CAPE NEWS

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From the Editor's desk

Firstly, I thank the ISPAE office bearers for giving me an opportunity to work as Editor of CAPE NEWS and providing me a wonderful Editorial team to work with. I also thank the previous Editorial team who have done a wonderful job to provide CAPE NEWS a new perspective.

My special thanks to Dr Anju Virmani, the backbone of CAPE NEWS, for joining back the team to help lead it to new horizons. In the current issue, she has put whole hearted efforts to make this a fantastic issue. I thank all my team members for their active participation in designing this issue and for their valuable contributions.

Dr Vijaya Sarathi H A, Editor, CAPE NEWS

A Tribute to a legend: Dr Ammini AC

Prof Ariachery Ammini, former Professor and Head of the Department of Endocrinology at the All India Institute of Medical Sciences, New Delhi, passed away in New Delhi on 20 April 2015 after a recently diagnosed illness. She was 66 years old.

I had known Dr Ammini for about four decades now. We came into contact with each other while doing post-graduation at AIIMS, New Delhi. Dr Ammini had joined after graduating from Maulana Azad Medical College, New Delhi. After doing post-graduation in Internal Medicine, she went back to her native state, Kerala, and joined the Department of Neurology at Sree Chitra Thirunal Institute of Medical Sciences, Thiruvananthapuram, for a brief period. We were pleasantly surprised when she joined the DM program at the Postgraduate Institute of Medical Education and Research, Chandigarh. She joined as a faculty member in the Department of Medicine at AIIMS in November 1980, and was one of the founder faculty members when the Department of Endocrinology was set up at AIIMS, along with Prof MMS Ahuja, Prof N Kochupillai, and Prof MG Karmarkar. She also had special training with international experts such as Prof Maria New at New York, USA, and Prof Maguelone Forest at Lyon, France. She became Professor of Endocrinology in July 2001, and superannuated as Head of the Department in June, 2014.

She was a brilliant student, an astute clinician, an avid academic reader, and yet very humble and quiet in demeanour. She was a physician with few words; yet very attentive to the needs of the vast variety of patients and their families. She was a very good listener, a caring and gentle doctor, who would often make interesting observations about patients and the course of illness. She was a brilliant teacher and a prolific writer, immensely liked and admired by her students, research collaborators and faculty colleagues. Her clinical presentations were great learning experiences. All this made her a very popular and admired teacher in various pediatric (and adult) endocrine programs throughout the country. She was a regular attendee at ISPAE scientific meetings, and contributed immensely with her learning and gentle wisdom. Needless to say all of us learnt a lot interacting with her and I cherish every moment of those days. Her sudden and untimely demise has left a vacuum in the field of endocrinology and is a huge loss to us in the pediatric endocrine community.

Personally speaking, her demise is a great loss to our family and we are still grieving. We shared a common floor as faculty and had wonderful academic interactions. At the campus at Ansari Nagar and later the Asian Games Village, we were neighbours, where our children grew together. She was always there with a helping hand whenever we needed any medical help. We will miss her.

May her soul rest in peace!

Dr P S N Menon

Secretary's Message

Dear members,

Congratulations to Dr Vijaya Sarathi and his team for bringing CAPE NEWS with newer ideas and latest information. All the editions of CAPE NEWS, the official news letter of ISPAE, published last year were wonderfully informative, for which the whole credit goes to the team headed by Dr Archana Arya and Dr Hemchand Prasad.

This year we are conducting the 4th ISPAE Biennial meet at Gurgaon from 27th to 29th November, along with ISPAE PET from 24th to 27th of November. Dr Ganesh Jevalikar and his team are doing a wonderful job to make it a grand success. We request all the members to register and make this event a grand success.

We have already circulated the bids for applying for the next ISPAE Biennial meet to be held in 2017 and also for the midterm meet proposed in 2016. Members are requested to go through the guidelines and apply for these prestigious events of ISPAE.

You will find in this issue a report by Dr V Bhatia on the International Consortium for pediatric endocrinology. ISPAE is represented in this Consortium, which is in the nascent stages of formation. Members who have regularly attended the Joint Meetings of pediatric endocrinology, which were organised by the ESPE or the PES alternately, every 4 years, will be interested to know that this meeting will now be organised by the Consortium, in international locations.

It was decided to give the ISPAE Observership Awards 2015 to 2 members - Dr Sanjay Kumar and Dr Deepty Kumar. They will be doing their training from Bharati Vidyaphith University, Pune, and SGPGI, Lucknow, respectively. We congratulate them for being selected, wish them all the best, and request them to use their knowledge for the betterment of little children affected by various endocrine problems, and thus make the flag of ISPAE fly high.

We have also announced ISPAE Charity Awards 2014. The Charity Committee decided to give reimbursements to 2 of our members, Dr Ganesh Jevalikar and Dr Hemchand Prasad. You will see reports of their activities later in this issue. I hope these gestures on our part will encourage all members to do more and more charity related activities for needy children.

Our website has come out with a new look and has become more user-friendly, with lots of space dedicated for latest information. We congratulate the previous team with the able leadership of Dr Shaila Bhattacharyya, and the new team headed by Dr Karnam Ravikumar, who had already shown his capability earlier.

The dedicated work of our members under the banner of ISPAE has created a lot of interest in the field of pediatric endocrinology among our young generation of Pediatricians. On behalf of ISPAE we invite all the new members to this group.

With best wishes

Dr M. Vijayakumar

Challenges in the Diagnosis of Obesity and Metabolic Syndrome in Children

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Introduction

The American Medical Association has recognized obesity as a disease, and childhood obesity is not an exception to this. Recently World Health Organization (WHO) stated that the problem of obesity is global and steadily affecting many low and middle income countries, particularly in urban settings [1]. Approximately 21-24% of American children and adolescents are overweight, and another 16-18% are obese [2]. Various studies in India have also shown the increasing prevalence of overweight and obesity. A meta-analysis of nine studies including 92,862 subjects estimated the prevalence of overweight to be 12.64% (95%CI: 8.48-16.8%) and of obesity to be 3.39% (95%CI: 2.58-4.21%) [3].

Body mass index (BMI) is a simple, cheap and reliable screening tool for adiposity in adults, but in children and adolescents is less sensitive than waist circumference (WC) [4]. BMI assessments do not reflect fat distribution or lipid partitioning in specific fat depots, which in turn decide the relation of obesity and peripheral insulin resistance (IR). Perhaps for these reasons, an American Heart Association statement has recommended the inclusion of WC measurements in evaluating children for IR or the metabolic syndrome (MS) [5]. There are many criteria in vogue for definition of MS in adults, but in children there is even less consensus, since the impact on CV risk in adulthood is less clear. Perhaps MS score (discussed below) may help predict adult cardiovascular (CV) risk better.

Does BMI underestimate obesity in children?

There are several fallacies in using BMI to estimate obesity in children. In childhood, the age (since normal BMI changes with age in children), sex, and ethnicity specific BMI centile has to be looked at as a measure of obesity. Moreover, BMI cannot differentiate between muscular individuals (e.g. athletes have higher lean body mass) and fatty individuals, both of whom may have same BMI. Shaw et al (UK) demonstrated that from age 5 years onwards, South Asian girls and boys have higher percentage body fat compared to White or African Caribbean ethnic groups, the difference increasing with age [6]. BMI percentile graphs are not available to define obesity in children less than two years of age. Finally, up to 25% of children with normal BMIs will have an excess amount of fat when measured by other means [7]. Hence WC centile is a better parameter than BMI centile to assess childhood obesity.

Definition of obesity according to CDC and KN Agarwal data

1. **Overweight**: Children having BMI ≥ 85 centile but < 95 centile are called overweight.
2. **Obese:** Children having BMI centile ≥ 95 centile are called obese.

Ideally, we need data based on a large, multiregional population representing the whole country, for developing reference growth charts. Recent IAP growth charts have BMI centile charts and tables for 5-18 years old children with adult equivalent cut offs which are more relevant for Indian children [8]. BMI centiles are sometimes fallacious. Here is an example demonstrating limitation of BMI percentiles charts.

	Case 1	Case 2
Age/sex	5 yr 2 mo old boy	12 yr old girl
Weight (kg)	11.7	40.3
Height (cm)	87.5	137
BMI (kg/m^2)	15.3	21.5
BMI centile according to KN Agarwal chart	75th-85th	75th-85th
Examination findings	Pallor, pot belly, hepatomegaly	

Both children have the same BMI centile, but one is malnourished, with retardation of both height and weight, and perhaps with some edema; the other looks overweight.

In India, central obesity is more prevalent than general obesity. The central distribution of fat correlates with higher CV risk, and WC has been shown to be the strongest correlate of central fat distribution in children. Hence WC is a measure of central obesity, and a WC cut off of 71 cm is useful in diagnosing central obesity [9]. Indian data on childhood WC percentiles is very limited; Kuriyan et al studied 9060 children to create age and sex specific WC percentile charts, and found that WC of Indian children was higher than that of age and sex matched European children. A WC of more than 75thpercentile is called abdominal obesity [10].

Challenges in the diagnosis of MS in children

Obesity in children does not necessarily mean that MS is invariably present. However, in general, as in adults, childhood obesity also predisposes to IR and type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, liver and renal dysfunction, and reproductive dysfunction. Childhood, especially adolescent, obesity also increases adult onset obesity and CV disease [11], with 80% of obese teenagers continuing on to becoming obese adults. We did a retrospective analysis of prevalence of co-morbidities in children weighing more than normal, in our tertiary care referral center, and found pre-diabetes in 64.3%, T2DM in 3.8%, pre-hypertension in 33.9% and hypertension in 23.07% [12]. It is therefore of clinical relevance to identify children who are at risk, as early in childhood as possible, as they would probably benefit from lifestyle modifications, and a definition of MS that guides clinical practice would be useful.

Existing definitions of pediatric MS

Various definitions of pediatric MS [13] are listed in table 2. All definitions share some common features:

1. An obesity element (WC or BMI)

2. Dyslipidemia elements (elevated triglycerides and low HDL cholesterol)

3. Elevated blood pressure (BP)

4. A dysglycemia component (impaired fasting glucose or impaired glucose tolerance)

Table 1: Various definitions of pediatric MS [13]

Definition	***Excess adiposity***	***Blood pressure***	***Serum lipids***	***Plasma glucose/ serum insulin***
Cook *et al.*	WC ≥ 90th percentile	Systolic BP (SBP) or Diastolic BP (DBP) ≥ 90th percentile	Triglycerides 110 mg/dl or HDL-cholesterol ≤ 40 mg/dl	Fasting plasma glucose ≥ 110 mg/dl
Viner *et al.*	BMI ≥ 95th percentile	SBP ≥ 95th percentile	Triglycerides ≥ 150 mg/dl or HDL-cholesterol < 35 mg/dl or Total cholesterol ≥ 95th percentile	Fasting serum insulin ≥ 15 mU/l or fasting plasma glucose ≥ 110 mg/dl
IDF (International Diabetes Federation)	WC ≥ 90th percentile	SBP ≥ 130 mmHg or DBP ≥ 85 mm Hg	Triglycerides ≥ 150 mg/dl or HDL-cholesterol < 40 mg/dl	Fasting plasma glucose ≥ 100 mg/dl
NCEP ATP III	WC > 90th percentile	SBP ≥ 90th percentile or DBP ≥ 90th percentile	Triglycerides ≥ 110 mg/dl or HDL-cholesterol < 40 mg/dl	Fasting plasma glucose > 110 mg/dl
IDEFICS-monitoring level	WC ≥ 90th percentile	SBP ≥ 90th percentile or DBP ≥ 90th percentile		Homeostatic model assessment-insulin resistance (HOMA-IR) ≥ 90th percentile or fasting plasma glucose ≥ 90th percentile

Firstly, all these definitions are based on population-derived percentile thresholds for each component. Secondly, all definitions use each component of the cluster as a dichotomous variable (dichotomous variables are nominal variables which have only two categories or levels), defined by a threshold, and share the concept that all components have an equal "value" in the cumulative score. These two principles simplify the use of such definitions in everyday practice, yet seem problematic in the sense that CV risk factors such as elevated fasting glucose and triglycerides or the degree of obesity, represent continuous variables that signify risk, not necessarily in a linear fashion. Thus, for example, increasing BMI during childhood represents a continuous risk factor for the development of coronary heart disease in adulthood, even within the normal BMI range [14]. It has been shown in adults that the presence of some combinations of components of the syndrome confer a worse prognosis than others, although no such data exists for pediatric populations.

Ideally how should MS be defined in children?

An ideal definition should have the following features:

1. The components should be easy to measure and represent a “stable” diagnosis, similar to other conditions and syndromes typically diagnosed in childhood.

2. The anthropometric and biochemical components should be ethnicity specific and derived from outcome data of the relevant population.

3. The definition should be able to reliably predict future clinical outcomes.

Limitations in defining MS in Indian children

1. There is no large population based Indian data available for WC and BP.

2. There is wide data variation among low, middle, and high socioeconomic status populations.

3. Parents, and society at large, do not accept obesity in childhood as a disease, till complications occur (e.g. T2DM or hypertension).

