CAPE NEWS

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EDITOR'S MESSAGE

Dear Friends,

Welcome to the latest issue of Cape News. This issue has been dedicated to "Precocious Puberty" and I would like to thank our ISPAE members for sharing their clinical experience with all of us. The forthcoming issue will cover "Delayed Puberty" and I look forward to getting inputs from other members as well.
Wish you all a very Happy Diwali and hope you all enjoy the festive season.

Warm Regards,
Archana Dayal Arya
Editor Cape News

INSIDE THIS ISSUE:

GnRH Stimulation test – Opening a Pandora's box

Dr Hemchand K P, Consultant Pediatric Endocrinologist, Mehta Children's Hospital, Chennai

What is the principle of GnRH stimulation test?

To test the gonadotrophin secretory response of pituitary to GnRH. It is useful in distinguishing between Central precocious puberty, Peripheral PP , premature thelarche and variants.

Is fasting needed?

No

What are the available protocols for the stimulation test?

Reference	Dose	Sample time for LH, FSH	Sample time for Testosterone/ estradiol	Interpretation
Mark Sperling text book of ped endocrinology	1 µg/kg GnRH (Gonadorelin) - IV 10 µg/kg Lupride – sub cutaneously	0, 30 min 0,4 hours	0 hour 24 hours	Peak LH > 4.1 IU/L
Charles Brook text book of ped endocrinology	2.5 µg/kg GnRH (Gonadorelin) - IV	0, 20, 60 min	0 hour	Increment of LH > 4 IU/L, Stimulated LH > FSH
Sydney protocols	2 µg/kg or 100 µg GnRH (Gonadorelin) - IV	0, 30, 60 min	0, 60 min	50% increment over baseline LH
Nicolas Bridges ped endocrine protocol book	2.5 µg/kg GnRH (Gonadorelin) - IV	0, 30, 60 min	0 hour	Significant increment of LH over baseline
Hammer smith protocols in pediatric endocrinology	100 µg GnRH (Gonadorelin) - IV	0, 30, 60 min	O hour	Stimulated LH > 10
Columbia children hospital protocol book	100 µg GnRH (Gonadorelin) - IV	0,20, 30,40, 60 min	0 hour	-

What are the pitfalls of the GnRH stimulation test?

Bizzari C et al (JCEM 2014) - The response to gonadotropin releasing hormone (GnRH) stimulation test does not predict the progression to true precocious puberty in girls with onset of premature thelarche in the first three years of life.

Ng SM et al (JPEM 2005) - The gonadotrophins response to GnRH test is not a predictor of neurological lesion in girls with central precocious puberty**.**

What is the published Indian experience on GnRH stimulation test?

GnRH analogue testing is an effective alternative to the conventional intravenous GnRH stimulation testing in Indian setting. (**Khadilkar et al IJEM 2012**)

Patients with neurogenic CIPP had significantly higher levels of baseline and GnRH-stimulated levels of LH and FSH and LH:FSH ratio than those with idiopathic CIPP.(**Bajpai A et al 2002 in JPEM**)

Three-hour LH value following IM depot leuprolide injection (11.25 mg) can be used for monitoring therapy in patients with GDPP because of its convenience and cost effectiveness (**NS Shah et al in Pituitary 2009)**

What are the available protocols for GnRH analogue testing which have recently gained lot of importance owing to the lack of Plain GnRH availability?

GnRH analogue test is based on the principle that the immediate sample would indicate the gonadotrophin reserve and the 24-hour sample would gauge the gonadal response to endogenous gonadotrophins

Author	**Journal**	**Study design**	**Key observation**
Poomthavom P et al	Hormone research 2009	Retrospective	Peak LH measured at 60 min following GnRH-A (100 mcg) of 6 IU/l provided the cut-off level in diagnosing CPP (sensitivity 89.1%, specificity 91.3%)
Eckert L et al	Pediatrics 1996	Prospective	Peak LH of 8 IU/L at 40 minutes after injection of 100 mcg sub-cutaneous lupride. Good correlation between IV and SC testing reported.
Houk CP et al	JPEM 2008	Retrospective	GnRHa test with one LH measurement obtained 30 minutes after injection – CPP diagnosis
Yazdani P et al	Int J ped endo 2012	Retrospective	3 hours post 20 mcg/kg lupride challenge – LH cut-off > 5 mIU/ml diagnoses Central precocious puberty

The use of GnRH analogue test is serving as a viable alternative for the conventional GnRH stimulation test.

Can a single value of stimulated Gonadotrophin replace the cumbersome multiple sampling practiced with IV GnRH stimulation test? – An area of extensive research. Final word not out.

Author	**Journal**	**Sample**	**Study design**	**Key observation**
Cavallo A et al	Clin endocrinol 1995	Cincinnati, Ohio, USA	Retrospective	LH cut-off (15 IU/I) at 30 minutes after plain IV GnRH had sensitivity > 90% and specificity > 80% - CPP diagnosis
Kandemir A et al	JCRPE 2013	Ankara Turkey	Retrospective	Peak LH > 5 IU/ml at 40 minutes after IV GnRH can be used to diagnose CPP

Can Basal gonadotrophin levels serve as an alternative to GnRH stimulation test?

Author	Reference	Key observation
Houk C P et al	Pediatrics 2009	Basal LH > 0.83 Iu/L is a pointer to the onset of CPP. Basal FSH levels have a poor discriminatory value
Supornsilchai V et al	J Med assoc Thai 2003	Girls with CPP have a basal LH/FSH ratio greater than 0.2 and this can be used as a cut-off point for the diagnosis CPP (75 per cent sensitivity, 85 per cent specificity)
Pasternak Y et al	Eur J Endocrinol	Low basal LH < 0.1 mIU/ml rules out CPP. Basal FSH and LH/FSH ratio are not contributory
Neely E K et al	J Pediatr 1995	Spontaneous LH levels in excess of 0.1 IU/L detected true puberty with 94% sensitivity and 88% specificity. Random LH levels in excess of 0.3 IU/L had 100% specificity for CPP

How to assess GnRH analogue adequacy of suppression?

Free leuprolide present in a depot leuprolide injection is equivalent to gonadotropin-releasing hormone in stimulating a rapid rise in serum gonadotropin concentrations. A single serum sample for LH after depot leuprolide injection in children provides an assessment of treatment efficacy.

