CAPE NEWS

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

www.ispae.org.in

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NOTICE OF THE ANNUAL GENERAL BODY MEETING

Notice is given of the annual GBM to be held during AIIMS-ISPAE-ISPAD meeting at New Delhi on 4th November 2012, at 6 pm, in Jawaharlal Auditorium, AIIMS, with Dr PSN Menon/ Dr Anju Seth in the chair. The agenda is:

1. To read and confirm minutes of the AGBM at Calicut in November 2011.
2. To present the audited accounts.
3. To welcome new members.
4. To discuss ISPAE 2013 and ISPAE PET 2013, and other Chapter activities for the year 2013, including future meeting plans, and the program for Pedicon 2013.
5. Any other agenda with permission of the chair.

STEROID RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS (SREAT)

Wg Cdr SK Patnaik, drskp1973@yahoo.com

INTRODUCTION

Over last half century, there has been a gradual recognition of a concept of non-vasculitic autoimmune meningoencephalitis (NAIM) owing to frequent association of autoimmune antibodies with 'investigation negative encephalopathy'.

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SECRETARY'S MESSAGE

Dear ISPAE members,

Since our last communication through CAPE NEWS, there have been developments on several fronts… that I am happy to share with you.

… Contd on page 2

WEBSITE www.ispae.org.in
Must See ** Interactive Discussion Forum

ISPAE-ISPAD-AIIMS CME: Delhi: 4-5 November 2012. Org. Secretary: Dr Vandana Jain, child.diabetes.ispae@gmail.com

PEDICON 2013: 50th Annual IAP Conference: Kolkata: 17-20 January 2013. Organizing Secretary: Dr Jaydeep Choudhry.

ISPAE 2013 & ISPAE-PET 2013 (Pediatric Endocrine Training): Bengaluru. Organizing Secretary: Dr Shaila Bhattacharya, email: shailashamanur@gmail.com

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SECRETARY'S MESSAGE

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… The process for formation of the ISPAE scientific council is well on its way, the Executive Council having decided upon the method to be followed. I shall soon be writing to you all for nominations for this Council laying out the selection criteria.

The process for selection of the first awardees of ISPAE Travel Award commencing this year is also over. The name(s) will be announced as soon as a formal approval is accorded in the EC meeting currently nearing conclusion.

The European Society of Pediatric Endocrinology is going to organize the third ESPE Science School in May 2013 at Israel. They have offered two seats to ISPAE members. I shall soon be writing to you all about the details of the same and the process of selection of participants from ISPAE.

In September, members would be interested in the annual ISBMR meeting at Lucknow, and PEP 2012 in Bengaluru. I am also looking forward to meeting you all in Delhi at the forthcoming AIIMS-ISPAE-ISPAD diabetes meeting in November 2012. The Annual GBM of ISPAE would also be held during this meeting.

Dr Raghupathy and Dr Shaila Bhattacharyya are preparing for ISPAE 2013 in Bengaluru. Work will shortly begin for ISPAE-PET 2013 under the stewardship of Dr Preeti Dabadghao.

Last but certainly not the least, I urge you all to visit the beautiful new web-site of ISPAE designed very painstakingly by Dr Ravi Karnam and his team. The Discussion Forum is picking up and proving useful in exchanging information and ideas in patient care.

With warm regards,

Anju Seth, Secretary, ISPAE

AIIMS-ISPAE-ISPAD CME on Childhood Diabetes 4th - 5th November 2012, AIIMS, New Delhi

All India Institute of Medical Sciences, New Delhi (AIIMS) and ISPAE are organizing the CME in association with the International Society for Pediatric and Adolescent Diabetes (ISPAD) on 4-5th November, 2012 (Sunday & Monday) at AIIMS, New Delhi.

This meeting targeted at MD Pediatrics & DM Endocrinology trainees, pediatricians, endocrinologists, general physicians and other health professionals in the field of childhood diabetes, will comprehensively cover all aspects of management of type 1 diabetes, including advances (flexible regimens, insulin pump therapy, continuous glucose monitoring, closed loop systems), management of DKA, long-term complications; diagnosis and management of glucose intolerance and type 2 diabetes in adolescents; and monogenic diabetes. The faculty comprises of well-known national and international experts in the field.

Registration fee (cheque/ draft in favor of 'CME on Childhood Diabetes', payable at Delhi)

Category	Till 30th Sept.	1st Oct onwards
Resident (MD or DM)*/ ISPAE member	Rs 1,000/-	Rs 1,500/-
Others	Rs 1,500/-	Rs 2,500/-

Details of the scientific program can be downloaded from www.ispae.org.in/New, and the registration form downloaded from http://www.ispae.org.in/New/download_docs/Events/CME_diabetes.pdf. For more details, please contact **Dr Vandana Jain** or **Dr Rajesh Khadgawat** at child.diabetes.ispae@gmail.com or call +918595368936 (Mr Brijesh).

ISPAE 2013, ISPAE-PET 2013: Bengaluru

Warm greetings from the Organizing Committee of ISPAE 2013! It gives us great pleasure to welcome you all to the beautiful garden city of Bengaluru for the 3rd Biennial ISPAE Conference: ISPAE 2013 and the Pediatric Endocrine Training (PET) Program. The preparations for a grand ISPAE 2013 are on full swing. We hope to cover wide range of topics in Pediatric Endocrinology which would interest both practicing pediatricians and pediatric endocrinologists. We look forward to make sure the national and international experts provide fruitful science, while getting together gives us the ideal platform to exchange views on common and rare pediatric endocrine problems.

Details and registration form are available at our website, www.ispae.org.in.

We are sure you will enjoy not only the academic feast, but also the art, music, food and culture comprising the ultimate southern hospitality! Looking forward to meeting you all soon,

With warm regards and best wishes,

Dr P Raghupathy (Organising Chairperson) &
Dr Shaila S Bhattacharyya (Organizing Secretary)

Registration Fee for ISPAE 2013

Dates	Delegates	Students	Associate Delegates
July- Dec 2012	3000/-	2000/-	2000/-
Jan- June 2013	3500/-	2500/-	2500/-
June- Sep 2013	4000/-	2500/-	2500/-
Sep 2013- Spot Registration	4500/-	3000/-	3000/-

NEW MEMBERS: A VERY WARM WELCOME!!