Should other components be included in the definition of MS in childhood?

Additional elements not included in traditional definitions of pediatric MS, which can significantly improve the predictive value of having MS in adulthood, are positive family history of T2DM or CV disease, low birth weight and early catch up growth, "early versus late growth" and maturation patterns, socioeconomic status in childhood, sedentary behaviour, and specific dietary constituents. Besides this, certain visceral-fat-derived inflammatory markers like increased levels of interleukin 6, C-reactive protein, tumor necrosis factor-α and decreased levels of adiponectin can be other factors accompanying the classic components of MS, which would help in predicting MS in adulthood [14].

Prevalence of MS

Friend et al reviewed pediatric MS literature till 2013 [15]. When all studies were considered, the median prevalence of MS in whole populations was 3.3% (range 0%-19.2%), in overweight children was 11.9% (range 2.8%-29.3%), and in obese populations was 29.2% (range 10%-66%). Within-study analyses confirmed higher prevalence for obese compared to overweight ($P=0.012$) and obese compared to non-obese, non-overweight children ($P<0.001$). Within-study analyses also revealed higher median MS prevalence for boys compared to girls (5.1% vs. 3.0%, $P<0.001$) and for older compared with younger children (5.6% vs. 2.9%, $P=0.001$).

Does MS in childhood have predictive value?

It has been shown in several longitudinal cohorts that meeting the criteria of MS in childhood predicts the development of CV disease and T2DM in adulthood, increased intimal-medial thickness in childhood and adulthood. The presence of childhood obesity seems to be the strongest predictor of MS in adulthood [14].

How stable is the diagnosis of MS in childhood?

The individual components of MS have been shown to track from childhood to adulthood, emphasizing the importance of identifying abnormalities early in the life course [14]. Tracking of the clusters of the components during an 8 yr follow up has been shown to be stronger than the tracking of individual components [14]. The diagnosis of the syndrome as a whole during a follow up of 1-3 yr

in adolescents was shown to be relatively unstable in many studies, which may be due to the hormonal changes of puberty that induce a transient significant reduction of peripheral insulin sensitivity, the pubertal growth spurt, and the limited reproducibility and reliability of a single assessment of BP and glucose metabolism parameters in this age group [14].

Rather than simply dichotomising the population into healthy (no MS) and unhealthy (MS) children using an arbitrary cut-off, the MS score provides a more 'physiological' variable that accounts for gradual changes, and thus better reflects the continuum between a (putatively) unhealthy and a healthy metabolic profile. Such a continuous variable is particularly useful for research purposes and the evaluation of interventions [13].

For children we have no reliable data with regard to the relative impact of each component on the incidence of CV and metabolic diseases later in life. As argued before, given this lack of knowledge with regard to the predictive value of each component of MS, the best decision seems to be to assign equal weights to each parameter. This is assured by a statistical approach. Statistically the MS score can be calculated by the following formula [13]:

MetS score: $-z_{WC}+(z_{SBP}+z_{DBP})/2+(z_{TRG}-z_{HDL})/2+z_{HOMA}$.

Strength of the MS score

It accounts for age- and sex-specific distribution of its parameters. The parameter estimates are valid for a large, heterogeneous and unselected population of healthy pre-adolescent children. Age- and sex-specific cut-offs for the two proposed definitions of MS score with the 90th percentile corresponding to the monitoring level, and the 95th percentile corresponding to the action level, are very useful.

Limitations of score

The parameter values included in the score are population-specific. Smaller populations may reveal different distributions; therefore it is desirable to provide data for the calculation of the MS score in individuals or other populations using a large and diverse sample.

Conclusion

The obese adolescent is more likely to be an obese adult (80% chance). BMI centile is the most popular measure of obesity in children, but it does not necessarily predict CV and metabolic risk in adulthood, MS being a more useful predictor. The MS score is an even better predictor than defining simple MS in the pre-adolescent age group. Age- and sex-specific cut-offs for the two proposed definitions of MS score with the 90th percentile corresponding to the monitoring level and the 95th percentile corresponding to the action level are very useful. Early recognition of high risk children and adolescents is important for taking action towards reversal, to prevent adult CV and metabolic disease. This is especially useful in girls, in preventing future gestational diabetes.

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Recent Advances in Anthropometric Parameters to Detect Obesity in Indian Children

Dr Meghna Chawla, Assistant Professor, Department of Pediatrics, Smt Kashibai Navale Medical College, Pune

Introduction

Obesity in children is a global health concern with growing prevalence. A recent analysis of 450 nationally representative cross sectional surveys from 144 countries showed that 43 million children are estimated to be overweight and obese, of which 35 million are in developing countries [1]. Indian children too have shown an alarming rise in obesity, the incidence from various studies being between 1-12.9% [2].

The following are the anthropometric parameters to measure obesity in Indian children:

1. **Body Mass Index (BMI):** It is an accepted standard measure of overweight and obesity for children. According to the 2015 IAP recommendations, new BMI charts for Indian children for the age group of 5-18 years have been constructed by Khadilkar et al [3]. They recommend BMI 23 adult equivalent as the cut off for overweight, and BMI 27 adult equivalent as the cut off for obesity percentiles. These are more appropriate for Indian children, as Asians are prone to develop obesity and its metabolic consequences at a lower BMI than children in the developed world. Despite BMI being used so commonly, its shortcomings are its inability to discriminate between fat mass and lean mass, and to capture the anatomical distribution of adipose tissue.

2. **Waist Circumference (WC):** Visceral fat accumulation as assessed by the WC is strongly associated with metabolic syndrome (MS) in childhood and coronary artery disease in later life. Data from the Bogalusa Heart Study showed that increase in WC between 5 and 17 years was associated with high levels of triglycerides, LDL-cholesterol and insulin [4]. It is also a strong predictor of hypertension. This simple anthropometric parameter overcomes the limitations of BMI, and can help screen children who could benefit from early interventions. Thus the International Diabetes Federation definition for MS in children uses WC as a criterion. WC percentiles for Indian children have been published by Khadilkar et al in 2014 [5], suggesting the 70th percentile as a cut off for MS risk. WC was measured with the child standing, using a non-stretchable tape with a constant 100g of tension maintained by a special indicator buckle. The tape was applied just above the upper lateral border of the right ileum, each measurement being made at the end of a normal expiration and recorded to the nearest 0.1 cm.

3. **Waist-to-Height ratio (WTHR):** Panjikkaran (2013) proposed WHTR as a more sensitive and specific index for detecting increased cardiovascular and metabolic risks in Indian children [6]. She stated that it is more sensitive than WC in different populations, since it adjusts to different statures. Height was measured using a stadiometer, and WC with a plastic tape, midway between the lower rib margin and the iliac crest. The optimum cut off proposed in the study for children from South India was 0.48.

4. **Newer Anthropometric Markers of Obesity**

4.1: Wrist circumference: Based on in vitro studies, Capizzi et al (2011) suggested that insulin may have anabolic effects on bone formation by stimulating osteoblastic proliferation, thus making it a

good parameter to detect Insulin Resistance and potential cardiovascular risk in overweight/ obese children [7]. Dominant Wrist Circumference was measured with the subject in a seated position, using a tension gated tape positioned over the dorsal tubercle of the distal radius and distal ulna, about 1 cm proximal to the radiocarpal joint. It is easily accessible and measurable.

4.2: Neck Circumference (NC): It is an emerging marker for pediatric obesity. A higher NC is indicative of central body fat distribution, and has been shown in different studies to be associated with the complications of obesity, including obstructive sleep apnea. Katz et al (2014) published reference curves for NC in Canadian children. They found NC above 50th percentile correlated with BMI > 85th percentile, and recommended that any child above the 75th percentile should be evaluated for obstructive sleep apnea [8]. NC was measured using the most prominent portion of the thyroid cartilage as a landmark, the measurement being taken to the nearest 0.1 cm using a measuring tape.

4.3: Mid Upper Arm Circumference (MUAC): Craig et al (2014) suggested MUAC as a potential clinical marker for identifying overweight/ obese children in resource poor settings [9].

There is a need to collect and collate Indian data for designing and constructing reference curves for the newer markers.

To conclude, the importance of anthropometry cannot be overemphasized for early detection of obesity, thus preventing its dreaded complications.

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Polycystic Ovary Syndrome in Adolescents

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, affecting 6-8% of adult women. The classic clinical features of adult PCOS - chronic anovulation, hyperandrogenism and multiple ovarian cysts - can be part of normal adolescent physiology during puberty and may mimic PCOS, and thus create a diagnostic dilemma.

Diagnostic criteria

The European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine (ESHRE/ ASRM) recommend the diagnosis of PCOS in adults be based on the presence of two out of three of the following criteria, after exclusion of other causes: chronic anovulation, clinical or biochemical hyperandrogenism, and the presence of polycystic ovaries (PCO) on ultrasound [1]. Since each of these features can be a part of normal adolescent physiology, the ESHRE/ ASRM Consensus Recommendations 2012 suggest that for the diagnosis of PCOS in adolescents, oligomenorrhoea or amenorrhoea should be present for at least 2 years after menarche (or primary amenorrhoea at 16 years or older), there should be both clinical and biochemical hyperandrogenism, and the ultrasound diagnosis of PCO should include increased ovarian size (>10 cm^3) [2].

The Endocrine Society Clinical Practice Guidelines 2013 similarly suggested that the diagnosis of PCOS in an adolescent girl be made based on the presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of persistent oligomenorrhoea [3]. Anovulatory symptoms and PCO morphology were deemed insufficient to make a diagnosis in adolescents.

Differential diagnosis and diagnostic evaluation

The diagnosis of PCOS in adolescents depends on the clinical presentation and documentation of unequivocal biochemical hyperandrogenism, with caution to avoid confusing it with extremes of normal puberty. A detailed history, including family history for known PCOS or menstrual irregularities, infertility, acne, hirsutism, ovarian cysts and/ or surgery, may point to a strong genetic/ familial predisposition. Family history of type 2 diabetes, dyslipidaemia, non-alcoholic fatty liver disease, and increased cardiovascular disease morbidity or mortality, should be carefully sought. Additionally, history of low birth weight and/or premature pubarche could be associated with increased risk of PCOS. Since PCOS is a diagnosis of exclusion, ruling out other causes of hyperandrogenism, including late-onset congenital adrenal hyperplasia (CAH), Cushing syndrome, hyperprolactinaemia, hypothyroidism, and ovarian or adrenal tumours, is imperative. A typical initial laboratory work up of an adolescent with suspected PCOS is given below in table 1.

Table 1: Initial laboratory evaluation of adolescent polycystic ovary syndrome (PCOS)

Laboratory test	**Findings**
TSH/ T4	Rule out hypothyroidism before diagnosing PCOS
Prolactin	Rule out hyperprolactinemia before diagnosing PCOS
LH/ FSH	↔ or ↑, LH: FSH ratio >2 not commonly seen in obese adolescents
Oral glucose tolerance test (OGTT) with insulin levels	To look for impaired glucose tolerance or Type 2 DM. Insulin levels can be used in research settings to calculate homeostatic model assessment-insulin resistance (HOMA-IR), for Insulin Resistance.
ALT and AST	↔ or ↑, to screen for non-alcoholic steatohepatitis
Fasting lipid profile	To screen for dyslipidaemia, especially if the patient is obese
Total testosterone	↑, If levels > 2 ng/ml-rule out androgen-secreting neoplasm (ovarian or adrenal)
DHEA-S	↔ or ↑; if levels > 800 µg/dl, evaluate for an androgen-secreting adrenal neoplasm
17-hydroxyprogesterone	↔ or ↑, to screen for late-onset congenital adrenal hyperplasia; ACTH stimulation test needed if 17-OHP is 2-10 ng/ml
Dexamethasone suppression test	May be considered to rule out endogenous Cushing syndrome

Treatment

Treatment of the adolescent with PCOS includes management of hyperandrogenism as well as prevention and treatment of PCOS-related comorbidities such as obesity, insulin resistance (IR) and dyslipidaemia. Treatment modalities include lifestyle modification, hormonal contraceptives (HC), androgen receptor blockers, and insulin sensitizers, specifically metformin. These treatments, their mechanism of action, clinical effects and side effects, are summarized in table 2.

Summary

Diagnosing PCOS in adolescents remains a challenge, as anovulation, hyperandrogenaemia, and polycystic-appearing ovaries could be part of normal pubertal maturation. Many adolescent girls with PCOS are overweight/ obese, and have a heightened risk for comorbidities such as dysglycaemia, dyslipidaemia, fatty liver disease and cardiovascular disease. Therefore, early and accurate diagnosis is essential for implementation of appropriate treatment and management. Diagnosis rests on a detailed personal menstrual and family history, besides excluding other causes of menstrual irregularity/ hyperandrogenism, including hypothyroidism, hyperprolactinemia, LOCAH, androgen producing ovarian and adrenal neoplasms. Lifestyle modification is associated with improvement in endocrine and ovarian function, and is regarded as a first-line therapy. Other treatment options including HC, metformin, and anti-androgenic drugs, could be used as per the clinical and biochemical profile of the patient.