Author	Setting	Time of sample post analogue	Cut-off for LH level	Comment
Kandemir N et al	JCRPE 2011	20 minutes	5 IU/L	100% sensitivity in assessing adequacy of suppression
Demirbilek H et al	Clin endocrinol 2012	90 minutes	2.5 mIU/ml	Sensitivity (100%) specificity (88%)
Brito N V et al	JCEM 2004	2 hours	6.6 IU/L	

CONCLUSION:

Considering the available evidence: GnRH analogue testing may serve an alternative for conventional IV GnRH stimulation test and assessment of LH post injection may be useful. The applicability of basal hormones, single sample etc need more clarity. There is a need for a consensus statement in this regard in the near future.

What is the practice of pediatric endocrinologists in India pertaining to GnRH stimulation test?

As a part of understanding the practice of pediatric endocrinologists in India, a small questionnaire was devised and circulated and the key observations include:

a) **Preparation used:**

   Leupride/ leuprolide (90%); Relefact (5%); Triptorelin (5%)

b) **Dose of administration**

   Highly varied: 10-25 µg/kg; Maximum dose also highly varied: 0.5-1 mg max

c) **Route of administration**

   IV (5%); IM (15%); Sub-cutaneous (80%)

d) **Time of sample**

   Highly varied

   0,4h, 24h – 30%

   Rest: 0, 30 , 60 min; 0,1hr,3hr,24hr; 0,30 min, 90 min; 0 hour and 3 hour

e) **Samples taken**

   Only gonadotrophins (70%); Sex hormones checked (30%) – Baseline (15%) and at 24 hours in 15%

f) **Assessment of adequacy**

   Not assessed, only clinical (40%); prior to the next injection (30%) and post injection (30%).

   Post injection, samples are taken at 2 hours, 3 hours and 4 hours in 2 practitioners each.

g) **Cost of the test: INR 1000/- to INR 3000/-**

This, further is a pointer in the need for a consensus amongst the Pediatric Endocrinologists of our country

MCCUNE-ALBRIGHT SYNDROME

Dr Ruchi Parikh, DNB, Fellowship in Pediatric Endocrinology
Bai Jerbai Wadia Hospital for Children, Parel, Mumbai

McCune- Albright Syndrome (MAS) was first described by McCune and Bruch and by Albright et al. in 1937. This disorder was classically defined by the clinical triad of polyostotic fibrous dysplasia (PFD), café-au-lait skin pigmentation and precocious puberty (PP). Schwindinger et al. in 1991 proposed that the same somatic mutation is found in PFD and in growth hormone secreting tumors of the pituitary. As proposed by Lumbroso et al, in 2004, this disorder can involve other endocrinologic anomalies such as growth hormone excess, hyperprolactinemia, Cushing syndrome, hyperthyroidism and renal phosphate wasting with or without rickets/osteomalacia. So, the triad is formed by PFD, café-au lait skin pigmentation and autonomous endocrine hyper function. The diagnosis is generally accepted if 2 of the 3 symptoms are present. Atypical form includes 1 or 2 of these classical symptoms.

Patho physiology:

Activating mutations of GNAS1 gene, which is regulated by cAMP protein, the alpha subunit of the Gs protein, is a result of post zygotic somatic cell mutation appearing early in the course of development. These mutations lead to impaired GTPase activity and result in cAMP increase and unregulated hormone production. The extent of the disease is determined by the proliferation, migration and survival of the cell in which mutation spontaneously occurs.

Clinical Presentation:

Onset is most often seen in early childhood with PP or PFD and rarely at birth or neonatal period, due to presence of café-au-lait spots or Cushing's syndrome.

Skeletal:

No bone is spared with a strong tendency to asymmetry. It can involve single or multiple sites. Most commonly involved are skull and facial bones or proximal femora, with deafness and blindness resulting from impingement of the bony process on the cranial foramina. Limp/ pain or pathologic fracture or bone deformity may be the presenting manifestations and pseudoarthrosis occurs frequently. Hypophosphatemic rickets has been observed in 1976 by Dent and Gertner.

As a result of the combination of PP, recurrent fractures, hypophosphatemic rickets, majority are short in stature, unless there is co-existing excess growth hormone.Scoliosis is common and may be progressive.

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Skin:

Skin lesions involve large café-au lait spots with irregular margins; giving them a coast of Maine configuration as opposed to the more regularly outlined coast of California café-au lait spots of neurofibromatosis. Like bony lesions, the pigmentary lesions of the skin may be limited to one side and stop sharply at the midline and follow the lines of Blashko. Most common site is nape of neck. They usually appear in the neonatal period.

Endocrinopathy:

The leading endocrinologic feature is precocious puberty-i.e. GIPP , which occurs in half of female cases, with vaginal bleeding or spotting occurring in the first months of life, accompanied by development of breast tissue. Autonomic activation of ovarian tissue leads to ovarian follicular cysts and estrogen hyper secretion. Progression to GDPP may occur at follow up. It has also been reported in males, with testicular and penile enlargement and precocious sexual behavior. GnRHa stimulation test reveals prepubertal response with FSH response blunted suggestive of autonomous hyper function of Sertoli cells, with no evidence of Leydig cell activation. The second most common endocrinopathy is hyperthyroidism ranging from asymptomatic subclinical hyperthyroidism to thyrotoxic crisis. There is increase in free T3/ free T4 ratio and autoimmunity does not accompany this status.

Rarely, other organ systems may be involved: Hepato- biliary dysfunction- neonatal jaundice, chronic cholestasis and steatorrhea; cardiac disease- cardiac arrhythmias, sudden death; multiple hamartomatous gastrointestinal polyps in the stomach and/or duodenum, pancreatitis; hyperparathyroidism, usually secondary to Vitamin D deficiency.

DISORDER	PREVALENCE IN MAS	FEMALE: MALE (F:M)
Precocious Puberty- GIPP	64-79%(F), ~15%(M)	F>M
Hyperthyroidism	2.7-21.9%	F>M
GH/PRL hyper secretion	Up to 21%	F=M
Cushing's Syndrome	Up to 5%	F=M
Fibrous dysplasia	46-98%	F=M
Skin hyper pigmentation	53-92%	F=M

Investigations:

Its diagnosis is usually made on clinical grounds.