1. Dr KRITI JOSHI, Dehradun
2. Dr SHRIRAAM MAHADEVAN, Chennai
3. Dr RUNA MAJUMDAR, Kolkatta
4. Dr SATINATH MUKHOPADHYAYA, Kolkatta
5. Dr BHAVEN A SHAH, Nadiad
6. Dr KARTHIK THIAGARAJAN, Chennai

APPES NEWS

Vijayalakshmi Bhatia, vbhatia@sgpgi.ac.in

The most important event in the APPES (Asia Pacific Pediatric Endocrine Society) calendar draws near, as the Indonesia team headed by Jose Batubara, Aman Pulungan and Bambang Tridjara get ready to host the 7th biennial meeting at Bali, in November 2012. Paul Hofman has put together an exciting scientific program. It will be preceded by the Fellows' Meeting, in which APPES offers slots to applicants from member countries. The five Fellows selected from India are Tushar Godbole (SGPGI), Rakesh Kumar (Asst Prof, Pediatrics, PGI Chandigarh), Sachin Mittal (TNMC), Ramkumar Selvarajan (AIIMS), and V Srinagesh (Osmania).

Other exciting news from APPES includes an exchange arrangement with Sociedad Latino-Americana de Endocrinología Pediátrica: SLEP (the Latin American Pediatric Endocrine Society) for speakers at each others' meetings. This arrangement has already been in place with ESPE, resulting in good speakers from other regions speaking at APPES meetings.

Of course, APPES will continue to collaborate with ISPAE to sponsor one speaker for our biennial meetings, a valuable resource for us. Pik To had come in 2009 and Reiko Horikawa in 2011 on behalf of APPES.

The APPES secretariat has overhauled its website, with conference notifications are being posted re abstract submission and other information. The website is working well, and has received good feedback. APPES also operates a facebook site, with the number of interested persons growing slowly. Do check them out, become a member if you are not already one, and make use of the educational opportunities offered.

Pedendoscan

Leena Priyambada, leenapriyambada@gmail.com

A single sample GnRHa stimulation test in the diagnosis of precocious puberty. Parvin Yazdani, Yuezhen Lin, Vandana Raman & Morey Haymond. **International J Pediatr Endocrinol 2012, 2012:23**

Gonadotropin-releasing hormone (GnRH) has been the standard test for diagnosing central precocious puberty (CPP). Because GnRH is rarely available, GnRH analogues (GnRHa) are now used. Retrospective analysis of multi-sample GnRHa stimulation tests was performed in 155 children (age 1-9y) referred for precocious puberty to Texas Children's Hospital. After 20 mcg/kg of SQ leuprolide acetate, samples were obtained at 0, 1, 3, and 6 h [LH, ADVIA Centaur immunoanalyzer (a two-site sandwich immunoassay) and FSH, direct chemiluminometric technique (ICMA, third-generation assay)].

Of 71 children with clinical evidence of CPP, 59 showed a peak LH >5 mIU/mL. Of these responders 52 (88%) had positive responses at 1 h, whereas all 59 children had a peak LH response >5 mIU/mL at 3h (P = 0.005). Maximum plasma concentrations of LH was seen at 1h in 21% children, at 3h in 54%, at 6h in 25%; 2 children had a maximum concentration at both 3 and 6 h. Of the 12 children who did not have an elevated stimulated LH response, only one girl subsequently required GnRHa therapy. Basal LH > 0.1 mIU/mL correlated strongly with pubertal stimulated LH concentration (>5 mIU/mL at 3h) in pubertal subjects (r = 0.842, P, 0.0001). The authors conclude that a single serum LH sample collected 3h post GnRHa challenge is the optimal sample to establish the diagnosis of CPP.

The gonadotropin levels at 4h were not assessed (as is the practice in some centers). The graph provided shows decline of mean LH levels from 3 to 6h. Clinical judgment and careful follow up are essential when monitoring a child with suspected precocious puberty.

Assessment of central adrenal insufficiency in children and adolescents with Prader–Willi syndrome (PWS). Andrea Corrias et al on behalf of the Study Group for Genetic Obesity of the Italian Society of Pediatric Endocrinology and Diabetology. **Clinical Endocrinology (2012) 76, 843–850.**

Gonadotrophin and growth hormone secretion anomalies are well demonstrated in PWS. Several reports have estimated mortality rate in PWS to be 3% yearly. Hypothalamus-hypophysis-adrenal (HHA) axis function in 84 pediatric patients with PWS was assessed with basal cortisol levels and the responses to a Low-Dose Tetracosactrin Stimulation Test (LDTST). Mean baseline ACTH and cortisol were 4.1 ± 2.7 pM and 341.7 ± 172.8 nM respectively. Pathological cortisol peak responses to LDTST were seen in 14.3% who had reduced basal (169.4 ± 83.3 nm) and stimulated (428.1 ± 69.6 nm) levels. In patients with deletion on chromosome 15, the cortisol peak was significantly lower than that in uniparental disomy. Standard-dose (250 mcg) tetracosactrin test confirmed CAI in 4/12 patients (4.8% of the cohort). None of the patients reported signs or symptoms suggestive of adrenal insufficiency. All had a normal course of previous infections, including recovery from surgical interventions.

The significance of these findings in face of the clinical picture (no suggestion of adrenal insufficiency) is controversial. However, during emergency stress conditions, perhaps a trial of hydrocortisone in stress doses may be considered.