Table 2: Treatment options including their mechanism of action, clinical effects, and potential side effects in adolescents with PCOS

Treatment	**Mechanism of Action**	**Decreased Menstrual irregularity**	**Reduction in Hirsutism**	**Potential Side Effects**
Lifestyle modification and weight loss in obese PCOS	Secondary to ↓ hyperinsulinaemia	Yes	Yes	Nil
Hormonal contraceptives	↓ ovarian androgen production via inhibiting pituitary gonadotropin secretion ↓ free testosterone by increasing SHBG	Yes	Yes	↑ risk of venous thromboembolism
Insulin sensitizers (Metformin)	Secondary to ↓ hyperinsulinaemia	Yes	No	GI discomfort (diarrhoea, nausea, vomiting). Rarely risk of lactic acidosis (esp in renal failure, dehydration etc.)
Androgen receptor blockers (Spironolactone)	↓ androgen action	Yes	Yes	Hyperkalaemia, GI discomfort (nausea, vomiting, diarrhoea)

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Metformin in Childhood and Adolescent Obesity: The Evidence So Far

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Introduction

Metformin is an insulin-sensitizing biguanide that is approved for treatment of type 2 diabetes (T2DM) in adults and children older than 10 years. In adults, metformin has been found to be effective in inducing weight loss in obese patients with diabetes as well as reducing the progression to overt diabetes in patients with pre-diabetes. Due to these observations, metformin has been used in obese children and adolescents in the hope of encouraging weight loss and preventing future complications.

Obese children often have features of insulin resistance (IR) and develop a vicious cycle of hyperinsulinemia and further weight gain, ultimately leading to metabolic decompensation in the form of Metabolic Syndrome, T2DM and cardiovascular disease. Though lifestyle modifications including diet, exercise, and behavioural therapy are the cornerstone of obesity management, they may have limited success, and pharmacological therapy may be warranted. Metformin is thought to be beneficial in this subgroup of patients. However, currently it is not licensed as an anti-obesity drug.

Here, I discuss some important double-blind randomized controlled trials (RCT) and meta-analyses on the role of metformin in obese children and adolescents <18 years of age without T2DM. Most of the studies were carried out in obese hyperinsulinemic patients, and metformin was used in combination with some lifestyle modification program in all except one study. There was some heterogeneity in the studies with regards to the characteristics of the participants (age, sex, BMI cut-off used, whether failed previous interventions, ethnicity). Clinical outcome was assessed by change in BMI; metabolic parameters including lipids, blood sugar, adipocytokines (adiponectin, leptin); various measures of insulin sensitivity including insulin levels, minimal model, the quantitative insulin sensitivity check index (QUICKI), homeostasis model assessment insulin resistance index (HOMA-IR) indices, whole body insulin sensitivity index (WBISI); and inflammatory markers.

Double-Blind RCTs

Freemark *et al*. [1] (2001) were the first to conduct an RCT on the effects of metformin (500 mg twice daily) vs. placebo in 29 obese adolescents (BMI > 30 kg/m^2) aged 12-19 years, for 6 months. All patients had hyperinsulinemia with fasting insulin level > 15mIU/L and a family history of T2DM. Metformin caused a statistically significant decline of 0.12 standard deviation score (SDS) in BMI (-0.5 kg/m^2) in study participants, while BMI increased by 0.23 SDS in the placebo group. Metformin also caused a decline in fasting blood glucose and insulin levels, and some improvement in insulin sensitivity as assessed by insulin glucose ratio, QUICKI and HOMA (IR). However, insulin sensitivity assessed by minimal model rapidly sampled intravenous glucose tolerance test did not improve.

Srinivasan *et al*. [2] (2006) conducted a cross-over trial lasting 1 year in 28 patients (9-18 yr), with metformin (1000 mg BD) or placebo for 6 months each, with a 2 week washout period. The

metformin group had significant reduction in BMI (-1.26 kg/m^2, p = 0.002) and fasting insulin levels, but non-significant decrease in insulin sensitivity assessed by the minimal model.

Atabek *et al*. [3] (2008) from Turkey evaluated metformin in 120 moderately obese adolescents (9-17y) with hyperinsulinemia. The groups received 500 mg metformin (n = 90) or placebo (n = 30) twice daily for 6 months, plus individually tailored diet, exercise and behavioural therapy. After metformin, there was a significant decline in BMI compared to placebo (-2.1 ± 2.3 vs. 0.7± 2.5, p= 0.001), fasting insulin and 120 min insulin levels; and significant improvement in HOMA-IR and QUICKI as well.

Love-Osborne *et al*. [4] (2008) studied the effects of addition of metformin (850 mg BD) to a lifestyle modification program in 85 adolescents, predominantly of Hispanic and African-American ethnicity, with mean BMI of 39.7 kg/m^2 and features of IR. There was no statistical difference in weight loss or fasting insulin levels between metformin and placebo after 6 months of therapy. However, the authors observed significant weight loss did occur among those females who had good adherence to metformin and lifestyle change, particularly a decrease in portion sizes.

Clarson *et al*. [5] (2009) compared the efficacy of metformin (1500 mg daily) alone, with structured lifestyle intervention and metformin, in obese adolescents (10-16y) with IR. BMI decreased by 1.8 kg/m^2 with lifestyle and metformin, but did not change with lifestyle alone. Surprisingly, HOMA significantly decreased in the lifestyle group, but not following metformin, while the adiponectin/ leptin ratio improved significantly in both groups. Lipid profiles improved more significantly with metformin.

Wiegand *et al*. [6] (2010) randomized obese European adolescents with previous unsuccessful lifestyle intervention, into placebo (n=34) or metformin group (500 mg BD, n=36), in addition to ongoing lifestyle intervention, for 6 months. BMI remained unchanged in both groups; HOMA-IR and fasting insulin improved similarly in both groups; while the insulin sensitivity index improved only in the metformin group. The authors speculated that the metformin dose may have been too low to see any significant effect.

Wilson *et al*. [7] (2010) evaluated the effect of extended release (XR) metformin 2000 mg OD in obese adolescents (13-18y) in a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. Mean BMI increased 0.2 kg/m^2 in the placebo group, and decreased 0.9 kg/m^2 in the metformin XR group (P = .03). No significant effects of metformin on body composition, abdominal fat, or insulin indices were observed.

Yanovski *et al*. [8] (2011) randomized younger children (6-12y) with severe obesity (mean BMI 34.6 ± 6.6 kg/m^2) and IR to metformin 1000 mg BD (n = 53) or placebo (n = 47) groups for 6 months, followed by open-label metformin treatment for 6 months. All children and their parents participated in a monthly dietitian-administered weight-reduction program. In the 85% who completed the 6-month randomized phase, the metformin group had significantly greater decrease in BMI (difference -1.09 kg/m^2, P = 0.006) and BMI z-score (difference between metformin and placebo groups -0.07, CI -0.12 to -0.01, P = 0.02), and greater improvement in HOMA-IR. However, insulin sensitivity measured by hyperinsulinemic clamp did not differ in the 2 groups.

Mauras *et al*. [9] (2012) studied the effect of metformin on inflammatory markers and intrahepatic fat (by liver MRI). Obese children (7-18y) with elevated highly sensitive C-reactive protein (hs CRP)

and/or fibrinogen concentrations were randomized to structured diet/ exercise alone or diet/exercise with metformin for 6 months. Weight loss was modest but more pronounced in the metformin group (-4.9 ± 1.0 kg cf. -1.7 ± 1.1 kg, p <0.03), whereas hs CRP and fibrinogen decreased more in the diet/exercise group. Baseline intrahepatic fat was high but decreased only in the diet/exercise (not metformin) pubertal group.

The MOCA trial [10](Metformin in obese children and adolescents) conducted at 6 pediatric endocrine centers in the United Kingdom, included 151 obese subjects with hyperinsulinemia and/or impaired fasting glucose or impaired glucose tolerance (metformin 1000 mg BD: 74, placebo: 77, for 6 months). Metformin was associated with a significant reduction in BMI-SDS at 6 months, mean difference -0.1 SD (95% CI -0.18 to -0.02, P = 0.02), and significant improvements at 3 months in fasting glucose, alanine aminotransferase levels and adiponectin leptin ratio.

Meta-analysis and Systematic Reviews

There are two meta-analyses and one systematic review regarding the benefit of metformin in childhood and adolescent obesity [11-13]. The first meta-analysis [11] (2009) based on 5 double-blind RCTs of > or =6 months duration (n = 320 individuals), concluded that metformin reduced BMI by 1.42 kg/m^2 (95% CI 0.83-2.02) and HOMA-IR score by 2.01 (95% CI 0.75-3.26) compared with placebo.

The second meta-analysis by McDonagh et al [12] (2014), based on 14 eligible RCTs, found moderate-strength evidence for reduction of BMI by -1.38 kg/m^2 (95% CI, -0.82 to -1.93) from baseline compared with control at 6 months, and a similar effect for studies less than 6 months. However, 2 studies of one year duration did not show any statistically significant difference and the pooled estimate from all studies was not statistically significant. Subgroup analyses indicated smaller, but significant, effects in the following categories: baseline BMI below 35, Hispanic ethnicity, presence of acanthosis nigricans, patients who had tried and failed diet and exercise programs, and adolescent girls.

Regarding the safety of metformin, no serious adverse events were reported. Overall, 26% patients reported a gastrointestinal event compared with 13% in control groups (relative risk, 2.05; 95% CI, 1.19-3.54), although there was no difference in discontinuations due to adverse events. [13]

Conclusions

It appears that metformin in combination with lifestyle measures is efficacious in the short-term in reducing BMI and increasing insulin sensitivity in obese hyperinsulinemic children in a small but statistically significant way. However, the clinical relevance of a (perhaps unsustained) BMI loss of 0.82-1.93 kg/m^2 on long-term cardiovascular risk and T2DM remains unclear. Furthermore, there are no studies assessing the long-term > 1 year benefit and safety of metformin, and more data on final outcomes are needed before it can be put to routine clinical practice for the treatment of obesity.

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Prader-Willi Syndrome: Endocrine Aspects

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Introduction

Prader–Willi syndrome is a complex genetic disorder with a prevalence of 1/10,000- 1/30,000. It results from lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 which accounts for 70% of cases. Maternal uniparental disomy (UPD) of chromosome accounts for 25% of cases. Imprinting defects account for most of the remaining 5% [1].

Clinical manifestations of PWS include hypotonia with weak suck and poor feeding in infancy, leading to failure to thrive, with later development of hyperphagia. Other clinical manifestations includes short stature, excessive appetite with progressive obesity, mental retardation, behavioural abnormalities (specifically stubbornness, obsessive-compulsive behaviour, and skin picking), sleep disturbances (including sleep apnea), and dysmorphic features i.e. the presence of a thin upper lip, almond shaped eyes, acromicria (short hands and feet), hypogonadism and genital hypoplasia. Hypothalamic dysfunction has been implicated in many manifestations of this syndrome including hyperphagia, sleep disordered breathing, and insufficiency of pituitary hormones, which includes growth hormone deficiency, central adrenal insufficiency, hypogonadism and hypothyroidism. With improved recognition and availability of testing methodologies, PWS is being diagnosed earlier, often in the first month of life, allowing for earlier intervention and anticipatory guidance [2,3].

Clinical diagnostic criteria were established by consensus in 1993 by Holm *et al*. when sophisticated genetic analysis was not available [4]. However, Gunay-Aygun *et al.* [5] proposed revised clinical criteria to identify the appropriate patient for DNA testing in 2001, improved by Goldstone *et al.* [2] in 2008 (table 1). In this article, the focus is on current evidence regarding endocrine manifestations and their management.

Appetite and nutrition

The complex transition from poor feeding to hyperphagia is explained by Miller *et al.* [6] in seven nutritional phases in PWS (table 2). Eating behaviour and functional MRI studies have identified decreased satiety and increased reward response to food as major factors contributing to hyperphagia. The orexogenic hormone ghrelin is very high in individuals with PWS but decreasing its level does not have an effect on appetite. Strict diet control and food security, both physical and psychological, are critical in management. Principles of psychological food security include “no doubt, no hope, no disappointment”, which means ‘no doubt’ that the next meal is coming, ‘no hope’ of food outside of what is provided, and ‘no disappointment’ as what is promised is followed.

