thyroiditis there may be a transient, mild increase in anti-thyroid antibodies.
3. In Graves' disease, less than 30% patients have lasting remission with 24 months of anti-thyroid drugs (ATD). However, it is a reasonable option to continue medical

therapy if there are no adverse events. Watch for progressive thyromegaly on treatment, and consider definitive treatment if it develops.

4. Avoid block-and-replace regimen in Graves' disease, since hyperthyroidism worsens the autoimmunity, which leads to generation of more TRAb and worsening of hyperthyroidism. So only suppressive therapy should be given.
5. Side effects of ATD occur mostly in the first 6 months of therapy.
6. If giving Radioiodine therapy, stop ATD 3-5 days before therapy. Begin beta-blockers when ATD are stopped. There is no need to restart ATD. Check T4 every 30 days after therapy. About 5% patients need retreatment (usually in 3-6 months).
7. Radio-iodine is less effective if the gland is greater than 80 gm: then surgery becomes the preferred option.
8. If surgery is required, it should be done by high volume thyroid surgeons (>30 thyroid cases per year).
9. Transient hypothyroidism in the newborn due to maternal carbimazole therapy should not be treated due to risk of hyperthyroidism.
10. Neonatal hyperthyroidism is a medical emergency. Even if it is transient, it has to be controlled with Lugol's iodine and propranolol to prevent CCF (carbimazole will take many days to produce effect).

**Thyroid nodules and cancers**

1. Normal Thyroid gland size= ½ of age in years, in grams, e.g. at age 10y: 5 g
2. Indication of ultrasound in thyromegaly: symmetry, goiter without antibodies and large gland.
3. Ultrasonographic characteristics suggestive of malignancy in a thyroid nodule are: solid, hypoechoic, irregular border, absence of halo, intranodular blood flow, calcification and presence of abnormal lymph nodes.
4. USG cannot definitively determine malignancy; it helps to identify the location of the nodule for FNAC
5. Any persistent nodule larger than 1 cm is to be aspirated by FNAC.
6. More than 30% of thyroid nodules that are > 1 cm in size are malignant.
7. A thyroid nodule is more likely to be cancerous in a child (25% risk) than in adults (5% risk).
8. Twenty percent of children with thyroid cancer have metastases at presentation.
9. Prognosis for children with well-differentiated thyroid cancer is very favorable, and there is nearly 100% 10-year survival.
10. RAI is most effective in nodules with high risk features if TSH >30 IU/ml (either by thyroid hormone withdrawal or rhTSH). Also the patient should be iodine deficient (via diet).
11. It is unclear whether RAI ablation increases the risk of non-thyroid secondary malignancies.
12. The largest growing group of patients with thyroid nodules and thyroid cancer are childhood cancer survivors. They should be monitored with thyroid function tests annually and ultrasound 5 years after treatment, repeated thereafter every 2 years.

# Publications by ISPAE Members

**Dr Devi Dayal Arya, Professor, Department of Pediatrics, PGIMER, Chandigarh**

1. Dayal D, Prasad R. Congenital hypothyroidism: current perspectives. Res Rep Endocr Disord. 2015;5:91-102
2. Mishra A, Dayal D, Sachdeva N, Attri SV. Effect of 6-months' vitamin D supplementation on residual beta cell function in children with type 1 diabetes: a case control interventional study. J Pediatr Endocrinol Metab. 2015;Aug 5
3. Dayal D, Bhalla AK. Factors affecting growth in children. Chapter 19, Growth: normal and abnormal. Postgraduate Textbooks of Pediatrics. 1st Edn. 2015;638-40
4. Sachdeva N, Paul M, Badal D, et al. Preproinsulin specific CD8+ T cells in subjects with latent autoimmune diabetes show lower frequency and different pathophysiological characteristics than those with type 1 diabetes. Clin Immunol 2015;157(1):78-90
5. Dayal D, Samprathi M, Jayaraman D, Kohat D, Bhalla AK. Secular trends of body mass index in North Indian children with Type 1 diabetes do not support the Accelerator Hypothesis. Clinical Endocrinology. 2016; Mar;84(3):338–41
6. Dayal D, Didel SR, Agarwal S, Sachdeva N, Singh M. Acute Hypercalcaemia and Hypervitaminosis D in an Infant with Extra Pulmonary Tuberculosis. J Clin Diagn Res. 2015 Oct;9(10):SD03–4
7. Devi Dayal, et al. Preservation of residual beta cell function with vitamin D supplementation in type 1 diabetes. Immunoendocrinology 2015; 2: e1093
8. Dayal D. It's high time to revise Indian guidelines on vitamin D supplementation in children. J Pediatr Endocrinol Metab. 2015; Dec 2
9. Sindhuja L, Dayal D, Sodhi KS, et al. Thyroid dysfunction and developmental anomalies in first degree relatives of children with thyroid dysgenesis. World J Pediatr. 2015; Dec 18
10. Dayal D, Bakshi J. Early Diagnosis and Surgery is Crucial to Survival Outcome in Rhinocerebral Mucormycosis. Indian J Otolaryngol Head Neck Surg. 2016;January 7