45,X/46,XY Mosaicism: Phenotypic Characteristics, Growth, and Reproductive Function—A Retrospective Longitudinal Study. Marie Lindhardt Johansen, Casper P Hagen, Ewa Rajpert-De Meyts, Susanne Kjærgaard, Bodil L Petersen, Niels E Skakkebæk, Katharina M Main & Anders Juul. **J Clin Endocrinol Metab 97: E1540–E1549, 2012.**

Comprehensive evaluation of 25 patients (18 boys, 7 girls: according to gender of rearing) with 45,X/46,XY mosaicism and its variants is presented with cytogenetic, clinical, biochemical, and histological characteristics. Fourteen of 18 males had external masculinization scores consistent with normal virilization. Ten of 11 males experienced spontaneous puberty. Both males and females were considerably shorter than genetic potential, median height SD score being -2.0 (range, -3 to 0.3) for males and -2.2 (range, -2.5 to -1.4) for females. Median 1yr height gain after GH treatment in 7 patients was 0.5 SD (0.1 to 1.2). All tissue samples from 15 patients (8 boys, 7 girls) revealed abnormal gonadal histology. Four patients had carcinoma in situ (CIS); two had tissue samples available from early childhood, one showing CIS.

An interesting description. Analysis of gender identity in the subjects reared as females would have been of interest. It is noteworthy that 10/ 11 boys achieved spontaneous puberty. Cancer surveillance in such patients is important.

Emerging Effects of Early Environmental Factors over Genetic Background for Type 1 Diabetes (T1DM) Susceptibility: Evidence from a Nationwide Italian Twin Study. Lorenza Nistico` et al for the Study Group on Diabetes of the Italian Society of Pediatric Endocrinology and Diabetology. **J Clin Endocrinol Metab, August 2012, 97(8):E1483–E1491.**

Eighty eight pairs (34 monozygotic, MZ; 54 dizygotic, DZ) and one triplet were recruited (104 diabetic). Median age at onset of T1DM was 6.9y in index twins, and 9y in co-twins. Proband-wise concordances were 45.5 and 16.4% in MZ and DZ pairs respectively (P=0.01). After 1y from diagnosis in the first twin, 18% of MZ co-twins developed T1DM as opposed to 2% of DZ co-twins; at 10y the corresponding figures were 37% for MZ and 12% for DZ. Genetic contribution to T1DM susceptibility was 40%, and the shared and individual-specific environmental components were 51% and 9%, respectively. 11.5% were affected by Hashimoto's disease and five (4.8%) by celiac disease.
The authors noted a significant role of environmental effects shared within twin pairs and have stated that it "may reflect a higher relative weight of non-heritable phenomena occurring during intrauterine life and/or the early postnatal period… also none of the 65 non-twin siblings of the twins were affected by type 1 diabetes".

A Pilot Study of Discontinuous, Insulin-Like Growth Factor 1–Dosing Growth Hormone Treatment in Young Children with FGFR3 N540K-Mutated Hypochondroplasia. Anya Rothenbuhler et al. **J Pediatr 2012;160:849-53.**

N540K mutations in the fibroblast growth factor receptor 3 gene (FGFR3) cause one of the most severe forms of sporadic hypochondroplasia. Six children (mean age 2.6 $\pm$ 0.7y; mean height SDS - 3.0 $\pm$ 0.5) with the N540K mutation of FGFR3 gene received recombinant GH; with dosage titrated to an IGF-1 level of 1.5 SDS of the normal range. All 6 had low IGF-1 level at baseline (range -0.8 to -2 SDS) but normal GH response to stimulation tests. rGH therapy was interrupted 1 day per wk, 1mo per year, and 6mo every 2y. Breaks were given because the authors felt that "breaks from rGH treatment alleviate the burden of daily injections while allowing active catch-up growth if timed appropriately". The average cumulative rGH dose was 0.075 $\pm$ 0.018 mg/kg/day. After an average of 6.1 ± 0.9 years of rGH treatment, mean height SDS was -1.1 ± 0.2. Mean bone age gained was 1.04 ± 0.2 years per year of therapy. Trunk/leg proportion was consistently improved in all 6 patients, as indicated by a 2.3 SDS decrease in the sitting height-to-height ratio, but remained severely abnormal in all. Fasting serum glucose levels remained normal during rGH treatment, whereas serum insulin levels increased.

Management of short stature in children with skeletal dysplasia is disappointing. GH therapy in children with skeletal dysplasia is controversial, though other reports of benefit are present in literature (Acta Paediatr 2005 Oct; 94(10):1402-10). The presence of low IGF-1 levels in all these 6 children without GH deficiency, as authors themselves have described, is unexplained. Whether the response to GH was because of the low IGF-1 levels will need further studies.

Efficiency of Neonatal Screening for Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (21-OHD) in Children Born in Mainland France Between 1996 and 2003. Bénédicte Coulm; Joel Coste, Véronique Tardy, Emmanuel Ecosse, Michel Roussey, Yves Morel, Jean-Claude Carel, for the DHCSF Study Group. **Arch Pediatr Adolesc Med. 2012; 166(2): 113-120.**

In France, 21-OHD screening was introduced for all neonates as part of the national screening program in 1996. Between 1996 and 2003, a little over 6 million neonates were screened with dried filter paper 17OHP assay on day 3 of life. The prevalence of CAH was 1 in 15 699 births. The positive predictive value of screening was 2.3%, with a sensitivity of 93.5% and a specificity of

99.7% in term newborns. Efficiency of screening was very low in preterms (positive predictive value 0.4%). The authors conclude "Neonatal 21-OHD screening was efficient in term newborns, with a variable effect on clinical management, given that most affected female newborns are easy to identify without screening. By contrast, the efficiency of screening was very low in preterm newborns, resulting in large numbers of false-positive cases, flooding the system and leading to its dysfunction". Hence discontinuation of newborn screening for 17OHP in pre-term babies was recommended.

The Endocrine Society recommends that screening for 21-OHD be incorporated into all newborn screening programs, 'using a two-tier protocol (initial immunoassay with further evaluation of positive tests by liquid chromatography/ tandem mass spectrometry with norms stratified by gestational age'. (J Clin Endocrinol Metab 95: 4133–4160, 2010). This paper highlights that for newborn screening, issues such as what diseases a country or state decides to take up, and what cut offs are used to define normal vs. abnormal, are very much a question of finances, health systems policy, and logistics; there is no single recommendation which will suit all regions.