Growth hormone deficiency

The reported prevalence of growth hormone deficiency (GHD) in PWS ranges from 40-100%, depending upon the diagnostic criteria used, with most studies reporting prevalence at the higher end. Clinical manifestations include short stature and abnormal body composition. Even infants and toddlers have increased fat mass and decreased lean body mass compared to normal children of the same age. Growth velocity decreases significantly after 2-3 years of age. Recombinant hGH was approved by FDA in 2000 in USA for growth failure due to PWS. Consensus guidelines on hGH

therapy in PWS were recently published, recommending hGH treatment for patients with genetically confirmed PWS in conjunction with dietary, environmental and lifestyle interventions, following multidisciplinary expert evaluation [7]. RCTs of hGH therapy have shown significant improvement in body composition and height, with maximum effect seen in first year of therapy. RCTs have also shown benefits on development and cognition. The optimal age to start hGH, as per expert consensus, is prior to the onset of obesity, which occurs by 2 years of age. Clinical guidelines recommend a starting dose of 0.5mg/m^2/day, with progressive increase to 1 mg/m^2/day. The aims of GH therapy in children with PWS are to improve growth during childhood, adult height and body composition. Before starting GH therapy, complete evaluation for sleep disordered breathing, orthopaedic reference for scoliosis, and glucose metabolism by oral glucose tolerance test (OGTT) is recommended. During hGH therapy also, regular assessment of scoliosis, OGTT, sleep disordered breathing, body composition and orthopaedic referral every 3-6 month is recommended.

The association of hGH therapy with sudden death in PWS has received significant attention but evidence for a causal relationship is not convincing.

Adrenal insufficiency

Central adrenal insufficiency occurs in PWS but the frequency is unclear. Children and adults with PWS are at risk for adrenal insufficiency due to generalized hypothalamic dysfunction. One published cross –sectional analysis (n=25) of adrenal insufficiency in children with PWS found that 60% tested insufficient by overnight single dose metyrapone testing, while subsequent studies using different methodology, including low dose and high dose synacthen and insulin tolerance test, showed the frequency did not exceed 14-15% [8]. No consensus exists on the appropriate evaluation and management of central adrenal insufficiency in PWS. One group recommends considering stress dose steroid for all patients with PWS during stress [9] while another recommends prophylactic stress dose steroid only for major surgery [10].

Hypogonadism

Hypogonadism is a consistent feature in both males and females with PWS. Clinical presentation includes genital hypoplasia, delayed or incomplete puberty, and infertility, in the vast majority. Genital hypoplasia manifests in females as hypoplasia of the clitoris and labia minora, and in males as cryptorchidism (unilateral or bilateral in 80-90%), hypoplastic scrotum and small penis. Some authors recommend considering a trial of hCG to promote testicular descent, but there is no published data on efficiency of this practice in PWS. Surgical correction of cryptorchidism should be considered in the 1st or 2nd year of life.

Hypogonadism was classically thought to be of hypothalamic etiology; however, recent evidence has emerged supporting primary gonadal failure as a significant contributor to male hypogonadism. Studies have shown a combined picture of hypogonadotropic hypogonadism with relatively low LH levels, and primary hypogonadism with low inhibin B and relatively high FSH level [11]. In a longitudinal study of gonadal function in 61 girls with PWS, maturation of follicles and progression of pubertal development were impaired. LH levels were relatively low for the low estradiol levels observed, and FSH levels were normal. Pubertal onset was similar in timing to the normal population, but progression was delayed. Most patients present with delayed or incomplete puberty; however precocious adrenarche occurs in 15-30%, and precocious puberty has been reported in 4%. Treatment of precocious puberty with GnRH analog is not indicated as precocity is not sustained.

No consensus exists as to the most appropriate regimen for pubertal induction or promotion but experts agree that the dosing and timing should reflect as closely as possible the process of normal puberty. Sex hormone replacement therapy may be beneficial to hypogonadal patients in a number of ways. Obviously, the development of secondary sexual characteristics would be encouraged, but there is also potential for improvements in bone mineral content and bone mineral density. No cases of paternity have been reported, but four pregnancies (two normal offspring and two offspring with Angelman syndrome) have been documented.

Hypothyroidism

Hypothyroidism has been reported in approximately 20-30% of children with PWS: a recent study of children under 2 years of age revealed that 72.2% had abnormalities in the hypothalamic-pituitary-thyroid axis [12]. Studies of adults with PWS, however, show that the frequency of thyroid disease is 2%, similar to that of the general population. T4 and TSH should be screened at birth or within the first 3 months and annually thereafter (every 6 months if the patient on GH therapy), with initiation of levothyroxine if hypothyroxinemia is discovered.

Glucose intolerance and diabetes

Type 2 diabetes mellitus (T2DM) has been reported in 25% of adults with PWS, with onset at a mean age of 20 years; diabetes and impaired glucose tolerance (IGT) are less frequent in children. A study of 74 children (median age 10.2 years) showed that none had T2DM and only 4% had IGT [13]. Periodic surveillance for diabetes and metabolic syndrome should be undertaken in obese children as per guidelines for obesity in the general population. Recent expert consensus recommends surveillance of A1C, fasting glucose, and fasting insulin, for those receiving hGH therapy, and consideration of an OGTT for those who are obese, and/or >12 years old, and/or have a family history of diabetes.

Conclusion

Over recent years, increasing appreciation and availability of important management strategies have made significant improvements in the life of those with PWS, *e.g.* early diagnosis, use of multidisciplinary teams, introduction of GH treatment, control of the food environment, and better understanding of the behavioural and psychiatric aspects.

Areas where further research is needed include the etiology and management of hyperphagia, optimal surveillance of sleep disordered breathing, further elucidation of the effect of hGH on cognition, the impact of hGH therapy in adulthood, frequency and management of adrenal insufficiency, and the frequency and natural history of hypothyroidism.

Useful links are:

Prader-Willi syndrome Association, USA (www.pwsausa.org)

The Foundation for Prader-Willi Research (http://fpwr.org)

The International Prader-Willi syndrome Organization (www.ipwso.org)

Table 1: Indications for DNA testing

Age at assessment	**Features sufficient to prompt DNA testing**
Birth to 2 years	Hypotonia with poor suck
2-6 years	Hypotonia with a history of poor suck, Global developmental delay, Short stature and/or growth failure associated with accelerated weight gain
6-12 years	Hypotonia with a history of poor suck (hypotonia often persists), Global developmental delay, Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
13 years through adulthood	Cognitive impairment, Usually mild mental retardation, Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled, Hypothalamic hypogonadism and/or typical behavioural problems (including temper tantrums and obsessive-compulsive features)

Table 2: Nutritional phases in Prader-Willi Syndrome [6]

Phase	**Description**	**Median Age of Onset and Completion**
0	Decreased foetal movement and lower birth weight	In utero
1a	Hypotonia with difficulty in feeding	0-9 months
1b	No difficulty in feeding and growing appropriately	9-25 months
2a	Weight increasing without increase in appetite or excessive calories	2.1-4.5 years
2b	Weight increasing with an increase in appetite	4.5-8 years
3	Hyperphagic, rarely feels full	8 years – adulthood
4	Appetite no longer insatiable	Adulthood

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Rapid Onset Obesity & Ondine's Curse: a Deadly Syndrome!

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Introduction

ROHHADNET syndrome is a rare disorder with approximately 100 cases reported in the literature to date. It includes abnormalities of the endocrine system (hypothalamic dysfunction), autonomic nervous system, and respiratory control (hypoventilation). Children with ROHHADNET appear "normal" until its onset between 1.5 and 10 years of age [1-3]. Often, the first sign is hyperphagia with rapid, dramatic weight gain. Hypoventilation develops a few months after the onset of obesity. During subsequent months, problems encountered include hypothalamic dysfunction, diabetes insipidus, hyperprolactinemia, precocious or delayed puberty, growth hormone (GH) deficiency, adrenocorticotropic hormone (ACTH) deficiency, central hypothyroidism, autonomic dysfunction, light-nonresponsive pupils, constipation, temperature dysregulation, sweating disorders, reduced pain sensation, developmental/behavioural disorders, seizures and alveolar hypoventilation [4].

Case report

A 2 yr 4 mo old girl presented with history of inability to be aroused from sleep, associated with an episode of generalized tonic-clonic seizure. At admission, she was obtunded and had hypoventilation, with oxygen saturation of 85% on room air. Physical examination revealed facio-truncal obesity and marked adipomastia. Sexual maturity rating was pre-pubertal (Tanner stage I), with normal appearing female external genitalia. Her blood pressure (BP) was 132/80 mmHg (>95th centile), with systolic BP varying between 140-170 mmHg. Initial blood gas showed severe respiratory acidosis (pH 7.21, pO_2 84 mmHg, pCO_2 80 mmHg, HCO_3 32 mEq/L). She was started on non-invasive ventilation. Her sensorium normalized after 10 hours and blood gas improved (pCO_2 43 mmHg).

The child was born to non-consanguineous parents with maternal history of diabetes mellitus and hypothyroidism during pregnancy, with birth weight of 4000 grams. Neonatal period and infancy were uneventful, and her developmental milestones appropriate. On further interview, it was found that she had been demanding excess food, and had had significant weight gain for the preceding 6 months. Review of her growth chart revealed rapidly increasing weight after 1½ years of age, crossing 3 SD, while her height centile remained within the normal range (figures 1 and 2).

During the hospital stay, she had several episodes of hypoventilation, which were more pronounced during sleep, along with hypoxia and hypercarbia. An attempted sedation for a procedure was followed by hypoventilation, severe hypercarbia (PCO_2 115 mmHg, pH 6.9), and seizures, requiring a brief period of intubation and ventilation. A conventional respiratory physiological study was attempted, but could not be performed in view of severe hypoventilation and desaturations during sleep. Cardiac ultrasound revealed moderate pulmonary hypertension, in keeping with hypercarbic respiratory failure.

Figure 1: Growth chart depicting rapid weight gain after 1½ years of age.

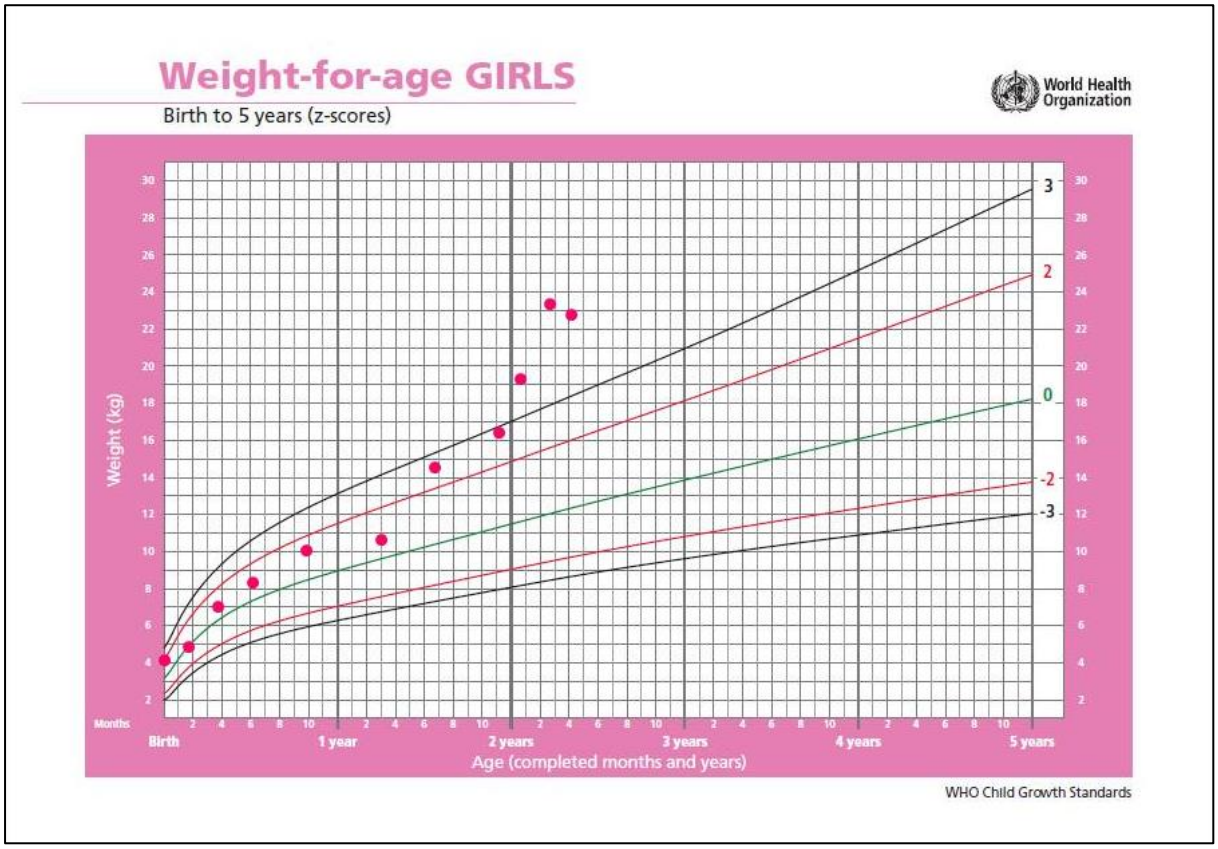
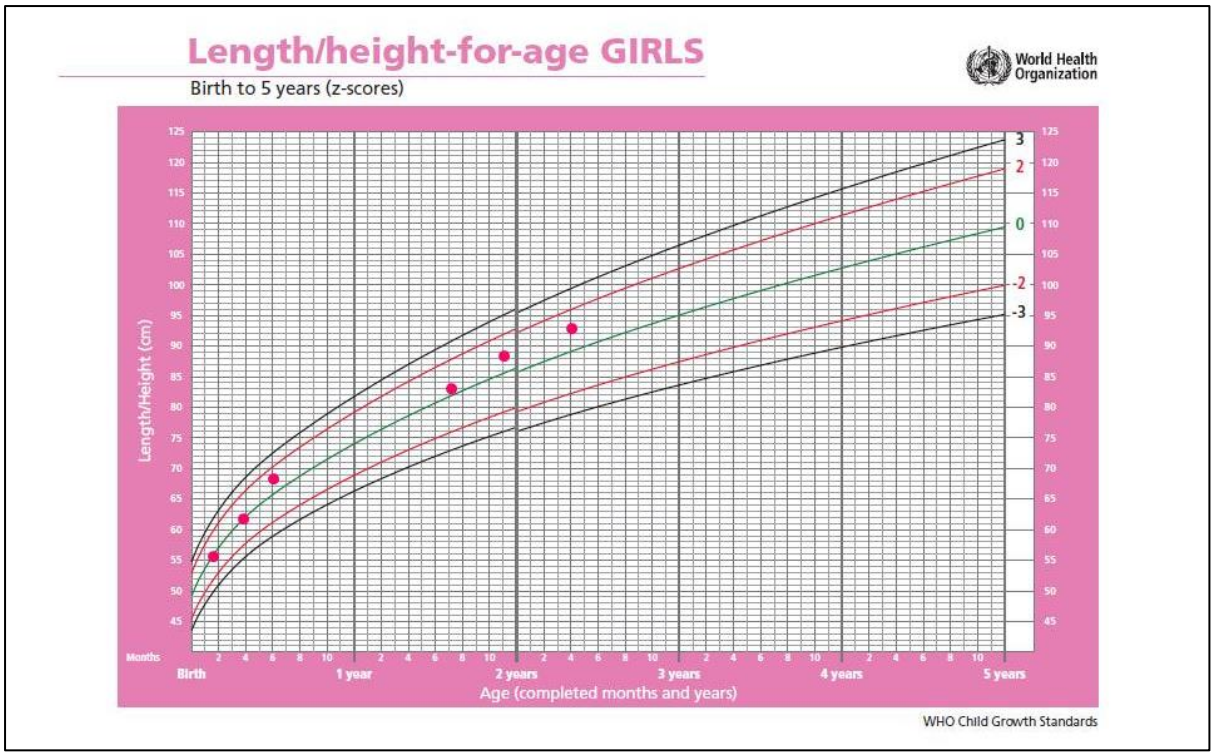