For GIPP, baseline Luteinising hormone (LH),Follicle- stimulating hormone (FSH) and Estrogen levels (in males, free and total testosterone levels) which will show suppressed LH, FSH and elevated estrogen/ testosterone levels with a prepubertal response on GnRHa stimulation test .USG Pelvis is required for the morphology of uterus and ovaries, for ovarian follicles and cysts. Bone Age will be advanced.

For hyperthyroidism, Thyroid function tests and USG thyroid for nodules are required and rarely FNAC to rule out malignancy.

MRI pituitary for assessment of associated endocrine lesions, such as pituitary adenoma, and serum cortisol, Prolactin levels and IGF-1.

Plain radiographs which demonstrate typical expansile lesions with endosteal scalloing and thinning of cortex with matrix of intermedullary tissue demonstrating ground glass appearance or bone scans are required to make the diagnosis of PFD and biopsy of the lesions can confirm the diagnosis. Blood and urine chemistries for excessive bone turn over, along with alkaline phosphatase, serum Calcium, Vitamin D and PTH levels. For hypophosphatemic rickets, serum phosphorus and assessment of tubular reabsorption of phosphorus status is required. Assessment of vision and auditory status is warranted.

For non-endocrine causes, liver function test and cardiac status to be evaluated.

Molecular analysis of GNAS1 gene from leukocyte DNA or tissues presenting with hyper functionality like bones or follicular fluid.

Management:

Treatment depends on the tissues affected and their extent.

Skeletal: Treatment includes Calcium and Vitamin D supplementation and surgical intervention. FD lesions have high interleukin-6 levels, leading to increased osteolytic activity. Bisphosphonate treatment prevents this by inhibiting IL-6.Pamidronate is effective in reducing bone pain. But there is no radiologic evidence of filling of lytic lesions or thickening of the bone cortex surrounding the lesions. Strengthening exercises help to maintain musculature around the PFD bone and minimize the risk of fracture.

PP: Treatment options include- Aromatase inhibitors such as Testolactone, Anastrazole, Letrozole; Estrogen receptor modulator such as Tamoxifen ; Medroxyprogesterone Acetate, which has local anti-estrogen property; or Ketoconazole which blocks steroidogenesis. Sometimes Oophorectomy or cyst removal is required. Addition of long-acting GnRH analogues, in case it progresses to secondary GDPP.

Management is multidisciplinary and will include pediatric endocrinologist, orthopedic, physiotherapist and pediatric surgeon.

Patient Information Page - DR. SHALMI MEHTA, AHMEDABAD

WHAT IS PRECOCIOUS PUBERTY?

At puberty, the body changes and sexual characteristics begin to appear. This usually happens in girls between the ages of 8 and 13 and boys between the ages 9 and 14.

Puberty is triggered when the brain, more specifically the pituitary gland, releases signals that stimulate the ovaries or testes to begin making sex hormones. These hormones are what allows for sexual maturation.

Sometimes, the hormonal trigger comes too early, and sexual characteristics begin to appear before they should. If a girl under 8 or a boy under 9 yrs old begins to show signs of puberty this is termed as precocious or early puberty.

SIGNS OF PUBERTY **-** Your child may display one or many of these signs as listed below. These signs should be brought to the doctor's attention.

1**. SEXUAL CHARCTERISTICS**

- Breasts begin to develop and monthly periods begin (girls).
- The penis and testes grow larger, spontaneous erections occur (boys).
- Facial hair, pubic hair and underarm hair appear.
- Body odour changes and becomes more obvious.

2. **HEIGHT**

A growth spurt will occur and the child may be taller than his or her friends. Before puberty, a child grows at a fairly steady rate, averaging 2-3 inches a year. The hormonal trigger at puberty speeds up the growth. At the end of puberty, the growth centres in bone close off, after which a person won't grow any taller. If puberty comes early, your child will experience the adolescent growth spurt too soon, will stop growing at a much younger age than normal, and will likely not reach his or her potential height as an adult.

3. **BEHAVIOUR**

As well as producing physical changes, sex hormones also affect mood. Some boys become more aggressive and develop a sex drive. Mood swings and irritability are common in girls.

It is easy for people to forget that the child who started puberty prematurely is not as old as he or she looks, and to begin expecting more mature behaviour than is appropriate at their age.

SHOULD PRECOCIOUS PUBERTY BE TREATED?

There are both physical and psychological reasons for treating precocious puberty. Stopping the growth spurt gives the child a better chance of eventually reaching his or her full expected height. Body changes such as breast development may also make children very self conscious. Boys may behave inappropriately.

Because treatment can only partially reverse changes which have already occurred, it is important to recognize signs of precocious puberty and where it is judged necessary, begin treatment as soon as possible.

WHY IS PUBERTY EARLY IN YOUR CHILD?

The tendency to develop early can be inherited, but in the majority of cases the cause is not known. Precocious puberty can be caused by abnormalities in the pituitary gland, the sex glands (ovaries or testes) or the adrenal glands. Some types of tumors can also release hormones and trigger puberty earlier than usual. Tests are required to determine whether the signals to start puberty are coming from the gland themselves or from the brain.

WHAT DOES TREATMENT INVOLVE?

When precocious puberty is suspected, a physical exam will be done, along with the X-rays of the hand, blood tests and (in girls) an ultrasound of the pelvis to determine the extent of pubertal development and growth. A scan of the brain (called MRI) may be done to look for a tumor. These tests are used to determine from where the signal to start puberty is originating. If your child is found to have "central" precocious puberty (meaning that the signal is coming from the brain or pituitary gland), your doctor may recommend a new drug called GnRH agonist, which makes it possible to temporarily stop puberty. This drug tells the brain to stop signaling the body to make sex hormones, which prevents any further development of sexual characteristics. Growth will slow to a more reasonable rate.

HOW IS TREATMENT GIVEN? FOR HOW LONG?

Treatment is given by injections which can be given every month or 3 monthly. The injections should continue until the child reaches an age at which it is appropriate for puberty to begin.

WHAT WILL HAPPEN ONCE TREATMENT BEGINS?