Drug information

We are starting a regular new column by Dr Bhakhri to keep members abreast of the different preparations of relevant drugs available in India. This information will then remain on the website, and be updated periodically. Members are welcome to contribute. Ed.

LEUPROLIDE ACETATE

Bhanukiran Bhakhri, drbhanu04@gmail.com

Class of drug: Gonadotropin releasing hormone agonist (GnRHa).

Indication in pediatric endocrinology:

1. Dynamic testing for the diagnosis of pubertal disorders
2. Treatment of gonadotropin dependent precocious puberty

Pharmacologic basis for GnRHa therapy: Suppression of the episodic secretion of gonadotropins by overriding the obligatory episodic release of GnRH with continual occupation of the GnRH receptors on the pituitary gonadotropes by high levels of GnRHa. GnRHa causes an initial LH and FSH release, followed, with adequate dosage, by down-regulation of responsiveness, including decrease in GnRH receptor numbers. Circulating gonadotropins levels decrease, with concomitant return of sex steroids to prepubertal levels. With adequate dosing, suppression occurs within weeks of the onset of therapy.

Adverse reactions: Injection site reactions, general pain, headache, acne, rash, seborrhea, emotional lability, vaginitis, vaginal bleeding vaginal discharge, anaphylaxis. Initial flare up in pubertal parameters may be observed due to agonist effect which can be kept suppressed with simultaneous administration of cyproterone acetate 100mg daily for the first one month.

Institution of Therapy

It is available as

a) short-acting injections for dynamic testing (20 mcg/kg/dose, with maximum dose of 500 mcg) and

b) intramuscular depot injections for treatment of precocious puberty. The dose for the monthly depot is ~300µg/kg: i.e. 3.75-15 mg per month. The 11.25 mg depot, which is given at 12 week intervals, offers greater convenience. Depending upon clinical response, either the dose can be adjusted, or the duration between doses altered. Depot preparations are usually available as dried powder, with solvents in prefilled syringes. Special care is needed for reconstitution and administration of the drug, as per the instructions provided.

Available preparations

Brand name	Manufacturer	Preparation	Approximate market price
Short acting injection			
Lupride	Sun (Inca)	1mg/0.5 ml	Rs 200
Luprofact	Zydus Cadila	1mg/0.5 ml	Rs 200
Progtase	Wockhardt	1mg/1 ml	-
Luprova	Celon (Evalife)	1mg/0.5 ml 4mg/4 ml	Rs 135 Rs 530
Intramuscular depot preparation			
Lupride depot	Sun (Inca)	3.75 mg 11.25 mg	Rs 4000 Rs 10600
Lupact depot	Celon (Pristilon)	3.75 mg 11.25 mg	Rs 3700 Rs 9300
Lucrin depot	Abbott	3.75 mg 11.25 mg	Rs 9250 Rs 15000
Luprova depot	Celon (Evalife)	3.75 mg	Rs 3900
Valeuprox depot	Xyata	3.75 mg 11.25 mg	Rs 4800 Rs 13600
Leusven depot	Sven Genetech	3.75 mg	-

… STEROID RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS (SREAT) *Contd from page 1*

… The hallmark of these disorders is cognitive impairment with varying grades of pyramidal/ extrapyramidal involvement, neuropsychiatric symptoms and seizure-like activity with diffuse slowing on EEG, essentially normal neuroimaging and CSF picture, demonstrable autoimmune antibodies in CSF and/or blood, with a dramatic symptomatic response to steroids, and a tendency to recur off steroids.

Amongst the autoimmune encephalopathies, paraneoplastic syndromes and those without cancer but with neural nonspecific serologic evidence of autoimmunity are the major groups. Amongst the latter, antibodies directed towards a) neurotransmitter receptors like NMDA/ AMDA or voltage gated potassium channels and, b) autoimmune thyroid antibodies are the 2 major subgroups. The former usually leads to a picture of limbic encephalitis, while the latter has been labeled as Hashimoto encephalopathy. Since the first description in 1966 by Brain et al of a patient with Hashimoto disease and encephalopathy, the term Hashimoto encephalopathy was used to connote an encephalopathy of presumed autoimmune origin characterized by high titers of antithyroid peroxidase (TPO) antibodies. Since anti-TPO antibodies do occur in the normal population as well as in many neurologic conditions, with characteristic response to steroids, the current view has been to abandon the link with Hashimoto, and rename these disorders as Steroid Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SREAT). A case vignette was presented in the last issue of CAPE NEWS. Carrying the attempt to increase awareness among our members further, the purpose of this article is to review this eminently treatable condition of childhood.

CASE DEFINITION

The following diagnostic criteria used by Castillo et al are the most comprehensive:

(1) encephalopathy: cognitive impairment and one or more of the following:

a) Neuropsychiatric features (e.g., hallucinations, delusions, or paranoia)

b) Myoclonus

c) Seizures - generalized tonic-clonic or partial

d) Focal neurologic deficits.

(2) Presence of serum thyroid antibody (TPO or microsomal)

(3) euthyroid status (serum sensitive TSH 0.3-5.0 mIU/L) or mild hypothyroidism (TSH 5.1-20.0 mIU/L) that would not account for encephalopathy;

(4) no evidence in blood, urine, or CSF analyses of an infectious, toxic, metabolic, or neoplastic process;

(5) no serologic evidence of the neuronal surface antibody syndromes (like voltage-gated calcium channel, voltage-gated potassium channel, or other currently recognized paraneoplastic autoantibodies to indicate another diagnosis);

(6) no findings on neuroimaging studies indicating vascular, neoplastic, or other structural lesions to explain the encephalopathy;

(7) complete or near complete return to the patient's neurologic baseline status following corticosteroid treatment.

EPIDEMIOLOGY

Prevalence is estimated to be 2.1 per 100 000 and it can affect children (usually teenage females) and adults. However, unawareness about this condition results in under-diagnosis, especially in younger children. No more than 200 cases of SREAT have been reported from all over the world till date; less than 50 of these are in children.

CLINICAL FEATURES

Presentation at Onset: acute or subacute; rarely chronic. There may be insidious development of cognitive impairment, or recurrent acute episodes of focal neurological deficit with confusion or seizures.