Figure 2: Growth chart depicting a less than anticipated acceleration of growth rate in the setting of rapid weight gain.



In view of seizures, EEG was done, and was normal. MRI brain done at the time of admission, showed non-enhancing T2/FLAIR hyperintensity in bilateral centrum semiovale, fronto-parietal subcortical white matter and right peri-trigonal region, with diffusion restriction. She was noted to have diminished sensitivity to pain as evidenced by absence of grimace/ cry during insertion of IV cannulas and arterial catheters. Formal assessment by the ophthalmologist revealed normal pupillary responses with bilateral alternating exotropia and a normal fundus examination.

She was evaluated for endocrine and genetic causes of obesity, the hormone testing being done on a day close to discharge, once she had been transferred from the ICU to the ward, and her overall condition had improved. Hormonal profile (Table 1) revealed normal plasma cortisol, appropriately suppressed with low dose dexamethasone (0.5 mg); hyperprolactinemia; central hypothyroidism; low IGF-1, and a sub-optimal GH response to 5 µg/kg of clonidine. Leptin levels were normal for age and weight. Oral glucose tolerance test, lipid profile, creatine kinase, serum ammonia, lactate, liver function tests, renal function tests and chest X ray were all normal. Her bone age corresponded to 2-3 years (Greulich-Pyle method).

Considering the possibility of ROHHADNET syndrome, screening thoracic and abdominal CT was performed to look for any neural crest tumour: it revealed an FDG avid, homogenously enhancing mass in the pre-sacral area on the left side, posterior to the rectum (Figure 3). The CT also revealed a mildly bulky right kidney, with ill-defined multifocal non-enhancing areas predominantly in the cortex, and a bulky pancreas. In view of hypertension and neurogenic tumour, urinary catecholamines and metanephrines were done, which were normal (Table 1).

Based on the co-associated abnormalities such as rapid onset of hyperphagic obesity after infancy, alveolar hypoventilation, hypothalamic-pituitary endocrine dysfunctions (hyperprolactinemia, central hypothyroidism, low IGF-1, failed GH stimulation test), autonomic dysregulation (fluctuating BP levels, strabismus, altered pain sensitivity), and neurogenic tumour, we diagnosed ROHHADNET syndrome in this child. She has been discharged on home BIPAP and thyroxine, and is being followed up at the endocrine and pulmonary departments.

Figure 3: Contrast enhanced CT abdomen and FDG-PET scan showing homogenously enhancing mass in pre-sacral region on left side posterior to rectum.

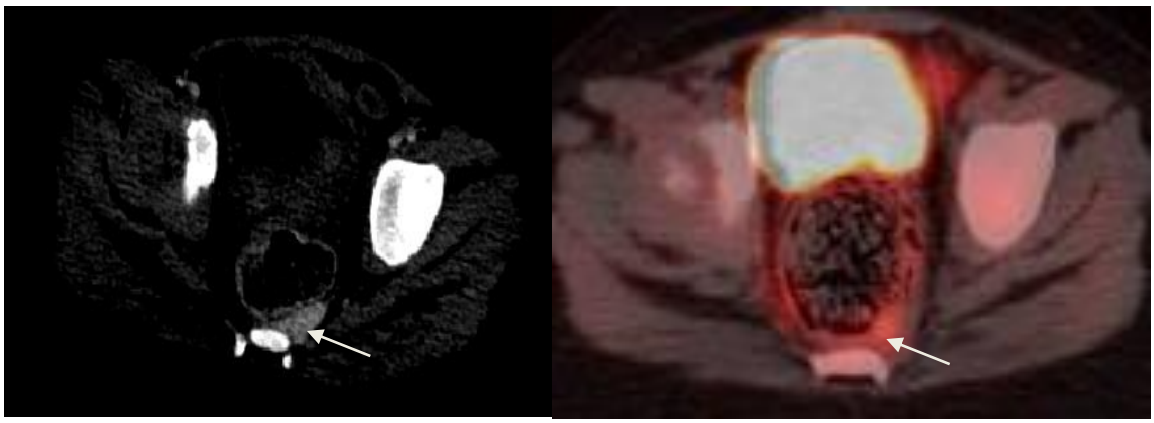


Table 1: Summary of endocrine evaluation

Test	Result	Normal Range
TSH	0.64 µIU/ml	(0.7-6.4)
Total T3	0.68 ng/ml	(0.9-2.4)
Free T4	0.89 ng/ml	(0.8-2.7)
Prolactin	27.82 ng/ml	(2.5 - 15)
Random serum cortisol	48.44 µg/dl	(0.49-58.6)
Dexamethasone suppression test	1.41 µg/dl	(< 1.8)
IGF-1	123 ng/ml	(51-303)
IGFBP-3	3.45 µg/ml	(0.8-3.9)
Clonidine stimulation test	GH Basal: 1.92 ng/ml GH 30 min: 0.27 ng/ml GH 60 min: 1.2 ng/ml	Peak GH: > 10 ng/ml
Fasting leptin levels	4.64 ng/ml	(3.63-11.09)
24 hour urinary VMA	2 mg	(< 13.6)
24 hour urinary total metanephrines	0.4 mg	(< 1)
24 hour urinary epinephrine	6.04 µg/g creatinine	(4-32)
24 hour urinary nor-epinephrine	89 µg/g creatinine	(20-108)
24 hour urinary dopamine	1069 µg/g creatinine	(295-1123)
Oral glucose tolerance test	Fasting 64 mg/dl post 1 hour 72 mg/dl post 2 hours 82 mg/dl	(60-90) (80-120) (80-120)
Total cholesterol	73 mg/dl	(< 200)
HDL-cholesterol (measured)	18 mg/dl	(35 -70)
LDL-cholesterol (measured)	52 mg/dl	(< 100)
VLDL-cholesterol (calculated)	12.3 mg/dl	(< 40)

Discussion

ROHHAD syndrome is an example of a genetic obesity syndrome. It was first described in 1965 [5] and was only re-named in 2007 [1] when it was shown to be distinct from congenital central hypoventilatory syndrome (CCHS) by absence of CCHS-related PHOX2B mutations. The disease is now also called ROHHADNET [6] because it is accompanied by ganglioneuroma located in the abdomen and lungs, and neuroendocrinal tumours such as ganglioneuroblastoma in about 40% of the patients [7].

Symptoms develop after one year of age, with dramatic and rapid weight gain associated with hyperphagia, followed by symptoms of hypoventilation. Before diagnosing central hypoventilation, it is important that diseases of the lung and heart are ruled out [8]. Other hypothalamic abnormalities include diabetes insipidus and hyperprolactinemia [3,5]. Autonomic dysfunction manifestations include eye abnormalities such as altered pupil response to light, strabismus, altered gastro-intestinal motility, temperature dysregulation, and decreased sensation to pain. Some children with ROHHADNET may develop seizures, though this feature may be related to episodes of hypoxemia. About 40% develop tumors of neural crest origin like ganglioneuromas or ganglioneuroblastomas [4]. 50% to 60% of these children ultimately suffer from cardiac arrest [9].

The differential diagnosis of early onset obesity includes Prader-Willi syndrome in which hyperphagia and obesity is associated with hypotonia, mental retardation, short stature, GH deficiency, hypogonadotropic hypogonadism, and sleep apnea - features that can all be found in the ROHHADNET syndrome. Bardet-Biedl syndrome is a rare, autosomal recessive disease characterized by obesity, mental retardation, dysmorphic extremities, retinal dystrophy or pigmentary retinopathy, hypogonadism, and structural or functional abnormalities of the kidney. Leptin deficiency, POMC gene mutation, and MCR4 gene mutation also have to be considered among the monogenic causes of early-onset obesity [8,10,11]. Normal levels of leptin and cortisol ruled out these causes of monogenic obesity in our patient. In contrast to most cases of exogenous obesity, where growth velocity and IGF-1 levels are high normal, in patients with ROHHAD syndrome, IGF-1 levels are depressed and GH response to stimulatory tests is sub-optimal, as seen in our patient.

Searches for a neuroanatomical pathology that can explain the symptoms of ROHHAD have not yielded consistent findings. Reported cranial MRI pathology associated with ROHHAD includes bilateral basal ganglia hypodensities, Rathke's cleft cyst, and areas of hypointensity in the pons and midbrain [1,2]. Hypothalamic inflammation with lymphocytic infiltrates was found in two cases [12,13]. MRI brain in our patient showed hyperintensity in bilateral centrum semiovale, frontoparietal subcortical white matter and right peri-trigonal region, with diffusion restriction, which is probably related to hypoxemia rather than directly to ROHHAD syndrome.

Previous reports have suggested that early intervention with nocturnal artificial ventilation may improve daytime ventilation [14]. Apart from aggressive early ventilation, it is also noted that sedation sometimes triggers respiratory arrest. This occurred in our patient as well as in the cases reported by Nunn *et al.* and Chew *et al*. [13,15].

At present there is no genetic testing available to diagnose ROHHAD, so the diagnosis is based on the clinical presentation and clinical course. There has been a report of “Retinoic acid Induced-1” gene (RAI-1) receptor mutation in one case [16]. Unambiguous identification of ROHHAD syndrome has been challenging; confirmatory laboratory testing is not yet available, and the patient population may represent a heterogeneous group of underlying etiologies. Hence, the diagnosis is based exclusively on the clinical findings.

Conclusion

ROHHADNET syndrome is a pleiotropic disorder defined by rapid onset obesity with hypoventilation, hypothalamic dysregulation, autonomic dysfunction, and neural-crest tumors. This disorder can mimic genetic obesity syndromes and several endocrine disorders, and is associated with various forms of hypothalamo-pituitary endocrine dysfunction. Because of the high prevalence of cardiorespiratory arrest and the probability of accompanying tumors, early recognition of ROHHAD syndrome in a child with rapid onset obesity is important.

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Prevalence of Fatty Liver and Cardio-metabolic Complications in Overweight Indian Adolescents

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Objectives: The aim of the study was to assess the prevalence of fatty liver and cardio-metabolic complications in overweight Indian adolescents.

Methods: We recruited 100 overweight adolescents aged 10-16 yr and their parents. Exclusion criteria were chronic liver disease, diabetes and syndromic /endocrine obesity. Fasting plasma glucose, lipid profile, ALT, AST and insulin were measured. Ultrasonography for fatty liver was done by a single radiologist for subjects and parents using Siemens Acuson S2000.