Outward physical signs of puberty such as breast development or growth of penis and testis will stop, and changes that have already occurred might even become less obvious. Monthly periods will stop, pubic and underarm hair may fall out, and body odor becomes less pronounced. Changes in behavior may also be noticeable and the premature increase in height will slow down, giving your child more time to grow

WHAT ARE THE SIDE EFFECTS?

In the first few weeks of treatment, pubertal signs and mood changes may become more noticeable. It is common for girls to have a menstrual period or spotting soon after treatment begins. These effects are temporary as the body begins to respond to the drug and should begin to reverse with continued therapy.

It is also possible that the injection site will become red and sore.

The long term side effects are not known, but there have been no harmful short term effects in patients of precocious puberty. The effect of the drug is reversed when the medication is stopped and sexual maturation resumes normally.

Do not hesitate to ask your child's physician for any questions or concerns your might have during the treatment.

CASE CAPSULES IN PRECOCIOUS PUBERTY

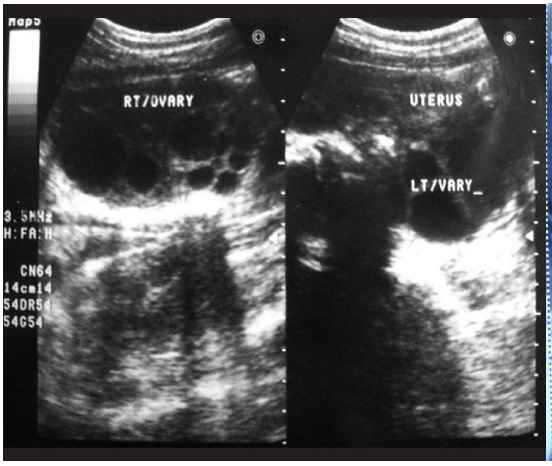
Hypothyroidism and precocious puberty

(Ramkumar S, Pediatric Endocrinologist, Apollo Children's Hospital, Chennai)

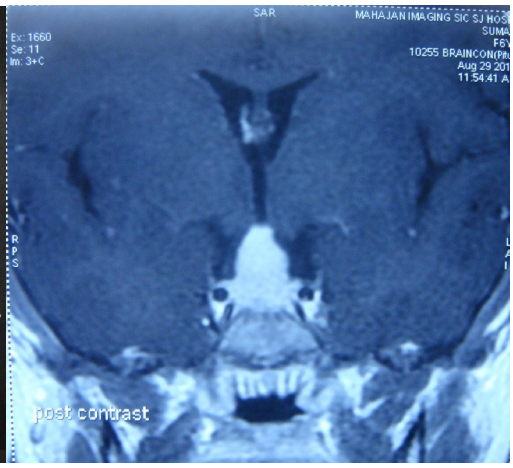
Primary hypothyroidism in juvenile population often leads to retardation of linear growth and/or delayed puberty. However, rarely sexual precocity may occur in juvenile hypothyroidism. This syndrome of incomplete isosexual precocity and juvenile hypothyroidism is called Van Wyk-Grumbach syndrome. Bone age is delayed unlike other forms of sexual precocity where advanced bone age is a rule. These two features (growth retardation and delayed bone age) point to primary hypothyroidism as the cause for sexual precocity. Juvenile hypothyroidism is due to auto-immune thyroid disease and rarely due to congenital hypothyroidism. Low free T4 and high TSH confirms the diagnosis. Prolactin and FSH can be elevated in this syndrome. Galactorrhoea occurs due to hyperprolactinemia and can be spontaneous or present on gentle manipulation. Pubarche is not a feature. Pituitary often enlarges due to hyperplasia of thyrotrophs, lactotrophs and gonadotrophs and may be mistaken for pituitary tumor. Ovaries show multi-cystic appearance due to stimulatory effect of TSH (called specificity spillover) and FSH.

The exact mechanism is poorly understood. The increase in prolactin is mediated by rise in TRH secondary to loss of feedback inhibition by low levels of thyroid hormones. TSH and FSH acts on the FSH receptors in the ovary resulting in multi-cystic appearance and increased production of estradiol. In boys, the FSH and TSH act on the FSH receptors in sertoli cells causing testicular enlargement. Since no testosterone is produced, secondary sexual characters do not develop in boys except testicular enlargement. All manifestations including pituitary enlargement and multicystic appearance improve with treatment of thyroxine except testicular enlargement in boys.

USG - multicystic ovaries



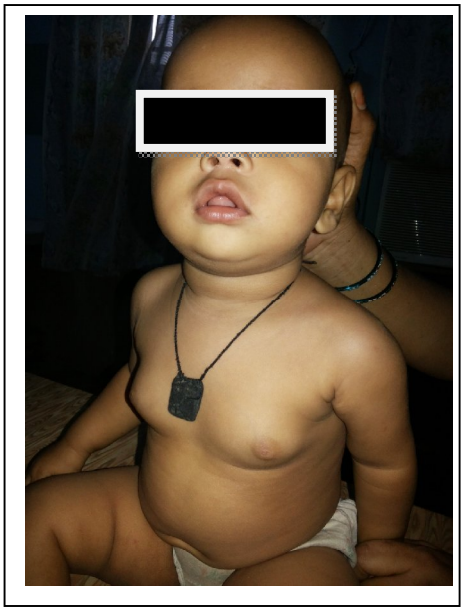
MRI - diffusely enhancing pituitary hyperplasia



A child with simple thelarche - Dr. Vijay Jaiswal, Assistant Professor, LLRM MEDICAL COLLEGE , MEERUT

8 months, female baby was brought to the pediatric OPD with complaints of breast enlargement on both sides since 4 months of age. There was no history of any vaginal discharge or sexual hair. Anthropometry, genitalia, bone age and ultrasound were normal. Parental were appropriately counseled and advised to continue follow-up.

Premature Thelarche is a term used for isolated breast development that is commonly noted at two age periods; first 2-4 years of life and the second peak is usually at 6 years. In some girls breast development is present at birth and persists till late childhood. It may be bilateral, unilateral or asymmetric and often fluctuates in degree. Growth and osseous maturation are normal or slightly advanced. Genitalia show no evidence of estrogenic stimulation. This condition is usually sporadic. Breast development might regress after 2 year, often persist for 3-5 years and is rarely progressive. It is probably due to oversensitivity of infant's breast tissue to ovarian estrogen secondary to transient secretion by follicular cyst of the ovary



Child with simple thelarche

PEDENDOSCAN

Dr Sachin Mittal, Mumbai

Diabetes

Higher insulin detemir doses are required for the similar glycemic control: comparison of insulin detemir and glargine in children with type 1 diabetes mellitus. Abalı S et al. Pediatr Diabetes. 2014 Jul 11.