**KVS Harikumar, Command Hospital, Chandimandir, India**

1. Hari K.V.S. Kumar. Cardiometabolic risks and obesity in the young. N Engl J Med. 2016; 374:591-3.

# Fellowships and Awards

**Dr Prashant Patil**, Consultant Pediatric Endocrinologist at Rainbow Pediatric Multispeciality Centre, Ghatkopar Mumbai has been awarded the ***Clinical Pediatric Endocrinology fellowship by The European Society for Pediatric Endocrinology (March-June 2016)***, at Alder Hey Children Hospital, Liverpool UK.

Dr Meghna Chawla, Assistant Prrofessor, Smt Kashibai Navale Medical College, Pune, has been awarded ***Clinical Pediatric Endocrinology fellowship*** **(Started on 01.04.2016) by the European Society of Paediatric Endocrinology** at Royal Manchester Children's Hospital, UK.

**Dr Devi Dayal Arya,** Professor, Department of Pediatrics, PGIMER, Chandigarh has been awarded the ***Clinical Pediatric Endocrinology fellowship by The European Society for Pediatric Endocrinology***, that will begin in June this year in Liverpool, UK.

**Dr Deep Dutta**, Assistant Professor, Department of Endocrinology, Post Graduate Medical Education & Research (PGIMER) and Dr. Ram Manohar Lohia (RML) Hospital, New Delhi has been awarded the **Fellow of American College of Endocrinology (FACE)** degree by the American College of Endocrinology (ACE). Formal award of degree will take place in the convocation planned on 28th May 2016 at the 25th Annual Scientific and Clinical Congress of the American Association of Clinical Endocrinology (AACE).

**KVS Harikumar**, Senior Adviser, Medicine & Endocrinology, Command Hospital, Chandimandir, Panchkula, received the **Best Reviewer Award** from Indian Journal of Endocrinology and Metabolism at ESICON 2015, Ahmedabad in Dec 2015.

# Activities by ISPAE Members

### Dr Hemchand K Prasad, Pediatric Endocrinologist, Dr Mehta Children's Hospital, Chennai

Prof Olaf Hiort from Germany visited department of pediatric endocrinology and diabetes, Mehta children's hospital and delivered a talk on 'Approach to DSD in the delivery room'. Cases of DSD from the unit were presented and discussed by DNB Pediatrics trainee Dr Aishwarya. Prof Olaf also had a clinic on difficult cases of DSD and discussed those cases with Dr Hemchand, Pediatric endocrinologist. The program was attended by 40 pediatricians in the city.

The Department of pediatric endocrinology and diabetes, Dr Mehta Children's Hospital, Chennai also celebrated 'Thyroid day' in the auditorium of Mehta children's Hospital on 14.2.2016. The program was divided into two sessions. In the morning session, there was an awareness meeting on congenital hypothyroidism where 30 families with children suffering from congenital hypothyroidism participated in the meeting and lectures and patient experiences were shared. A booklet on congenital hypothyroidism was released for the families. The program ended with a panel discussion on congenital hypothyroidism by the neonatologists in the unit. In the afternoon session, there was a meeting on juvenile hypothyroidism attended by 40 families with Hashimoto's thyroiditis. There were awareness lectures and experiences were shared by the families. Madlein, a child with Hashimotos gave a talk on importance of taking medicines regularly. The program ended with a question answer session mediated by senior paediatricians in the unit.

Dr Hemchand K Prasad conducted a workshop for teachers on various aspects on type 1 diabetes on 28.2.2016. 44 teachers participated and the program consisted of lectures in the morning and hands on experiences in the noon. They were all provided with glucagon and ketone testing kits.