Results: Mean age was 11.6±1.6 yr and BMI 26.7±4.8; 32% were prepubertal and 69% were boys (Table 1). 91% of mothers and 94% of fathers were overweight/ obese. Insulin resistance (IR) was present in 61% and impaired fasting glucose in 12%. Fatty liver was present in 57% adolescents, 56.4% mothers and 68% fathers (Table 2). BMI, waist circumference, body fat percentage and fasting insulin were significantly higher among the adolescents with fatty liver compared to those without.

Conclusion: IR and fatty liver are the commonest complications among overweight adolescents and are closely related. Screening for fatty liver should be mandatory in overweight adolescents.

Table 1: Clinical parameters of the study population

Parameter	
Waist circumference (cm) Girls Boys > 90th centile	 83.3±11.1 85.5±11.8 52%
Systolic BP (mmHg) Diastolic BP (mmHg) Systolic BP ≥ 130 mm Hg Diastolic BP ≥ 85 mm Hg	116±9.3 72.8±7.1 8% 6%
Prepubertal/ Pubertal	32/68

Table 2: Biochemical and ultrasonographic parameters

Body fat % (bioelectrical impedance)	37.2±5.3
Serum total cholesterol (mg/dl) Borderline high (170-199 mg/dl) High (≥ 200 mg/dl)	154.0±30.7 21% 7%
Serum HDL-cholesterol (mg/dl) Borderline low (35-40 mg/dl) Low (< 35 mg/dl)	42.5±9.5 30% 21%
Serum LDL-cholesterol (mg/dl) Borderline (110-129 mg/dl) High (≥ 130 mg/dl)	91.4±28.4 15% 7%
Serum triglycerides (mg/dl) Borderline high (90-129 mg/dl) High (≥ 130 mg/dl)	108.0±55.7 33.3% 21.8%
Fasting plasma glucose Impaired (100-125 mg/dl) High (≥ 126 mg/dl)	86.7±9.9 12% None
Fasting Insulin (mIU/L) HOMA-IR Borderline high (2.5 -3.5) High (>3.5)	17.7± 13.2 3.7 ± 2.7 22.4% 38.5%
Serum alanine transaminase (IU/L) High (> 30 IU/L)	44.3±32.1 66%
AST:ALT ratio > 1	39%
Fatty liver in subjects (n=86) Mild Moderate Severe	 34.8% 18.6% 3.5%
Fatty liver in mothers (n=85, Age: 36.5±4.7y) Mild Moderate Severe	 41.1% 11.8% 3.5%
Fatty liver in fathers (n=77, Age: 40.6±6y) Mild Moderate Severe	 19.5% 40.3% 7.8%

Childhood Obesity: A Patient Information Leaflet

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The current epidemic of childhood obesity affects 1 out of 10 children worldwide. Many of them end up developing conditions like diabetes, hypertension or metabolic syndrome in adulthood. Hence it is important to gain as much knowledge as possible about this rapidly rising problem.

How do I know if my child is obese?

There are various methods to measure obesity in children. The body mass index-for-age (BMI-for-age) percentiles, which use the child's height and weight, are presently the favored method. The child is classified as obese if the BMI-for-age percentile is greater than 95%, and overweight if BMI-for-age percentile is between 85% and 95%. The BMI charts vary from country to country. While the WHO charts are followed worldwide for children below 5 yr, for children between 5-18 yr, country specific charts are used. You can download the charts for your child from *www.iapindia.org/Revised-IAP-Growth-Charts-2015.php.* It is useful to enter your child's weight and height and calculate your child's status once a year.

How common is childhood obesity?

The problem is increasing worldwide: 20-30% children in developed countries are overweight, and even in developing countries like India the problem has become 4 fold more common in the last 30 years. This change is seen more in the cities as compared to the rural population. Children who are small at birth or very large at birth (birth weight less than 2.5 kg or more than 3.5 kg) are more prone to becoming fat later.

Is there a reason for obesity becoming more common?

One of the major reasons for this increase is the differing lifestyle of today's children, compared to the previous generations. The environment plays a major role in shaping the habits and perceptions of children and adolescents. Easy access to unhealthy food, and decreasing physical activity, make them more prone to become obese in childhood itself.

It is estimated that approximately one third to half of money spent on food, is spent on food outside the home, in restaurants, cafeterias etc. and on packaged foods (e.g. wafers, biscuits, pizzas, momos, samosas). Not only does this food have much more calories, when people eat out they tend to eat more than when they are at home. The consumption of sugar in general, and sweetened beverages such as cool drinks and juices (including so called "health drinks") in particular, has increased significantly in the last few decades, greatly contributing to children gaining weight. Scientific studies have documented a 60% increase in the risk of obesity for every carbonated drink consumed per day. Food portions also play an important role in unhealthy diet patterns. The prevalence of extra portions and buffets creates a trend in overeating. Parents and grandparents complain "the child hardly eats anything" while allowing them access to very high calorie foods.

Children today also have much less overall physical activity. Extra tuitions after school, increasing screen time (computers, smartphones, iPads, television), and decreased place and time to play in school and at home, all contribute to a more sedentary lifestyle. With the greater emphasis on academics, extracurricular activities have taken a backseat. Parents themselves do not walk or play sports, and think these are a waste of time. This attitude is imbibed by the children and adolescents.

Hence the end result is that children are consuming more and expending less, which naturally has resulted in the majority of children becoming unhealthily obese.

Why should I be worried about childhood obesity?

It is clear that once fat weight is gained, it is difficult to lose. Therefore parents should make sure that obesity does not happen, rather than trying to "treat" it when the child has already become obese. This applies particularly to children at risk: those who were born small or very large, preterm or other precious babies, children of fat parents, children of single parents, children with *any* chronic disease (e.g. asthma, nephrotic syndrome, heart disease, thalassemia, and so on). So if any of these categories applies to you/ your child, please be extra cautious. All children, but specially these at risk children, should be encouraged to stay "thin" and active.

Studies have showed that children who are obese, especially with big bellies, have higher blood pressure (BP), higher blood levels of insulin and triglycerides (bad type of fat), and lower levels of HDL ("good") cholesterol. They are at a higher risk of developing diabetes and high BP even during adolescence; and heart disease, strokes, and other health problems in adulthood.

Obese children are also prone to other complications such as sleep disorders (you should be worried if your child has begun snoring), breathing problems, fatty liver disease, bone problems such as knock knees, and skin problems such as acanthosis (ugly black color of the skin folds in the neck, underarms, thighs and even fingers), rashes in skin folds, or fungal infections, and hormonal imbalances such as early puberty or irregular periods and facial hair in girls.

One of the most ignored aspects of childhood obesity is the psychological burden on the child. Constant teasing and bullying by peers, or even adults, cause low self-esteem. This is worsened by falling grades due to sleep disorders, and difficulty in playing. Obese youth are more prone to develop psychiatric illnesses such as depression, anxiety, and/ or eating disorders such as anorexia nervosa (unwilling to eat all kinds of food) or bulimia nervosa (over-eating followed in induced forceful vomiting).

Is obesity hereditary?

Yes, obesity runs in families, because family members share the same genes and the same environment. So if you, your spouse, or others in the family are already fat, you should be even more alert to the possibility of your child becoming fat. Focus on having a healthy lifestyle yourself, and provide the right environment to your child from the very beginning. Make sure the child is never force fed, encourage use of low fat home-made foods, have regular enjoyable physical activity, and limit screen time to reasonable limits.

What are the causes for childhood obesity?

In more than 90% children, the obesity is not due to any disease, but due to external factors such as poor dietary habits and lack of physical activity ("exogenous obesity") which we have just discussed. The remaining less than 10% may have a genetic or hormonal cause ("endogenous obesity"). Usually such children are short and fat, with low rate of height gain (less than 5 cm every year), whereas children with exogenous obesity are tall for their age and family height. In genetic causes ("syndromic obesity", e.g. Prader Willi syndrome) the affected child may have other abnormalities like dysmorphia (abnormal shape of body parts including fingers, facial features, genitals, etc.). Suspect these conditions if the baby looks odd, or if s/he starts gaining weight rapidly early in life. These children generally do not recognize when they are full and so have a voracious appetite. Hormonal diseases which case obesity include thyroid or adrenal diseases. Most of the time, based on whether your child is tall or short for age, and whether s/he has findings like acanthosis (see above) or skin tags, your pediatrician would be able to distinguish whether your child needs to be

tested for such disorders or not. If not, you should consult a pediatric endocrinologist, a doctor who specializes in such conditions.

My child looks fat. What should I do?

It is important to get a detailed assessment done by a good pediatrician or pediatric endocrinologist, for physical development (including height, weight, BP, puberty stage), mental development, and relevant clinical features. A few blood and radiological tests may aid in arriving at a final diagnosis. If your child has exogenous obesity, please make sincere efforts to change the lifestyle for the entire family. Changing diet for the child alone is of no use. In the rare event of an endogenous cause being diagnosed, the appropriate treatment would be advised, but lifestyle modifications remain important.

What are the lifestyle modifications needed?

The components of lifestyle modification include dietary management, physical activity, behavioral modification and family involvement. With these strategies, we can aim at reasonable weight loss goals, as guided by your doctor. For growing children who are overweight, not obese (see above), just not gaining weight for a couple of years while they continue to gain height, may be sufficient. For obese children, the goal may be initial loss of 2-3 kg per month, followed by 1-2 kg per month. It is important to understand that when the child exercises regularly, there may be no weight loss initially, even though inches are lost. Even in those who lose weight rapidly initially, subsequent weight loss may take longer as the body tries to counteract the changes. At these junctures, a lot of emotional and psychological support is needed, to maintain discipline and not lose hope.

What are the dietary changes I should make?

The most important thing to remember is to respect your child's appetite. Serve small portions, and do not insist every meal must be finished. Most children develop a tendency to overeat because of force feeding at an early age. A healthy diet comprises of 30% or fewer calories derived from fat, and minimal sugar. This is ensured by limiting the availability of foods such as sweets, chocolates, fried food, pre-prepared and sugary foods, especially sweetened beverages. Fiber has been shown to decrease the absorption of fat and sugars and is strongly recommended. Fruits (preferably with peel) and vegetables are good source of fiber and are NOT fattening. Whole milk has a high fat content and should be substituted by low fat milk and milk products after age 2 yr, in all children, not just those who are obese. A dietician can be consulted to plan diet in detail, modifying the family's style of eating and based on the child's tastes and interests, to ensure the desired total number of calories, and recommended percentage of fat, protein and carbohydrates, along with all essential nutrients. Occasional treats, especially on festivals or special days (birthdays, friends' parties) are important to make sure the child does not get frustrated, and therefore uncooperative.

What form of physical activity is recommended?

All forms of physical activity are encouraged, ranging from simple play activities and ball games in the park, to organized sports coaching. Begin according to the child's fitness level, with an ultimate goal of 60 minutes per day (in addition to any school activity). Initially, your child's activity does not have to be a structured exercise program, the objective being to get him/ her moving. It should preferably be something the child enjoys, for instance, for the artistically inclined child, going to the park to collect leaves to make a collage. If your child likes to read, walk or bike together to the neighborhood library for a book. As much as possible, incorporate the habit of walking rather than driving or using lifts. After a few weeks, organized activities (dance classes, sports coaching, etc.) may ensure regularity and participation.

Limit TV, mobile usage, and recreational computer time to 1-2 hours a day, to be stopped at least an hour before bedtime. A good way to increase your child's activity levels is to limit all screen time (TV, video and computer games, mobile phones) to equal the time spent in physical activity. As in adults, the management of childhood obesity is based on a simple motto – "Eat less, move more". Physical activity not only burns calories, but also builds strong bones and muscles, reduces stress, and helps the child sleep well at night and stay alert during the day.

What behavioral changes should be incorporated?

Using food as a reward or for comfort should be strongly discouraged, as this get reinforced over time, and the child turns to food for celebrations and crises throughout life. The child/ adolescent should learn about healthy eating habits and be allowed to participate in decision making about what to eat, with appreciation for following the advice. Regular food and play timings, proper sleep and reduced availability of unhealthy snacks should be encouraged. Remember that the habits and attitudes your child gets used to today will stick with him/ her through adult life as well.

Recording in detail the diet and exercise can help in several ways. You, your child and the entire family become conscious of what is being eaten, and how much exercise is actually being done. Your doctor and/ or dietician can help you analyze the diary and discuss where and what to improve.

How can we contribute as a family?

Studies have shown that if the entire family adheres to the lifestyle recommendations, the child loses more weight and fat. Children are good learners and mimic what they see. Also by making healthy eating a priority and emphasizing the importance of physical activity for the whole family, you avoid singling out the obese child. Encourage the notion that all family members should eat together. Make meal times eventful - time to share news and tell stories. Discourage eating in front of a screen such as a TV, because it tends to lead to fast eating and lowered awareness of the amount eaten. Participate in physical activities along with the child; this increases bonding with the child, and ensures safety, regularity and cooperation. Emotional turmoil and a hostile family environment have been seen to increase the likelihood of obesity in children. Resolving family issues and maintaining a healthy family environment is important for proper physical and mental development of the child.