117 (53 females) children and adolescents with T1DM older than 4 yr of age, minimum diabetes duration of 2 yr, and receiving basal-bolus insulin regimen (at least 4 injections/d, insulin aspart or lispro as bolus insulin, insulin detemir (n□=□32) or glargine (n□=□85) as the basal insulin) were evaluated in this retrospective study with an aim to compare hemoglobin A1c (HbA1c), total and basal insulin doses, basal insulin injection frequencies. The authors concluded that Insulin detemir provides similar glycemic control as with glargine, but, approximately 27% higher mean basal and 19% higher mean total insulin doses with two-fold more twice-daily basal insulin injection requirement.

Growth and Puberty

Growth Hormone Dose-Dependent Pubertal Growth: A Randomized Trial in Short Children with Low Growth Hormone Secretion. Albertsson-Wikland K et al. Horm Res Paediatr. 2014 Aug 28:158-170

A multicenter, randomized, clinical trial followed 111 children from onset of puberty to adult height (AH). Patients were randomized to receive 67 µg/kg/day (GH (67)) given as one (GH (67×1); n = 35) or two daily injections (GH (33×2); n = 36), or 33 µg/kg/day dose (GH (33×1); n = 40). Pubertal height SDS gain and AHSDS was greater for patients receiving a high dose than a low dose GH. All groups reached their target height SDS. There were no differences between the once- and twice-daily GH regimens.

Stimulant Use and Its Impact on Growth in Children Receiving Growth Hormone Therapy: An Analysis of the KIGS International Growth Database. Miller BS et al. Horm Res Paediatr. 2014;82(1):31-7

Children enrolled in the KIGS (Pfizer International Growth Study) registry were evaluated for the associated diagnosis of ADHD prior to initiation of rhGH. The prevalence of ADHD in KIGS was 2.3% , with stimulants used in 1.8%. Those who received stimulants grew significantly less (1.1 cm) in the first year of rhGH therapy than expected. The authors suggested that the ADHD phenotype, alone or in conjunction with stimulant therapy, may impair the short-term growth response to rhGH.

Thyroid

Thyroid Surgery in Children: Clinical Outcomes. Sinha CK, Decoppi P, Pierro A et al. Eur J Pediatr Surg. 2014 Aug 21

To review the outcomes of thyroid surgery in children operated for both benign and malignant conditions, demography, clinical features, and surgical outcomes were noted retrospectively for 61 children (43 girls and 18 boys), who underwent thyroidectomy for benign (70%) and malignant (30%) conditions. Overall rate of complications, especially hypocalcemia, is higher after surgery for malignancy.

Correlation between severity of growth hormone deficiency and thyroid metabolism and effects of long-term growth hormone treatment on thyroid function in children with idiopathic growth hormone deficiency. Ciresi Aet al. Horm Res Paediatr. 2014;81(6):379-85.

To evaluate the impact of GH replacement on thyroid status in children with idiopathic GH deficiency (GHD), data of 105 GHD children (82 M, 23 F), during a 36-month follow-up was analyzed. GH treatment was associated with a significant increase in fT3 in the first 12 months, more pronounced in patients with more severe GHD, highlighting the strong correlation between severity of GHD and thyroid metabolism

Adrenal

Increased Prevalence of Testicular Adrenal Rest Tumours (TART) during Adolescence in Congenital Adrenal Hyperplasia. Claahsen-van der Grinten HL, et al Horm Res Paediatr. 2014 Sep 3.

To define the prevalence of TART, retrospective data evaluation was done in 41 paediatric male CAH patients aged 0-19 years regularly followed by high-frequency ultrasound techniques. There was a increase in the prevalence above 10 years of age and TART were detected in 100% of the patients above the age of 16 years. The tumours were not detectable by palpation. The authors recommended regular ultrasound from the onset of puberty in all boys with classic CAH

Bone and Vitamin D metabolism

Efficacy and Tolerability of a High Loading Dose (25,000 IU Weekly) Vitamin D3 Supplementation in Obese Children with Vitamin D Insufficiency/Deficiency. Radhakishun NN et al. Horm Res Paediatr. 2014;82(2):103-6.

The efficacy and tolerability of a high loading dose vitamin D3 supplementation of 25,000 IU weekly was studied in 109 obese children, 8-18 years of age, with vitamin D insufficiency/deficiency. In 84.4% of the children, the vitamin D status improved from insufficiency/deficiency (<50 nmol/l) to sufficiency (≥50 nmol/l). No side effects were reported, and the highest level reached was far below the threshold for toxicity.

Effect of Vitamin D3 Supplementation on Serum 25(OH)D, Lipids and Markers of Insulin Resistance in Obese Adolescents: A Prospective, Randomized, Placebo-Controlled Pilot Trial. Nader NS et al. Horm Res Paediatr. 2014;82(2):107-12.

In this double-blind, randomized, placebo-controlled trial, 58 obese adolescents received either vitamin D3 (2,000 IU/day) or placebo for 12 weeks. Total 25(OH)D, fasting plasma glucose, insulin and lipid profile were measured at baseline and following supplementation. 12 weeks of vitamin D3 supplementation in obese adolescents with 2,000 IU once daily resulted in a modest increase in 25(OH)D concentration in obese adolescents, but did not affect the lipid profile and markers of insulin resistance and inflammation.

A meta-analysis comparing the Biochemistry of Primary Hyperparathyroidism in Youths to the Biochemistry of Primary Hyperparathyroidism in Adults. Roizen J, Levine MA. J Clin Endocrinol Metab. 2014 Sep 2

To understand the difference in PHPT between adults and Youths, a systematic review and meta-analysis of 16 retrospective studies, describing 268 youths and 2405 adults with PHPT was done and the biochemistry of PHPT was compared. Youths with PHPT had significantly ($P < 0.05$) greater serum and urinary calcium than adults with PHPT There were no significant differences in serum intact PTH, phosphorus, or alkaline phosphatase. These observations suggest that there are differences in the pathophysiology of PHPT between juvenile and adult patients that reflect an apparent decrease in the sensitivity of the parathyroid adenoma to negative feedback by calcium and increased sensitivity of target tissues to the effects of PTH.