Natural History: Monophasic or remitting-relapsing course. While spontaneous remissions are also observed, dramatic response to corticosteroids within days/ weeks is characteristic.

Clinical Subtypes: Two distinctive clinical subtypes have been proposed - vasculitic and diffuse progressive. These may overlap and in a child may be impossible to differentiate.

a) Vasculitic presentation - stroke-like episodes and mild cognitive impairment.

b) Diffuse progressive presentation - Seizures have been reported to be the commonest presentation, followed by confusion, myoclonus, cognitive impairment and altered consciousness. Pyramidal, extrapyramidal, myelopathic or cerebellar involvements have also been described. Neuro-psychiatric features like psychosis, depression and dementia are well recognized and in rare cases may be the initial presentation.

In childhood, SREAT has been reported to be associated most commonly with epileptic seizures including status epilepticus at onset, behavioral problems ranging from rumination syndrome to breath holding spells, neurocognitive symptoms ranging from coma, stupor and confusion to subtle decline in school performance, and neuro-psychiatric manifestations like

acute personality changes, hallucinations, and psychosis. Extrapyramidal symptoms like ataxia, asymmetric chorea and cerebellar dysfunction, and myoclonus are also observed. Rare reports of optic neuritis and alternating hemiplegia also exist.

Associated Endocrinopathy: Most cases are euthyroid or subclinical hypothyroid though in some cases clinical hypo/ hyperthyroidism occurs at presentation. Apart from Hashimoto thyroiditis, Graves's disease also has been noted to be associated with SREAT.

Differential Diagnosis

Main subgroups include

a) Other autoimmune encephalopathies without cancer, but with neural nonspecific serologic evidence of autoimmunity like NMDA/ AMDA encephalitis
b) Paraneoplastic encephalopathies which present as limbic encephalitis
c) Central nervous system (CNS) vasculitis (primary or secondary)
d) Chronic CNS infections - Prion diseases especially Creutzfeld Jacob disease, HIV and neurosyphilis
e) Mitochondrial cytopathies especially MELAS.

ETIOPATHOGENESIS

While the exact mechanism remains controversial, vasculitis and autoimmunity directed against common brain-thyroid antigens represent the most probable etiologic pathways. Since thyroid hormones increase cortical serotonergic neurotransmission, and play an important role in regulating central noradrenergic and GABA function, antithyroid antibodies may interfere with the neurotransmitter pathways and result in the clinical picture of SREAT.

Apart from anti-TPO and anti-TG antibodies in serum and CSF, other autoantibodies, such as anti-parietal cell, anti-intrinsic factor, anti-alpha-enolase and anti-dimethylargininase-1 antibody may be seen in SREAT. The time lag between evidence of autoimmunity and presentation of SREAT is well documented. In the absence of a strong correlation between disease severity and antithyroid antibody titers, one school of thought considers SREAT as a mere endpoint manifestation of non-structural abnormalities of CNS function resulting in coincidence of endocrinopathies, epilepsy and psycho-neurologic disorders in children and adolescents. Thyroiditis and encephalopathy may just represent two concurrent autoimmune diseases.

Though this is considered as a non-vasculitic disorder, lymphocytic vasculitis of cerebral venules and arterioles, lymphocytic perivascular cuffs and microglial activation have been documented in a few cases who underwent brain biopsy prior to steroid therapy. Biopsy proven primary CNS demyelination has also been seen.

INVESTIGATIONS

Laboratory

The most frequent laboratory abnormalities were increased liver enzyme levels and increased ESR. Increased serum TSH is common even if hypothyroidism is clinically not evident. Serum ammonia level may be elevated, especially in the presence of hypothyroidism. Evidence of intrathecal inflammation in CSF occurs in <25% cases. Spinal CSF protein is elevated in most cases; pleocytosis is rare. CSF oligoclonal bands are noted in a few cases. **While the most important diagnostic clue is elevated levels of thyroid antibodies, especially anti-TPO, it is important to realize that the initial autoantibody screen may be negative and there may be a long time lag between the neurological symptoms and appearance of detectable autoantibodies.**

Neurophysiology studies

Apart from ruling out other causes of encephalopathy, EEG findings often parallel the disease activity, improving with improvement in the clinical condition and worsening during recurrence. Generalized or rhythmic bifrontal/ temporal slow wave abnormalities are commonest, followed by occasional focal spikes, triphasic waves, epileptiform abnormalities, photomyogenic response, and photoparoxysmal response. Myoclonic jerks may not have an EEG correlate. Anticonvulsant therapy is not helpful and may even worsen EEG features.

Neuroimaging

Usually the brain CT and cerebral angiogram are normal. Isotope brain SPECT may show patchy abnormal uptake reflecting impaired microvascular cerebral perfusion. Focal/ diffuse non-enhancing MRI abnormalities are seen in 50% of adult patients with SREAT; in children mostly the MRI is normal. Diffusion-weighted MRI may detect changes suggestive of vasculitis in the form of small, active ischemic areas, which improve with therapy. Rarely, there will be evidence of meningeal enhancement or increased fluid attenuated inversion-recovery signal in symptomatic regions on MRI.

Neuropsychological Assessment

Formal neuropsychological assessment after recovery can detect subtle abnormalities early on and can guide long-term steroid therapy.

MANAGEMENT

Immunosuppression

Corticosteroids

While no specific best regime has been recommended, the usual strategy has been to use IV methylprednisolone 10-20 mg/kg/day (max up to 1 gm/day) for 3-7 days followed by oral prednisolone (1–2 mg/kg/day, max 60 mg/day) for 6-8 wk. In less severe cases without coma, oral prednisolone alone, slowly tapered over weeks/ months depending upon the clinical course of the disease also has been used. IV high-dose dexamethasone (up to 8 mg q 8hrly) can be a cheaper and equally effective alternative. Despite treatment, patients may experience relapses, and adolescents with this condition may experience residual cognitive deficits.