Dr Hemchand K Prasad was also involved in the following academic activities:

1. Train the trainers of the IAP was organised by the department of pediatric endocrinology in association with the IAP Chennai city branch. 40 trainers were trained on the usage of growth charts. The program was moderated by Dr Vaman Khadilkar from Pune.
2. Lecture on practical aspects of usage of growth charts – IAP Salem, TN (26/12/2016)
3. Lecture on Precocious puberty – IAP Kochi, IMA House
4. Lecture on Advances in insulin therapy – National PEDICON, Hyderabad
5. Panel discussion on Type 1 DM – National PEDICON, Hyderabad

**Dr. Vishnu Agarwal, Assistant Professor, Department of Paediatric Medicine, SMS Medical College, Jaipur**

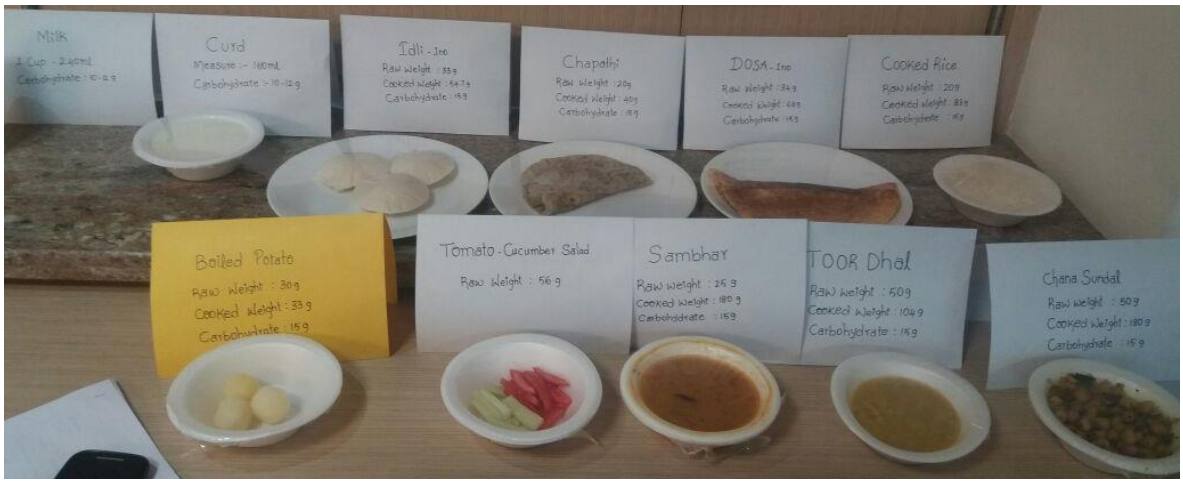
On 21.2/2016, a one day GROW India 5th practical paediatric endocrinology course (5$^{th}$ PPEC) was organized under aegis of Department Of Paediatric Medicine, JK Lon Hospital, SMS Medical College, Jaipur and GROW Society. Six modules on growth, puberty, thyroid, glucose disorders and calcium and metabolic disorders were implemented by Dr. P Ragupathy, Dr. Subrata De, Dr. Smita Koppikar, Dr. Anurag Vajpayee and Dr. Vishnu Agarwal.

These modules included a combinations of didactic lectures, case based discussion and practical exercises to provide detail insight into various aspects of paediatric endocrinology. This course was attended by 160 delegates from various parts of India including practising pediatrician and also residents from various medical colleges of Rajasthan.

**Dr Kavitha Bhat, Pediatric Endocrinologist, rainbow Children's hospital, Marathalli, Bengaluru**

A unique workshop on "Optimizing Blood Sugar Levels" in Childhood Diabetes was held on 3rd April at Rainbow Children's Hospital, Bangalore. The target audience for this program was parents of children with diabetes, dieticians, diabetes educators and doctors. It was meant for those who already had basic understanding of Type 1 diabetes but who wanted to gain knowledge, skill and confidence in making insulin adjustments based on blood sugar records and carbohydrate intake. The focus was on basal - bolus regimen using multiple daily injections of insulin.

Dr N Kavitha Bhat, Consultant Pediatric Endocrinologist, Rainbow Children's Hospital spoke on insulin adjustments in a MDI regimen, Dr Malathi V, Consultant - Nutrition and Dietetics, Rainbow Children's Hospital spoke on carbohydrate counting - basic and advanced and Dr Vijayasarathi, Associate Professor, Dept. of Endocrinology, Vydehi Institute of Medical sciences , gave a talk on exercise and diabetes.