Drugs used in precocious puberty (other than GnRHa)

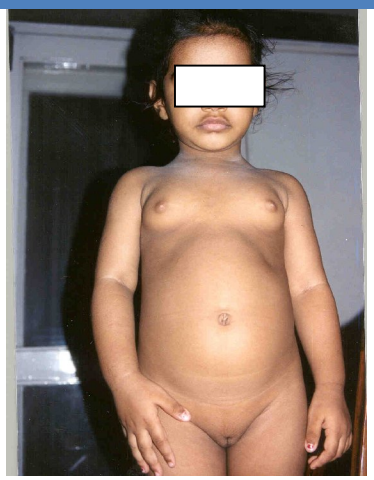
Dr Bhanu K Bhakhri, AIIMS, Rishikesh

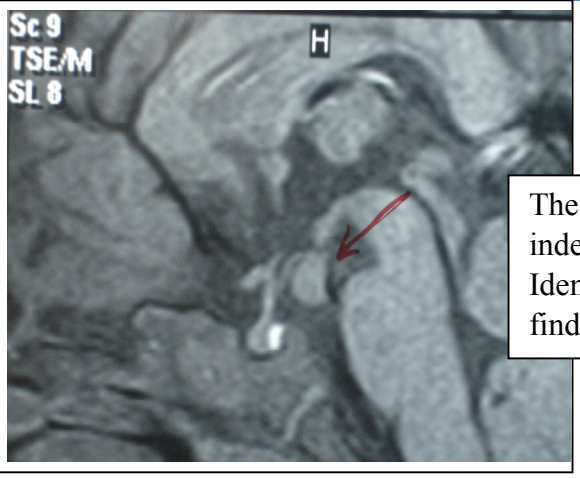
Various GnRH analogs are the mainstay of treatment in gonadotropin dependent precocious puberty (GDPP). They are also useful in patients with GIPP who eventually land up in GDPP due to progressive maturation of hypothalamo-pituitary-gonadal axis secondary to persistently increased sex hormones. Management option in GIPP include the surgical removal of the etiology behind the condition and in some cases the drugs blocking the action of offending sex steroid, by inhibiting their synthesis or by blocking the receptor. The therapeutic options include progestational, antiandrogen and antiestrogen agents.

Class of drugs	Mechanism of action	Drugs in the group	Usual dose	Adverse effects
Progestational agents	Suppression of gonadotropin release, blocking gonadal steroidogenesis	Medroxy-progestrone acetate	Oral 10-50 mg daily OR 50-100 mg IM every 2 weeks	Edema, weight gain, adrenal insufficiency
Antiandrogen	Receptor blockers	Spironolactone	Oral 2-4 mg/kg/day	GI intolerance, gynaecomastia, laboratory hypoadrenalism with cyproterone
		Cyproterone acetate	Oral 50-100 mg per sqm/day	
	Synthesis inhibitors	Ketoconazole	Oral 10-20 mg/kg/day	Hepatotoxicity, GI intolerance
Antiestrogens	Receptor modulator	Tamoxifen	Oral 10-20 mg/day	Hepatotoxicty, hypertricosis, hot flushes
	Synthesis blockers (aromatase inhibitors)	Testolactone	Oral 20- 40 mg/kg/day	Allergy, breast lump, vaginal bleed
		Anastrozole	Oral 1 mg daily	Hot flushes, GI intolerance, flu like syndrome, osteoporosis
		Letrozole	Oral 2.5 mg daily	

Class of drugs	Drugs in the group	Preparations, brands	Approximate price (INR)
Progestational agents	Medroxy-progestrone acetate	Tab 2-5,10 mg Meprate, Provera	2-10 per tab
		150mg/ml, 1 ml Inj- Depo-Provera, Petogen	150-250 per inj
Antiandrogen	Spironolactone	25,50&100 mg tablet	2-10 per tab
	Cyproterone acetate	50 & 100 mg tablet, Siterone, Cyprostat	70-100 per tab
	Ketoconazole	200 mg tablet, Fungicide, Ketotab	10-20 per tab
Antiestrogens	Tamoxifen	10 mg, 20 mg Oncomox, Caditam	2-5 per tab
	Testolactone	50 mg tablet, Teslac	-
	Anastrozole	1 mg tablet, Anabrez, Armotraz	50-60 per tab
	Letrozole	2.5, 5 mg tablet, Fempro, Letroz	10-30 per tab

PICTORIAL QUIZ FOR READERS (solution on last page) (images contributed by Dr Archana Dayal)





The clinical features of the index case are shown. Identify the radiological finding.

JUDICIOUS USAGE OF GNRH ANALOGUE THERAPY

Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children
March 30, 2009 ***Pediatrics Vol. 123 No. 4 April 1, 2009 – J C Carel et al***

- Progressive pubertal development and growth acceleration should be documented over a 3- to 6-month period before GnRHa therapy. This observational period may not be necessary if the child is at or past Tanner stage III (breast), particularly with advanced skeletal maturation.
- Girls with onset of progressive CPP before 6 years of age benefit most in terms of height from GnRHas. The decision to initiate therapy in girls with onset after the age of 6 should be individualized.
- Treatment should be considered for all boys with onset of progressive CPP before 9 years of age who have compromised height potential.
- The use of GnRHas solely to influence the psychosocial consequences of CPP or to delay menarche should be considered carefully given the absence of convincing data .
- Adopted children should be treated no differently than nonadopted children with CPP.
- Basal LH levels are useful screening tests and may be diagnostic. Stimulated LH levels are important, but interpretation suffers from assay variability and absence of clear diagnostic cutoffs. Gonadal sex-steroid levels can add information in support of the diagnosis but are not sufficient
- Pelvic ultrasound is helpful in differentiating CPP from premature thelarche as an adjunct to GnRH stimulation.
- All boys with CPP and girls with CPP at <6 years of age should have a head MRI. It is controversial whether all girls who develop CPP between 6 and 8 years of age require head MRI. Girls with neurologic findings and rapid pubertal progression are more likely to have intracranial pathology and require an MRI examination.
- A variety of GnRHa formulations are available and efficacious. The choice of a particular agent depends on patient and physician preference and on local marketing approval.
- GnRHa-injection dates should be recorded and adherence with the dosing interval monitored. Tanner stage and growth should be assessed every 3 to 6 months, and BA should be monitored periodically.
- The addition of GH or oxandrolone to GnRHas cannot be routinely recommended.
- There is insufficient evidence to rely on any one clinical variable (CA, duration of therapy, BA, height, target height, growth velocity) to make the decision to discontinue treatment. Therefore, it is reasonable to consider these parameters and informed parent and patient preferences, with the goal of menarche occurring near the population norms.