Non-corticosteroidal agents

Steroid intolerant/resistant cases may respond to cyclosporine, azathioprine, methotrexate or chloroquine. *Plasmapheresis/ Plasma Exchange/ Immunoglobulins have been used for recurrent remitting steroid resistant cases.*

LONGTERM PROGNOSIS AND FOLLOW-UP

While monophasic forms have a dramatic response to steroids, children with neuropsychiatric and behavioral abnormalities as the presentation may require long-term immunosuppression. Persistent long-term cognitive deficits and relapsing courses were identified in >20% children. Steroid therapy may be guided by neuro-psychological assessment. The antithyroid antibody titers may be a marker of treatment response but their long-term significance is not clear. One must look for other auto-immune endocrinopathies apart from thyroiditis in these cases. Though most cases are euthyroid at presentation, periodic monitoring in cases of recovered SREAT must be maintained for early identification of clinical hypothyroidism/ hyper-thyroidism and specific therapy.

CONCLUSIONS

Hashimoto encephalopathy or SREAT remains a fascinating but poorly understood clinically and electrographically heterogeneous steroid-responsive encephalopathy associated with thyroid autoantibodies. A high level of suspicion is necessary to establish the diagnosis in cases of 'investigation negative' acute or subacute encephalopathy and the diagnosis is often overlooked at presentation. Early recognition by measurement of antithyroid antibody titers if standard thyroid function tests are normal, and prompt steroid treatment, may lead to a favorable prognosis. Neuropsychological assessment is important in all cases.

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PEDENDOCON 2012 COIMBATORE: 13 May

Meenakumari Mohan, meenapaed@gmail.com

On behalf of Indian Academy of Pediatrics [IAP] and Indian Society of Pediatric & Adolescent Endocrinology [ISPAE], a regional CME in pediatric endocrinology was conducted at Aloft Hotel in Coimbatore on 13.05.12. The one day program was a great opportunity for practicing pediatricians and pediatric trainees in the region to update existing knowledge and to learn about new modalities of treatment. It was well attended with 125 delegates, who were benefited from the sessions on short stature, hypothyroidism, hypocalcemia, type 1 diabetes, DKA, childhood obesity, rickets, metabolic bone disorders, disorders of sexual differentiation and pubertal disorders. The topics were covered by two international faculty members, Dr Zulf Mughal and Dr Raja Padidela from Manchester, UK and Dr Anju Seth, Dr Anurag Bajpai, Dr Vaman Khadilkar and Dr Meenakumari Mohan, as national faculty members. Some ***pearls*** from this meeting:

** At each clinic visit, not just the weight, but also the height, should be measured, and also plotted on an appropriate growth charts, so that any faltering (gain or deficiency) can be addressed early.

** Since childhood obesity and thereby childhood type 2 diabetes on the increase, pediatricians should intervene early and appropriately with advice about diet and exercise.

** Insulin therapy should be advised in a physiological way by via basal bolus therapy (pump or MDI). The conventional 2 dose split-mix regimen gives poor control, and poor flexibility of lifestyle.

** Measurement of blood glucose is mandatory in any unwell child, especially in an ICU setting, so that DKA is not missed.

** Vitamin D deficiency is extremely common, so adequate supplements should be provided.
** Hypocalcemia can present as benign intracranial hypertension, dilated cardiomyopathy, stridor, recurrent seizures.
** Activation of HPG axis indicating onset of puberty correlates more with bone age than chronological age. Properly assessed bone age is essential in pediatric endocrinology.
** The commonest cause of symptomatic thyromegaly is autoimmune thyroiditis, followed by dyshormonogenesis.

** While dealing with families of children with disorders of sexual differentiation, we must make sure honesty and confidentiality are maintained at all times.

TALKS BY PROFESSOR RON ROSENFELD: CHENNAI, DELHI, MUMBAI

Mid July, we were fortunate to hear Prof Ron Rosenfeld, on "Optimizing Growth Hormone Treatment in Pediatric Indications". Dr Rosenfeld is Professor of Pediatrics at Oregon and Stanford, President of STAT5, LLC, and past president of LWPES. As part of the International Speakers' Program organized by Pfizer, he spoke in Chennai on the 13th, Delhi on the 14th, and Mumbai on the 15th. In **Chennai**, 46 pediatricians and endocrinologists from Tamil Nadu, Kerala, Karnataka and Hyderabad attended the meeting, which was preceded by an Expert Group Meeting of 15 doctors with Dr Rosenfeld. After the talk was a panel discussion chaired by Dr Usha Sriram, moderated by Dr Jaishree Gopal; panelists were Drs RV Jayakumar, Rakesh Sahay & PG Sunderaraman.

The **Delhi** Meeting was attended by 70 pediatricians and endocrinologists. The post-talk panel discussion was chaired by Dr Anju Virmani, moderated by Dr Archana Arya, with included Dr Anurag Bajpai. A local ISPAE meeting, chaired by Dr Sangita Yadav and moderated by Dr Anju Seth, preceded the meeting, where some cases which are difficult to manage were discussed. and organized and chaired this session.

The **Mumbai** Meeting was attended by 76 pediatricians and endocrinologists from Maharashtra, Gujarat, Kolkata, and Andhra Pradesh. The open discussion was moderated by Dr Nalini Shah.

CDiC TRAINING PROGRAMS

The theme of the continuing series of Diabetes Education Training Programs for health care professionals being organized as part of the Changing Diabetes in Children (CDiC) program by Novo Nordisk Education Foundation is "Treating Diabetes in Children is different from treating diabetes in adults."

After meetings in Hyderabad and Mumbai in April, a regional meeting was held in Indore on 12th August. Conducted by Dr Anju Virmani and Dr Ganesh Jevalikar, and attended by nearly 20 physicians caring for diabetes from Indore, Ujjain and nearby areas, it was much appreciated.

The next meeting at Kanpur on 26th August, was organized by Drs Rishi Shukla, Deepak Yagnik, Bhaskar Ganguli, Praveen Sachdeva, and also Shuchy Chugh, diabetes educator from Novo. It was inaugurated by Dr Rashmi Kapoor, conducted by Dr Shukla, Dr Anuj Maheswari, Dr Anurag Bajpai and Dr Virmani, and attended by 38 doctors from

Kanpur and suburbs, Faizabad, Farukkabad and Lucknow.