There was an interesting nutrition exhibition where different foods with their carbohydrate content, methods to calculate carbohydrate content of cooked food, glycemic index, planning meals and snacks were demonstrated. Around 70 people attended this workshop and most found it useful.

### Dr OS Santhosh, Pediatric and Adolescent Endocrinologist, Karnataka Institute of Diabetology, White Lotus Healthcare & Cloud Nine KIDS Hospital, Bangalore

**White Lotus Health care team** organized "**Manchester Insulin Pump Course – Interactive Lectures and Workshop" on** Jan 8th and 9th 2016 for medical professionals. Workshop was attended by 16 doctors and 2 nutritionists. The workshop received a very good feedback and encouragement.

**White Lotus Health care team** also organized an education program for type 1 diabetic children and their parents on "**Importance of good glycaemic control and role of Insulin pump in Type 1 diabetes**". Around 20 children with their parents took part in this program.

Dr OS Santhosh has also made available **'Type 1 diabetes education information in Kannada language'** at ISPAE website

### Dr Dr Swati Dublish, Assistant Professor, Department of Pediatrics, Lady Hardinge Medical College and associated Kalawati Saran Children's Hospital, Delhi

The division of pediatric endocrinology at Kalawati Saran Children's Hospital organized a half day training workshop for nurses in "Pediatric Diabetes". We have around 200 diabetic patients registered in our clinic and it was the felt need to educate the nurses regarding the disease, its pathophysiology, role of insulin and different regimes with special emphasis on administration of insulin, site rotation, storage and monitoring for complications. We also discussed about SMBG, dietary counseling and psychological and social aspects of the disease. The workshop was conducted by the faculty working in the pediatric endocrinology division along with two staff nurses and one dietitian assisting in the functioning of pediatric diabetes clinic. It was attended by 12 staff nurses including two from the adult medicine. The general feedback was very positive and highly encouraging.

## Answer to Photo Quiz

1. a) Moon face with acne, facial plethora and forehead hypertrichosis
   b) Wide depressed livid striae
   c) Pseudoprecocity (Pubic hair stage 3 with Testicular volume 2 ml each)
   d) Hyperpigmentation of knuckles and nail beds
   e) Multiple wedge and compression type of vertebral fractures (Osteoporosis)
   Hyperpigmentation of knuckles and nail beds is specific for ACTH dependent Cushing syndrome whereas other features could be seen in any form of Cushing syndrome.

2. The pre and post gadolinium contrast T1 weighted images suggest a nonenhancing hypodense lesion in the right carotico-cavernous region suggestive of pituitary adenoma in the right parasellar region.

3. A large adrenal mass with necrotic areas in an infant girl with virilisation and endogenous hypercortisolism suggest adrenocortical carcinoma.

4. The diagnosis is PPNAD. The clues for diagnosis are cyclical nature of Cushing syndrome, normal size of adrenals on imaging, pigmented adrenal glands and paradoxical elevation of LDDST cortisol.