Are there any medications for obesity?

Yes, there are a few medicines that target weight loss, but they are associated with significant side effects (e.g. the only one approved for use in adolescents causes abdominal discomfort and greasy stools), and are only minimally effective. Medicine should be used only after lifestyle modification has not been effective enough, (while continuing with lifestyle changes), or to treat other illnesses, e.g. high BP, diabetes, or high cholesterol levels.

Is there any role of surgery?

Weight-loss (bariatric) surgery is permanent, and has serious consequences for the entire life), so it may be thought of as an option only for severely obese adolescents who have been unable to lose weight using conventional weight-loss methods. As with any type of surgery, there are potential short term risks and long-term complications, so your doctor may recommend bariatric surgery only if your child's weight poses a greater health threat than do the potential risks. Bariatric surgery is not a miracle cure, all excess weight may not be lost, and weight gain may recur. It is important to keep in mind that surgery does not replace the need for following a healthy diet and getting regular physical activity.

Pedendoscan

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Growth & Puberty

Long-Term Continuous Suppression with Once-Yearly Histrelin Subcutaneous Implants for the Treatment of Central Precocious Puberty: A Final Report of a Phase 3 Multicenter Trial. Silverman LA et al. J Clin Endocrinol Metab. 2015 Jun;100(6):2354-63.
36 children with CPP participated in this phase 3, open-label study: demonstrated sustained hormonal suppression throughout the study (both treatment-naive and patients with prior GnRHa therapy). Bone age to chronological age ratio decreased and predicted adult height in girls increased significantly [151.9 cm to 166.5 cm at month 60 ($P < .05$)]. No adverse effect on growth or recovery of the hypothalamic-pituitary-gonadal axis was observed. The histrelin implant was generally well tolerated during long-term therapy.

Changing Etiological Trends in Male Precocious Puberty: Evaluation of 100 Cases with Central Precocious Puberty over the Last Decade. Alikasifoglu A et al. Horm Res Paediatr 2015;83:340-344.
Retrospective analysis of 100 male CPP subjects revealed no underlying cause in 74% and an organic cause in only 26%. Most of the organic cases were before the age of 7 years. The authors suggested that the number of idiopathic male CPP cases is increasing over time and in CPP above the age of 7 years, the odds of detecting an underlying pathology are very low - these cases are mostly idiopathic.

Risk of Neoplasia in Pediatric Patients Receiving Growth Hormone Therapy: A Report from the Pediatric Endocrine Society Drug and Therapeutics Committee. Raman S et al. J Clin Endocrinol Metab. 2015 Jun; 100 (6):2192-203.
GH and IGF-1 have been shown to affect tumour growth in vitro and in some animal models. After reviewing the available evidence on whether GH therapy in childhood is associated with an increased risk of neoplasia, the report concluded that GH therapy can be safely administered in children without known risk factors for malignancy. GH use in children with medical diagnoses predisposing them to the development of malignancies should be critically analyzed on an individual basis, and appropriate surveillance for malignancies should be undertaken. GH can be used to treat GH-deficient childhood cancer survivors who are in remission with the understanding that GH may increase their risk for second neoplasms.

Diabetes and Obesity

Characteristics of maturity onset diabetes of the young in a large diabetes center. Chambers C et al. Pediatr Diabetes. 2015 Jun 8.
Maturity onset diabetes of the young (MODY) includes monogenic forms of diabetes caused by mutations in single genes, often not requiring insulin. To estimate the frequency and clinical characteristics of MODY, genetic testing revealed a diagnosis of MODY in 22 of a total of 97 subjects with diabetes onset before age 25, a random C-peptide ≥0.1 ng/mL, and negative for all diabetes autoantibodies (GADA, IA-2, ZnT8, and IAA). HNF-1α and glucokinase mutations were the most common causes. Only 1 of the 22 subjects had been given the appropriate MODY diagnosis prior to testing. Compared with MODY-negative subjects, the MODY-positive subjects had lower A1C level and no diabetic ketoacidosis at onset; however, these characteristics are not specific for MODY. In summary, this study found a high frequency of MODY mutations in a subset of insulin autoimmunity negative diabetics, with the majority of them clinically misdiagnosed. Clinicians should have a high index of suspicion for MODY in youth with antibody-negative diabetes.

Presentation of youth with type 2 diabetes in the Pediatric Diabetes Consortium. Klingensmith GJ et al. Pediatr Diabetes. 2015 May 8.
Clinical presentation of 503 youth with T2D using data from eight pediatric diabetes centers in the USA showed that 67% presented with symptoms of diabetes, confirmed by laboratory data, 11% presented with diabetic ketoacidosis (DKA), and 2% in a hyperglycemic hyperosmolar state (HHS). The age range was 4.6-19.8 yr, with 38 (8%) less than 10 yr of age at diagnosis. The majority were female (65%) and had family history of T2D (92%). The median body mass index (BMI) z-score was 2.3. Social vulnerability was a significant factor with only 46% living with both parents, only 30% had parents with education beyond high school, and 43% lived in a household with low annual income. Metformin and insulin were the initial treatment in most youth.

Ethnic differences in the incidence of type 1 diabetes in Norway: a register-based study using data from the period 2002-2009. Dzidzonu DK et al. Pediatr Diabetes. 2015 Jun 25.
To investigate differences in incidence rates of childhood-onset type 1 diabetes between immigrant groups and ethnic Norwegians, the study included 2221 children 0-14 yr with new onset T1D during 2002-2009, registered in the population-based Norwegian Childhood Diabetes Registry. The overall incidence rate was 34.0 cases per 100,000 person-years with large variations in incidence across the immigrant groups ($p < 0.001$), ranging from 6.8 per 100,000 person-years for South/East Asians to 26.0 cases per 100,000 person-years for sub-Saharan Africans. The differences remained significant after adjusting for age and gender.

C-peptide levels in pediatric type 2 diabetes in the Pediatric Diabetes Consortium T2D Clinic Registry. Gregg B et al. Pediatr Diabetes. 2015 May 5.
C-peptide levels in 331 youth with T2D (mean age, 16.1 ± 2.5 yr; median T2D duration, 2.4 yr) cared for at eight US Pediatric Diabetes Centers are presented. Median (interquartile range) for 90 fasted C-peptide measurements was 3.5 ng/mL and for 241 random non-fasted C-peptide measurements was 4.2 ng/mL. C-peptide levels were lower with insulin therapy ($p < 0.001$), lower body mass index ($p < 0.001$), A1C ≥9% ($p < 0.001$), and T2D duration ≥ 6 yr ($p = 0.04$).

Food advertising to children and its effects on diet: a review of recent prevalence and impact data. Boyland EJ, Whalen R. Pediatr Diabetes. 2015 Apr 21.
The article reviewed key, recent (last 5 yr) international research findings with regard to both the prevalence and effects of food and beverage advertising on children's intake. Evidence relating to the two main avenues of food marketing exposure - television and the Internet- is explored. The consistent outcome was- food advertising is prevalent, it promotes largely energy dense, nutrient poor foods, and even short-term exposure results in children increasing their food consumption.

Pearls from ADA meeting, Boston, USA, June 2015

Dr Anju Virmani, Senior Consultant Pediatric Endocrinologist, Max, Pentamed, SLJ & Apollo Hospitals, Delhi

THE TODAY STUDY

Some interesting facts about the patients in the TODAY study and their long term story:

Of the 1211 children screened, 10% had insulin autoimmunity though clinically they had type 2 diabetes. Of the 927 children run in, 91% achieved an A1C below 8%: they were weaned off insulin and did well, maintaining A1C below 8%.

Having an A1C more than 6.3% meant a 4x risk of needing insulin later, at a median time of 11 months, especially in African American girls. This was more sensitive in the males, more specific in the females.

Weight loss was associated with decreased A1C, and improvement in other metabolic parameters. Weight loss of over 7% in 6 months was seen in 31% of the metformin + lifestyle group, and 17% of the metformin + rosiglitazone group. This difference disappeared after 2 yr as more children lost weight. Weight loss should be an important aim in these children as it results in improved glycemic and non glycemic control.

There were 63 pregnancies in this group. Apart from 7 elective terminations, there was a startling 26% rate of loss, from 5 lost early (< 13 weeks) to eventual still birth. Of the 39 live births, of which 33 were full term, major congenital abnormalities were seen in as many as 21%.

OBESITY

Every kilo lost in adolescence means a significant decrease in type 2 diabetes in adulthood.

Parent-child involvement always works better than the child alone being addressed.

It is important to advise replacing saturated fats with polyunsaturated fats, not with carbohydrates. High carbohydrate intake increases metabolic risk.

The Omniheart Trial suggested that hypertension or prehypertension and dyslipidemia improved with replacing carbs with protein, of which at least half should be from plant sources (aiming for 25% calories from proteins) or with unsaturated fats (canola or olive oil). [*This is important for us Indians as our diets tend to be low on proteins and high on carbs*.]

Processed foods have high levels of sodium, so it does not help to just say “avoid added salt”. Read food labels and look for low sodium options. [*This is important, but in India most food labels do not state amount of sodium/ salt added. Thus all breads have added salt but do not mention the amount*.]

Beige adipocytes found in white adipose tissue can covert to brown if required. Adiponectin can induce beige fat cells, and improve insulin sensitivity.

Adiponectin levels are low in those with increasing obesity, and rise (with a fall in inflammatory markers) in those with metabolic improvement. It decreases levels of ceramides (which are mediators of insulin resistance). Adiponectin receptors are being explored as potential drug targets.

INSULIN REGIMENS

Self-titration of insulin doses is very effective. Control is better and hypos are much less.

Providers are not very good at assessing adherence, and often over-estimate it. Decreased adherence may be due to a number of factors – look into them.

A patient on U-100 insulin was mistakenly dispensed U-500 insulin, and found dead at home several days later. [*This is relevant to us as patients often mix up U-40 and U-100 insulin*.]

COMMUNITY

Brazil has achieved 74% decrease in acute complications, and 42% decrease in hospital admissions for acute complications. Their health services provide insulin, metformin, anti-hypertensives and aspirin free.

Book Review

Dr Anju Seth, Professor and In-Charge, Division of Pediatric Endocrinology, Lady Hardinge Medical College and Kalawati Saran Children's Hospital, New Delhi

Book name: Metabolic Syndrome and Obesity in Childhood and Adolescence

Editors: W. Kiess, M. Wabitsch, C. Maffeis, A.M. Sharma

Publisher: Karger, Basel, 2015

Contents: This book is the 19th volume in the series on 'Pediatric and Adolescent Medicine' by Karger. It presents an exhaustive review of various aspects of obesity and the closely related metabolic syndrome (MS), which are undoubtedly amongst the most rapidly emerging and challenging clinical problems affecting all age groups in the current time. The contents of the book are categorised under five sections: definition, causes, consequences, prevention and management. The topics covered include not only the current state of information regarding various medical aspects, but also economic, environmental and societal aspects of obesity.

Who would this book interest and benefit: Apart from clinicians and nutritionists dealing with obese children and adolescents, the book would be of interest to social scientists and economists interested in understanding the phenomenal rise in global prevalence of obesity, evaluating its impact, and contributing towards development of strategies for its containment. It would also help researchers in the above fields in identifying current gaps in our knowledge and developing appropriate research protocols.

Strengths: The editors have made an excellent effort to present a holistic view of the complex problems of obesity and MS, not just the medical issues. They have taken care to include authors with expertise and personal experience in a wide variety of domains including endocrinology, paediatrics, nutrition, orthopaedics, social sciences, and environmental health. The contents are well organised and presented in a logical sequence in a lucid and crisp manner.

Limitations: Obesity is a global problem affecting both the developed and the developing countries. The perspective presented in this volume is primarily based on situations and experiences from the developed nations. The social/ environmental factors associated with obesity and therefore the prevention strategies, are different in the developing world. Thus, including the developing world's perspective would have enriched the book further.

Sister Societies Consortium: a Report

Dr V Bhatia, President ISPAE

This Consortium of pediatric endocrine societies worldwide is being made firstly to get wider commitment towards the responsibility of holding the Joint Meeting (which hitherto had been organised by ESPE or LWPES (now PES) alternately, once every 4 years) and also to foster other educational and research collaborations on an international basis. The formation of the Consortium is in its nascent stages. At present, represented in it are the major continental or subcontinental societies as well as country societies: ESPE, PES, SLEP (Latin American), APPES (Asia Pacific), ASPAD (African), APEG (Australasian), ASPAE (Arabic), JSPE (Japanese), ISPAE, CSPEM (Chinese), as well as the 2 global societies ISPAD and GPED (global pediatric endocrinology and diabetes). At present, the Consortium is viewed as a voluntary agreement between sister societies, without a financial commitment. The international Joint Meeting of 2021 will be the first one to be held by a member of this consortium, for which bids will be presented during a face-to-face meeting of the consortium members during the ESPE Barcelona meeting in 2015. Hitherto, two teleconferences have been held between representatives of the sister societies, to share these points and invite comments and suggestions, chaired by the current Chair of the consortium, Dr Peter Clayton. Our office bearers have participated in them.