In each session, talks were interspersed with case discussions: each participant discussed briefly a pre-allotted case scenario. This made the program very interactive, with everyone learning from others' experiences. The next meeting is scheduled in Aurangabad.

OTHER ACTIVITIES in/ around KANPUR

Anurag Bajpai, dr_anuragbajpai@yahoo.com

Celiac Society of Kanpur meeting, Regency Hospital: 12 June 2012

The Celiac Society of Kanpur meeting organized at Regency Hospital was attended by 60 children and their families. There were awareness lectures by Dr Rashmi Kapoor (pediatrician), Dr Arun Khanduri (gastroenterologist) and Dr Anurag Bajpai. *"Living with Celiac Disease"* a booklet in Hindi was launched on the occasion. The opening of the first gluten free shop in the region was announced during the meeting.

IAP Allahabad CME, Allahabad: 28 July 2012

Dr Bajpai delivered an informative talk on Calcium and Vitamin D in Pediatric Practice at IAP Allahabad, followed by an interactive panel discussion with pediatricians, orthopedic surgeons, and gynecologists.

IAP Lucknow Growth Workshop, Era Medical College, Lucknow: 12 August 2012

The Vth Growth Workshop in the series of growth modules was held at Era Medical College, Lucknow under the auspices of Lucknow Academy of Pediatrics. The faculty Drs Shrish Bhatnagar, Rafaul Kabeer and A Bajpai imparted practical knowledge regarding management of growth failure to 52 participants.

Growth Hormone Support Group Meeting, Regency Hospital: 13 Aug 2012

The first meeting of the newly formed *"Growth Hormone Support Group"* was conducted at Regency Hospital with participation of 52 children and their families. Dr Rashmi Kapoor (pediatrician), Dr Alok Bajpai (child psychiatrist) and A Bajpai (Secretary of the support group) discussed issues dealt by children on GH. Dr Bajpai informed that the group would work towards increasing awareness and making GH easily accessible for children.

Obesity Awareness Lecture and Camp, DPS Kalyanpur: 1 August 2012

Academy of Pediatrics, Kanpur and DISHAA (a nation-wide initiative for prevention of childhood obesity) conducted a Life Style Counseling program for students of Delhi Public School (DPS), Kalyanpur. Dr Bajpai enlightened the over 700 students who attended about the adverse impact of adolescent obesity and measures to prevent them. Dr AC Agrawal mentioned the life style diseases caused by adolescent obesity. Following this, growth and adiposity assessment of 630 students was done. A staggering 18% were found to be overweight and 5% obese. The students were provided educational material for life style modification along with letters to the parents.

CHARITY ACTIVITY AT SIDHBARI, HP

Anju Virmani, virmani.anju@gmail.com

ISPAE supported Dr Anju Virmani's annual Diabetes Endocrine camp at Chinmaya Organization for Rural Development (CORD) in Sidhbari, Dist Kangra, Himachal Pradesh. Dr Anjali Chavan, Nurse Sheetal Desai, Dr Harshita Singh (ophthalmologist) and Dr Tushar Sontake volunteered. ISPAE funds were used to provide subsidized glucostrips and insulin. A local lab, Naseeb Diagnostics, subsidized A1C, lipids and other tests. Families of young diabetics were also given diabetes education, and provision to come for follow up medical care and blood glucose testing by Dr Ishwar Sood and health worker Ms Darshana.

CONGRATULATIONS!

Our Executive Council member, Dr Ganesh Jevalikar, went for a 3 month observership in Melbourne with Dr Margaret Zacharin. He did a great basic science project, learnt a lot of statistics and molecular biology, gave talks, wrote two papers and is preparing two more.

MORE NEWS FROM DOWN UNDER

Margaret Zacharin, *Margaret.Zacarin@rch.org.au*

Global Pediatric Endocrinology & Diabetes (GPED) is a non-profit organization established in 2010 that

aims at improving the care of children in developing countries with endocrine disorders through the provision of training and educational opportunities, developing research studies and promoting advocacy. I have been fairly busy with education issues for GPED over the past year.

1.Over 2011 I put together and edited a book of Paediatric endocrinology in a limited resource setting, written by paed endos from all over the world, and published through the generosity of Serono, Australia, who paid for all the editing and publication costs as well as 1000 copies to be distributed free to those in need. To date we have given them to various centres in Africa where ESPE staff undertake teaching projects, to Winter school students in Kiev and for 2013 in Poland. We will also distribute 400 copies to those who are in financial difficulty, at this year's ESPE meeting in Leipzig.

2. Recently I have negotiated successfully with Elsevier USA and a contract has been offered is now ready to sign, for world -wide distribution for sale as hard cc and ebook. Royalties look promising, with all proceeds to go to GPED for research, projects etc.

3. Hindi versions of parent information books are being prepared and paid for by Serono, India, under the supervision of Viji Bhatia. I am negotiating with Serono to do Spanish and French versions, which will cover the Maghreb and South America.

4. JP Chanoine has worked hard on producing a website for GPED (www.globalpedendo.org).

5. Ze'ev Hochberg, JP Chanoine, Fernando Cassorla and I collaborated in trying to secure a grant from the Gates Foundation for a project on IUGR in India but were unsuccessful at the time - no doubt another attempt will be made. Preliminary talks have been undertaken with LHMC Delhi and CMC Vellore.

6. I hope to undertake some more exchange with India through programs made available via the Australia-India council.

FORTHCOMING MEETINGS

1. **PEP 2012**: Clinical workshop: Pediatric Endocrinology for postgraduates: Bengaluru: 15-16 September, 2012. Contact: P Raghupathy drp.raghupathy@gmail.com; Shaila S Bhattacharyya shailashamanur@gmail.com

2. **ESPE 2012**: 51st ESPE Meeting: Leipzig, Germany: 20-23 September, 2012. Email: espe@eurospe.org

3. **ISBMR 2012**: Annual Meeting: SGPGI, Lucknow, UP: 29-30 September 2012. Details on ISBMR website.