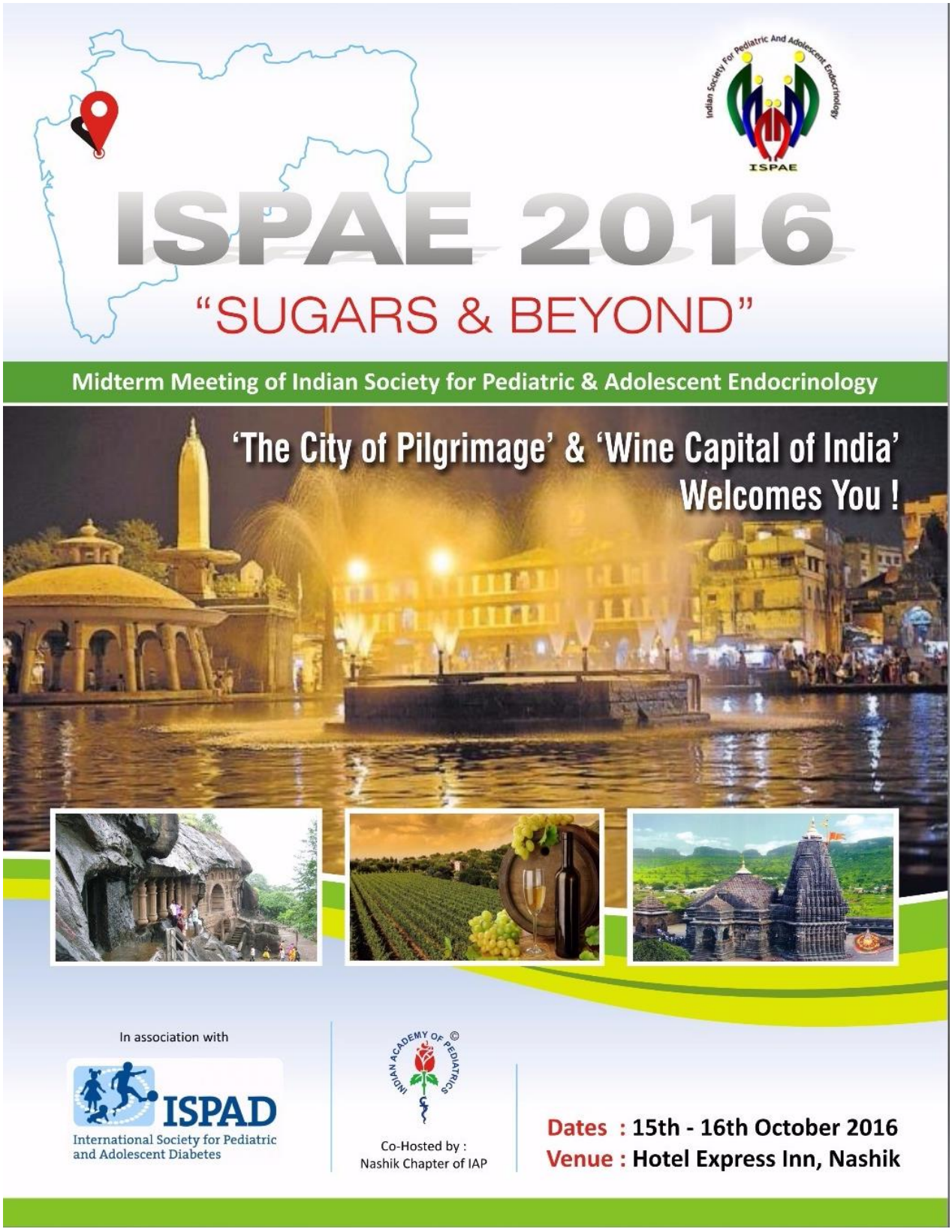
## Blood Ketone Testing Available

I am sure that some of the members are aware that facilities for blood ketone testing are available in India. For those who are unaware of it, this information may be useful. Freestyle optium beta-ketone strips are now available in India which can be used with glucometer devices from Abott (Optium, Optium Xceed, Freestyle Optium Neo). This testing offers accurate blood ketone (beta hydroxyl butyrate) testing with instantaneous results (10 seconds). Each pack contains 10 strips with MRP of INR 1750. Each strip is individually wrapped and no coding is required.

Dr Vijaya Sarathi, Editor, CAPENEWS

# Upcoming Events by ISPAE Members

The first west zone growth hormone research society symposium on growth & pediatric endocrine disorders has been organised by Dr Vaman Khadilkar (Organising chairman) and Dr Rahul Jahagirdar on 16$^{th}$ -17$^{th}$ April 2016 at Bharati Vidyapeeth University Medical College, Pune. For registration contact Mrs. Sucheta Agare, Department of Pediatrics, Bharati Vidyapeeth University Medical College, Pune, Telefax no. (020) 24375541 (9.00 am-4.00 pm), e-mail ID: ghrspune2016@gmail.com


ISPAE 2016
"SUGARS & BEYOND"
Midterm Meeting of Indian Society for Pediatric & Adolescent Endocrinology
'The City of Pilgrimage' & 'Wine Capital of India'
Welcomes You !
In association with
ISPAD
International Society for Pediatric and Adolescent Diabetes
Co-Hosted by :
Nashik Chapter of IAP
Dates : 15th - 16th October 2016
Venue : Hotel Express Inn, Nashik

# ISPAE 2016

## "SUGARS & BEYOND"

The Indian Society for Pediatric & Adolescent Endocrinology [ISPAE] announces its midterm conference, in collaboration with International Society for Pediatric & Adolescent Diabetes [ISPAD].