PUBLICATIONS FROM OUR MEMBERS

Dr Deep Dutta (IPGMER Kolkota)

- Dutta D, Mondal SA, Kumar M, Hasanoor Reza AH, Biswas D, Singh P, Chakrabarti S, Mukhopadhyay S. Serum fetuin-A concentration predicts glycaemic outcomes in people with prediabetes: a prospective study from eastern India. Diabet Med. 2014 Jun 30.
- Dutta D, Mondal SA, Choudhuri S, Maisnam I, Hasanoor Reza AH, Bhattacharya B, Chowdhury S, Mukhopadhyay S. Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: an open label randomized prospective study from Eastern India. Diabetes Res Clin Pract. 2014 Mar;103(3):e18-23.
- Dutta D, Choudhuri S, Mondal SA, Mukherjee S, Chowdhury S. Urinary albumin□:□creatinine ratio predicts prediabetes progression to diabetes and reversal to normoglycemia: role of associated insulin resistance, inflammatory cytokines and low vitamin D. J Diabetes. 2014 Jul;6(4):316-22.

Dr Ahila Ayyavoo (GKNM Hospital, Coimbatore)

- Ayyavoo, A., Derraik, J. G. B., Hofman, P. L., Biggs, J. and Cutfield, W. S. (2014), Metabolic, cardiovascular and anthropometric differences between prepubertal girls and boys. Clinical Endocrinology, 81: 238–243. doi: 10.1111/cen.12436
- Ayyavoo A, Derraik JG, Cutfield WS, Hofman PL. Elimination of pain and improvement of exercise capacity in Camurati-Engelmann disease with losartan. The Journal of Clinical Endocrinology & Metabolism. 2014.

Dr Ganesh Jevalikar (New Delhi)

- Greaves RF, Jevalikar G, Hewitt JK, Zacharin MR. A guide to understanding the steroid pathway: New insights and diagnostic implications. Clin Biochem. 2014 Jul 31.
- Jevalikar G, Solis J, Zacharin M. Long-term outcomes of pediatric Graves' disease. J Pediatr Endocrinol Metab. 2014 Jun 19.

Dr Ramkumar S (Apollo Hospitals Chennai)

- Ramkumar S et al. Ectopic insulin secreting neuroendocrine tumor of kidney with recurrent hypoglycemia: a diagnostic dilemma. BMC Endocr Disord. 2014; 14: 36

ACADEMIC ACTIVITIES BY ISPAE MEMBERS

Dr Vandana Jain (New Delhi)

A CME titled "Endocrinology for Postgraduates in Pediatrics" was organized by Prof Anju Seth and Dr Vandana Jain at AIIMS on 9th and 10th August, 2014, and was attended by 99 delegates. The faculty included Prof Ram K Menon, Prof Vijayalakshmi Bhatia, Prof Sudha Rao, Dr Rajesh Khadgawat and Dr Rajni Sharma.

Dr Veena V nair (Thiruvananthapuram)

Ananthapuri Hospitals and Research Institute (AHRI), Thiruvananthapuram, Kerala, organised a one day CME on 11 th of May 2014. Prof Ramdoss Pisharody, Principal Medical College, Thiruvananthapuram inaugurated the event. A patient education booklet on childhood diabetes was also released during the occasion. The entire spectrum of pediatric endocrinology was covered.

Dr Anurag Bajpai (Gurgaon and UP)

-Practical Pediatric Endocrine Course was organized by GROW India in association with Fortis Hospital and IAP Gurgaon at FMRI Gurgaon on July 27 2014.

-Growth workshop was held in Ghaziabad and Bareilly in association with their respective IAPs on May 17 and July 13, 2014 respectively by Dr Atul Agarwal and Dr Anurag Bajpai.

-Glucose Disorders workshop, was held by Dr Anurag Bajpai and Dr Samarth Vohra and IAP Kanpur, on July 19, 2014. The module covered key aspects of Type 1 DM and hypoglycemia.

Dr Ganesh Jevalikar (New Delhi)

Insulin pump workshop was held in association with Medtronic on 01 & 02 March 2014

Dr Sudha Rao (Mumbai)

An endocrinology update was held in Wadia Children's Hospital on 23rd and 24th of August.

PATIENT RELATED ACTIVITIES BY ISPAE MEMBERS

Dr Anju Virmani (New Delhi)

Members in Delhi: Dr Meena Chhabra, Dr Ganesh Jevalikar, and Dr Anju Virmani: have been holding quarterly picnics for children with type 1 diabetes and their families, in association with Masonic Lodge and Yog Dhyan Foundation. They combine fun and games with education, discussion, yoga, peer group support, and in the last camp in August 2014, free HBA1C testing.

Dr Sandeep Jhulka (Indore)

With the help of a grant from LIFE FOR A CHILD FOUNDATION free glucometers and strips for underprivileged children with Type One Diabetes were provided. It is an initiative of International Diabetes foundation and Diabetes Australia.

Dr Ramkumar S (Chennai)

Health Talk on 'Obesity in Children' in Apollo Clinic, Alwarpet, Chennai on 26th July 2014, attended by 30 parents & followed by an interactive session. As part of Apollo Hospital Initiative, a total 1200 school children of Bharathi Vidyala Higher Secondary School were screened over a period of 8 days for general and endocrine problems. Children with health issues including thyroid, hypertension and obesity were identified advice given. An article was written in Circle. 2014(july); vol 4: 24 on – is thyroid affecting my child.