4. **ISPAD 2012**: 38th Annual Meeting: Istanbul, Turkey: 10-13 October 2012.

5. **RSSDI 2012**: 40th Annual Meeting: Chennai: 26-28 October 2012. Theme for MMS Ahuja Symposium: Adolescent Diabetes; for Nutrition Symposium: Regional Differences in Food Consumption Patterns and Glucose Intolerance. Details: www.rssdi2012.com.

6. **ISPAE-ISPAD Symposium on Childhood Diabetes 2012**: AIIMS, New Delhi: 4-5 November 2012. Contact: Vandana Jain/ Rajesh Khadgawat at child.diabetes.ispae@gmail.com,

7. **APPES SCHOOL 2012**: Fellows' Meeting: Nausa Dua, Bali, Indonesia: 10-14 November 2012. email: appes@willorganise. com.au.

8. **APPES 2012**: 7th Biennial Scientific Meeting: Nausa Dua, Bali, Indonesia: 14 - 17 Nov 2012. email: appes@willorganise. com.au. Website: www.appes2012.com.

9. **ISPAD Research Course 2012**: Lodz, Poland: 16 - 21 Nov 2012. General Information: http://www.ispad.org/EventFiles/ISPAD%20Research%20Course%202012.doc. More information: http://pediatria.umed.pl/ispadschoolpoland/. Online Application Form http://pediatria.umed.pl/ispadschoolpoland/Registration.aspx. Wojciech Mlynarski, email: wojciech.mlynarski@umed.lodz.pl.

10. **ESICON 2012:** 42nd Annual Meeting of the Endocrine Society of India: Kolkata: 13-15 December, 2012. Organizing Secy: Dr Subhankar Chowdhury, esicon2012@gmail.com

11. **PEDICON 2013:** 50th Annual Meeting of the IAP: Science City, Kolkata: 17-20 January, 2013. Organizing Secy: Dr Jaydeep Choudhry, www.pedicon2013.org

12. **PES 2013:** Annual Meeting of Pediatric Endocrine Society (USA) (formerly LWPES): Washington DC. 4-7 May, 2013.

13. **ENDO 2013:** Annual Meeting of the Endocrine Society: San Francisco, USA. 15-18 June, 2013. Email: societyservices@endo-society.org

14. **ESPE-PES**: 9th Joint ESPE/ PES Meeting: Milan, Italy: 19-22 September, 2013. Email: espe@eurospe.org

15. **ISPAD 2013**: 39th Annual Meeting: Gothenburg, Sweden: 16-19th October 2013.

16. **PES 2014:** Annual Meeting of the PES: Vancouver, Canada. 3-6 May, 2014.

17. **ENDO 2014:** Annual Meeting of Endocrine Society: Chicago, USA. 21-24 June, 2014. Email: societyservices@endo-society.org

18. **ESPE 2014**: 53rd ESPE Meeting: Dublin, Ireland: 18-21 September, 2014. Email: espe@eurospe.org
19. **ISPAD 2014**: 40th Annual Meeting: Toronto, Canada.
20. **PES 2015:** Annual Meeting of the PES: San Diego, CA. 25-28 April, 2015.
21. **ENDO 2015:** Annual Meeting of the Endocrine Society: San Diego, CA. 20-23 June, 2015. Email: societyservices@endo-society.org
22. **ESPE**: 54th ESPE Meeting: Barcelona, Spain: 9-12 September, 2015. Email: espe@eurospe.org
23. **ISPAD 2015**: 41st Annual Meeting: Brisbane, Australia.
24. **PES 2016**: Annual Meeting of the PES: Baltimore, Maryland. 30 April-3 May, 2016.
25. **PES 2017**: Annual Meeting of the PES: San Francisco, California. 6-9 May, 2017.

MEMBERS' PUBLICATIONS

Kalra P, Das V, Agarwal A, Kumar M, Ramesh V, Bhatia E, Gupta S, Singh S, Saxena P, Bhatia V. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. Br J Nutr 2012; 1: 1 - 7.

Durba Pal, Suman Dasgupta, Rakesh Kundu, Sudipta Maitra, Gobardhan Das, Satinath Mukhopadhyay, Sukanta Ray, Subeer S Majumdar, & Samir Bhattacharya. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. Nature Medicine.

NEWS YOU CAN USE

ISBMR 2012 is to be held in SGPGIMS Lucknow on 29-30 September 2012. Eminent overseas speakers include Ian Reid from New Zealand and Sudhakar Rao from USA. Details are available on the ISBMR website.

APPES early bird fee extended, Poster submission open!

Do not miss the chance to register for the APPES Annual Scientific Meeting at the Early Bird rate, now available until Friday 14th September. Poster submissions have to be done before Friday 28th September. You can register online or submit your poster at the conference website: www.appes2012.com.

ESICON 2012 at Kolkata in December, 2012, has a themed symposium on pediatric endocrinology. Dates for registration have been extended!

First Practical Pediatric Endocrinology Workshop
October 27-28 2012, Kanpur

Organized by: Dept of Pediatric Endocrinology, Regency Hospital, Kanpur & Academy of Pediatrics, Kanpur

This two-day program would focus on practical issues related to Pediatric Endocrinology encountered by pediatricians in their daily practice. Six case based modules on Growth, Puberty, Thyroid, Calcium and bone, Glucose metabolism, and Electrolyte imbalance would be executed by eminent Pediatric Endocrinologists. The program is particularly suited for Pediatric Postgraduate Trainees and Practicing Pediatricians. The participants would be provided a comprehensive resource book with algorithms and case based approach to all topics covered during the program. The number of delegates would be limited to ensure active interaction.

For ***Registration*** please contact Dr Anurag Bajpai, Consultant Pediatric & Adolescent Endocrinologist, Dept Pediatric Endocrinology, Regency Hospital Limited, A2 Sarvodaya Nagar, Kanpur 208005, UP. dr_anuragbajpai@yahoo.com, Tel +91 9454081769, Fax- 0512-2213407.