Recognizing the rising burden of diabetes in childhood, the theme for ISPAE 2016 conference is 'Sugars and Beyond'.

**Dates : 15th - 16th October 2016 Venue : Hotel Express Inn, Nashik**

## Topics : Diabetes & Endocrinology

- Neonatal Diabetes
- Primary Prevention of Diabetes, Where Do We Stand ?
- Hypoglycemia Management
- Counting Beyond Carbs
- Newer Drugs In Diabetes
- Growth Hormone Therapy
- Hypothyroidism
- Childhood Obesity
- Insulin Resistance, Type2 DM
- Islet-Cell Transplant
- Secondary Diabetes
- Adolescent PCOD
- Newborn Screening
- Gadgets In Diabetes
- Pubertal Problems In Children

**Faculty :** International faculty **Dr. Carine De Beaufort** (Secretory General, ISPAD) & **Dr. Kim Donaghue** (Chief of Pediatric Diabetes, Westmead Children's Hospital (Sydney) National Faculty in the field of Pediatric & Adolescent Endocrinology.

## "NUTS & BOLTS OF DIABETES MANAGEMENT"

*ISPAE 2016 Pre-conference Workshop on Pediatric Diabetes* **Saturday 15th October, 8.00 am-1.00 pm**

[For Pediatricians, Diabetologists, Nurses, Nutritionists & Educators]

**Topics :** Insulin Basics, Newer Insulins, Home Blood Glucose Monitoring, Insulin Pumps, Choosing A Glucometer, Diet In Diabetes, Sick Day Management, Diabetes In Resource Limited Setting, Glycemic Control, Survival Skills, Dose Adjustment.

***Limited Entries, Registration Mandatory.***

Organizing Team

**Advisors :**
Dr. PSN Menon
Dr. Nalini Shah
Dr. Subhash Kashyape
**Organizing Chair :**
Dr. Sudha Rao

**Organizing Secretary :**
Dr. Tushar Godbole
**Scientific Chair :**
Dr. Preeti Dabadghao
**Workshop Convener :**
Dr. Anju Virmani

**Workshop Co-convener :**
Dr. VIjayalakshmi Bhatia
**Organizing Committee :**
Dr. Yashpal Gogate
Dr. Ganesh Jevalikar
Dr. Rahul Jahagirdar
Dr. Abhishek Kulkarni
Dr. Samir Dalwai
Dr. Ruchi Parikh
Dr. Ravindra Sonawane
Dr. Sagar Sonawane

**Visit our website www.ispae2016.com for further details.**

# ISPAE 2016

## "SUGARS & BEYOND"

**15th-16th October 2016 - Venue : Hotel Express Inn, Nashik**

## Registration Form

**Conference Registration Number :**

Name : ..... Sex : ..... Age : .....

Current Affiliation : .....

**Address for Correspondence :**

Phone Number : .....

Email ID : .....

**Membership Numbers (If any) :**

ISPAE / ISPAD : ..... CIAP : .....

**Amount Paid :**

Workshop : ..... Main Conference : .....

**Mode of Payment :** ☐ Online ☐ Cheque ..... ☐ DD ..... ☐ Cash

**Secretariat Address : Dr. Tushar Godbole,**

A104, Zion Herald, Rameshwar Nagar, Pipeline Road, Nashik - 422013. (M) +91-7774082834, email ispae2016@gmail.com

### *Registration Details for Main Conference*

| Registration Slot up to | ISPAE or ISPAD Members | Others |
|---|---|---|
| **30th April 16** | 3000/- | 3200/- |
| **31st July 16** | 3500/- | 3700/- |
| **30th Sept. 16** | 4000/- | 4200/- |
| **Spot** | 4500/- | 4500/- |
| PG Students / Nurse / Educator / Nutritionist (Letter from HOD required) | | 2500/- |

ISPAD
International Society for Pediatric and Adolescent Diabetes

### *Registration fees for Workshop :*

| Practising Pediatricians | Post-Graduate Students | Nurse / Educator / Nutritionists |
|---|---|---|
| 1500/- | 750/- | 500/- |

**Payment by cheque/online. Prior registration is compulsory.**

75% refund for cancellations before 31st July, no refunds after that.

**Block your dates & Register soon !**

Online Payments : IDBI Bank
Account No. : 1991104000005456
IFSC Code : IBKL0001991
Cheque / DDs in favour of "ISPAE 2016"

ISPAE

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