Dr Ahila Ayyavoo (Coimbatore)

A camp for 50 children with Type 1 diabetes mellitus and their families was conducted at G. Kuppuswamy Naidu Memorial Hospital on the 25th of May 2014.

Dr Anurag Bajpai (Kanpur)

World Thyroid Day was celebrated on May 24 2014 at Regency Hospital Limited Kanpur by a Patient awareness program and camp. Parents and children with congenital hypothyroidism were educated about the long term effects of hypothyroidism.

Inaugural GROW India Film Festival was organized at Methodist High School Kanpur on August 23 2014. This was preceded by a workshop on short film making for 100 children from

across the city. Eight schools from across Kanpur participated with short films on growth and growth disorders.

Dr Meena Mohan (Coimbatore)

Diabetes support group meeting that was held on 15.8.14 as part of Independence Day celebrations - 35 families attended and there were about 120 people in total. Yoga was taught to children as a way of continuing to promote the importance of exercise in day to day management of type 1 diabetes. The food was served with a menu in millets to encourage use of low GI food to prevent huge glycemic excursions. The program was well received by all the children and their families

Dr Hemchand K P (Chennai)

A educational initiative was conducted for children with type-1 diabetes in partnership with Eli lilly. A conversational map was used to educate the children with type-1 diabetes and their families at Mehta childrens hospitals, Chennai.

PRADER WILLI SUPPORT GROUP – SAGAR HOSPITAL BENGALURU

Dr. P. Raghupathy, Professional Delegate from India for the International Prader-Willi Syndrome Organization (IPWSO), organized the first PWS Parent Group Meeting in south India in association with the PWS association of India headed by Mrs. Shikha Harlalka.16 families from his clinic and from Kolkata participated in the program. The parents were provided with practical tips and guidance for management of their children with PWS by a team of pediatric specialists. It was unanimously agreed also to start a National Registry for PWS and to bring awareness among pediatricians and the general public, in order to facilitate early diagnosis. The meeting was sponsored by Novo Nordisk India (P) Ltd and by Sagar Hospitals.

PRADER WILLI SUPPORT GROUP – GANGARAM HOSPITAL, NEW DELHI

Dr. Archana D. Arya organized a meeting for children with PWS and their families along with PWS association of India at Sir Ganga Ram Hospital, New Delhi on 29th September 2014. 10 families participated in the meeting and were educated about the various endocrine, nutritional and behavioral aspects of PWS by a team of doctors from various pediatric specialties.

WELCOME TO OUR NEW MEMBERS

1. Vishnu Agarawal, Jaipur
2. Ayesha Ahmed, Aligarh
3. Jesinth Mohan, Kanyakumari
4. Fouzea Mol, Coimbatore

OBITUARY NOTE

Dr S S Rastogi Endocrinologist & Diabetologist, Delhi. A Regular attendee of ISPAE meetings and an associate member of ISPAE Our condolences to his family. May his soul rest in peace

Pictorial Quiz - answer

Pedunculated soft tissue lesion in the supra cistern arising from the hypothalamus - hamartoma

UPCOMING ISSSUE - DELAYED PUBERTY

CASE BASED REVIEWS IN ENDOCRINOLOGY

A book edited by Dr Vandana Jain, Additional Professor, Pediatric Endocrinology Division, AIIMS and Prof Ram K Menon, Director, Pediatric Endocrinology, C S Mott Children's Hospital, University of Michigan Centre, Ann Arbor, MI is available for use. Forewards by Dr Meena P Desai and Prof Vinod Paul, published by Jaypee brothers was released on 9th August 2014. Renowned endocrinologists from all over the world have contributed to the book which comprehensively covers the entire spectrum of pediatric endocrinology in a case based format. Radiological and nuclear imaging, protocols for dynamic stimulation tests and IEM are important additional themes well covered in the text book

A Novel observation - Dr Deep Dutta (IPGMER Kolkota)

The Department of Endocrinology & Metabolism, IPGMER Kolkata would like to share with all the members of ISPAE our observations of importance of fetuin-A (a novel hepatokine), in being an important predictor of prediabetes progression to diabetes. Increased fetuin-A was associated with higher systemic inflammation, more severe fatty liver disease, lower serum vitamin-D and increased progression to diabetes. In a randomized controlled trial, vitamin-D supplementation in vitamin-D deficient/insufficient prediabetes individuals was associated with decreased insulin resistance, inflammation, lower progression to diabetes and increased reversal to normoglycemia.

ISPAE EXECUTIVE COUNCIL ELECTIONS

Dear life members of ISPAE,

On behalf of the executive council of ISPAE, I am announcing the start of the election process for office bearers and executive council members of ISPAE for the year 2015-16. I have been appointed as the returning Officer by the current executive. Please see the attachment for the rules in our constitution relevant to elections. If you have any queries related to whether you are eligible to stand for office, please don't hesitate to email me.

Nomination on plain paper by a life member, seconded by another life member, must be emailed to me at this id **electispae2014@gmail.com**. The nomination form must mention the post applied for, names and address of candidate, proposer and seconder clearly, with all 3 signatures below, and the paper scanned and attached in the email. There is no limit to the number of candidates one may nominate, however one candidate can apply only for one post.

The last date for receipt of nominations is October 15th 2014. The last date for withdrawal of nomination is October 25th 2014.

Office bearers: 3 (President, Secretary-treasurer, and Joint secretary). Executive mem: 7.

ISPAE is still a very young society. Though the tasks before the executive are those of any bigger society, there is the added task of making our Society grow so as to be meaningful in the academic scene in India. The office bearers and executive have a responsibility towards the members to steer the ship for the next 2 years by sparing some of their valuable time, thoughts and efforts. If our professional society is strong and highly visible and useful, it can only be of benefit to all of us as individual professionals. Our adult endocrinology (nonvoting) colleagues form an equally important part of ISPAE, and contribute to our newsletter, our meetings, teaching and training in India, and all our other activities. So the current executive urges all, especially those who have never been part of the executive before, to consider standing for election and being an active part of this exciting phase of our existence.

Please be informed that email is the only method of communication for all executive council decisions, with paper documentation being a formality which is observed at the next nearest opportunity. So it is CRITICAL that all those who apply must be willing to download and reply regularly.

Ganesh Jevalikar

Returning Officer 2014, ISPAE