A short report by Dr Santosh Gupta

Washington University in St Louis, USA

In 2006 we took a daunting challenge to provide comprehensive T1DM management using MDI (multi-dose insulin) to children (< 26y) at the Rama Krishna Mission hospital (RKMH) in Haridwar. We used long acting analog insulin (Glargine) for the basal dose, and three injections of regular insulin for the bolus doses. Patients were provided with extensive diabetes self-management education (DSME). They used self-monitoring of blood glucose (SMBG) and carbohydrate counting, and attended monthly support group meetings. Diabetes care is provided by a dedicated team of a well-trained physician, a diabetes educator, and a community worker. Resources are provided by a grant from IDF's Life for a Child program (LFAC) and Insulin for life, USA.

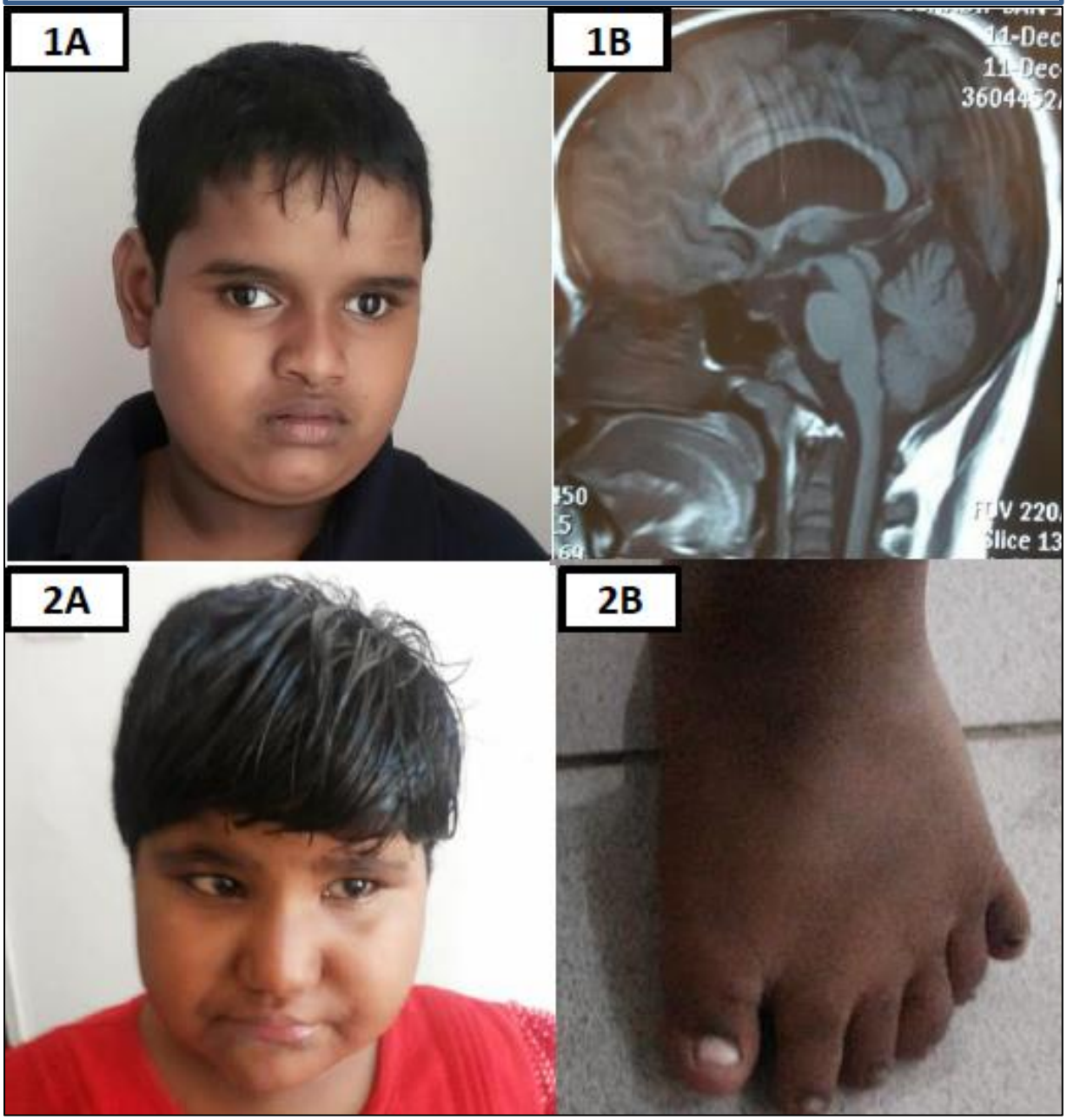
We learned that prior to 2006, at this facility diabetic children had not survived for long, due to unaffordability of insulin and lack of proper diagnosis/ treatment. Now in 2015, with our program, we have over 60 children with normal growth and development; leading healthy lives, with average A1C around 8%. It is remarkable that none of them needed readmission to the hospital with DKA or significant hypoglycemia. We are in the process of publishing our results.

Among other factors, DSME provided by our team was the key to the success of our program. In 2012 we started a certified diabetes educator India (CDEI) program at RKMH's Nursing School in Vrindaban. The candidates are graduate nurses and the program is of one year duration. Upon passing both the written and clinical exam of a standard no less than the one in USA, they are awarded CDEI certificates. In January 2015 this program received endorsement and a seal of approval from the International Diabetes Federation (IDF). Please visit the entire program at the IDF website or at the direct link to the program. There are two videos, one of which is also available at the IDF website.

http://www.idf.org/education/recognition-programme/2015-17/cdei-india

Photo Quiz

Dr Annie Pollikal, Senior Resident; Dr Vijaya Sarathi HA, Assistant Professor, Department of Endocrinology, Vydehi Institute of Medical Sciences and Research Center, Bangalore



1. Identify the obesity syndrome characterized by features shown in figures 1A and 1B. Which is the most common hormonal deficiency associated with this syndrome?

2. Identify the obesity syndrome characterized by features shown in figures 2A and 2B. Which is the other obesity syndrome that closely mimics this syndrome?

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Vandana Jain, AIIMS, New Delhi

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15. Menon PS, **Jain V**, Varma SK. Current issues in pediatric endocrinology. Indian J Pediatr. 2014;81:51-2.

Mary Abraham, Department of Paediatric Endocrinology, Princess Margaret Hospital, Perth, WA

1. **Abraham MB,** Rao S, Price G, Choong CS. Efficacy of Hydrochlorothiazide and low renal solute feed in Neonatal Central Diabetes Insipidus with transition to Oral Desmopressin in early infancy. International J Pediatr Endocrin. 2014;2014(1):11.
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Academic Activities by ISPAE Members

Symposium on Small for Gestation Age and Turner Syndrome: Report by

Dr Madhura Joshi, Fellow Pediatric Endocrinology, Bai Jerbai Wadia Hospital for Children, Mumbai

Symposium on Small for Gestation Age (SGA) and Turner syndrome (TS), organised by the Division of Paediatric Endocrinology, Department of Paediatrics, Bai Jerbai Wadia Hospital, was held on 9th August 2015 at the Auditorium, Nowrosjee Wadia Maternity Hospital, Parel, Mumbai.

With the increase in the number of births of SGA babies, the need to assess their long term outcomes in terms of growth, pubertal issues and complications, is of utmost importance. This symposium was held keeping the above in mind. The Symposium was a very informative one, attended by 125 pediatricians and gynaecologists from all over Mumbai and guided by eminent faculty members from Mumbai, Pune and Bangalore.

Dr Ruchi Parikh gave an insight into the normal pattern of growth in babies born SGA. Approximately 28% of SGA births are in India. 80% of these babies show catch growth by 6 months of age and nearly 90% by 4 years, thus 10% fail to catch up and remain short as adults. Maternal nutrition, perinatal, neonatal nutrition and environmental factors govern growth especially during the period of catch up, the major endocrine regulators being IGF-I, IGF-II and insulin.

Monitoring of growth in these babies is the key to identify the babies who are faltering. Dr Rajesh Joshi outlined the clinical approach to diagnosis and evaluation of short stature in children born SGA. He stated that Russell Silver Syndrome (RSS) was the commonest syndrome in SGA babies who remain short.

Rapid catch up growth is linked to early pubertal changes, early adrenarche and may lead to short adult height. Rapid catch up is also associated with obesity and metabolic syndrome (insulin resistance, diabetes, dyslipidemia). Dr Prema Varthkavi highlighted the Indian perspective and shared her experience of metabolic syndrome in children born SGA.

Dr Shaila Bhattacharya simplified some of the mechanisms involved in early adrenarche and pubarche in SGA babies. She stressed that since early onset of puberty and blunted pubertal growth spurt resultin short adult height, overzealous nutrition in these babies is detrimental and may push them into early puberty and metabolic syndrome. Parents must be counselled accordingly.

Dr Sudha Rao highlighted that Growth Hormone therapy should be offered to SGA babies with failure to catch up by 4 years of age, Height SDS < -2.5 or a growth velocity of 0. She shared her experience of GH therapy in children born SGA. She also pointed out that most of the SGA babies are GH- IGF 1 insensitive and GHD is rare.

The talk on the Genomics of SGA and TS by Dr Koumudi Godbole was very interesting. She discussed how genetic testing could complement our clinical diagnosis, giving information on available modalities like karyotype, FISH, and Micro-array.

Dr Vaman Khadilkar outlined the timing, dosing, and benefits of GH therapy, and role of low dose estrogens in optimising growth in children with TS. He explained that low dose estrogen could be started as early as by 5 years of age and that estrogen replacement when provided by 12 years of age rather than 15 years is more beneficial.

Pubertal induction and hormone replacement were discussed by Dr Prisca Colaco: the benefits of various estrogen formulations, and the role of continuous estrogen therapy.

A sensitive but very important issue in management of girls with TS is of fertility. Fertility potentiating and reproductive challenges in cytogenetic disorders, limitations of oocyte transfer, availability of surrogacy, and need to prevent pregnancy in TS women who have congenital heart disease were highlighted by Dr Rama Vaidya. Discussing cardiovascular morbidity in TS Dr Snehal Kulkarni stratified risk as mild, moderate and severe, and explained that children with TS are at a greater risk of aortic dissection. Hence echocardiography for aortic root dilatation monitoring is an essential part of their management.

The symposium concluded with a panel discussion on TS and SGA moderated by Dr Rajesh Joshi and Dr Ruchi Parikh, with distinguished panelists Dr Padma Menon, Dr Rama Vaidya, Dr Shakuntala Prabhu, and Dr Sudha Rao. It was a very interactive session with active participation by the audience. Dr Neha Dighe, Dr Mudita Dhingra, Dr Madhura Joshi (Fellows in Pediatric Endocrinology) ably compered the sessions.

Take Home messages

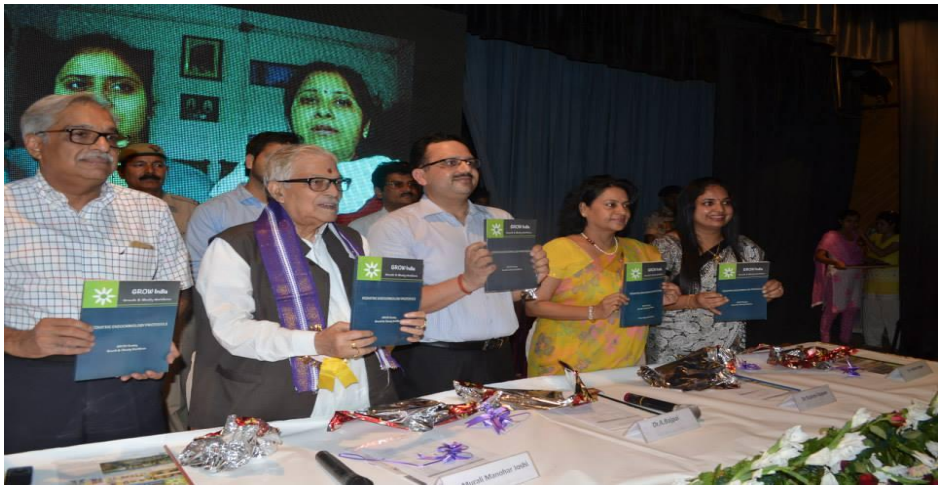
- SGA is a common condition in Indian population.
- 10% of babies born SGA fail to have catch up growth by 4 years of age.
- GH therapy is indicated in such children after careful monitoring, testing with a paediatric endocrinologist's advice and supervision.
- SGA children can develop obesity and metabolic syndrome, being programmed in-utero or genetically predisposed or with overzealous feeding. Recognising this helps in monitoring and early recognition and preventive measures.
- SGA children can go into early puberty, have a blunted pubertal growth spurt and hence a short adult height.
- Low dose estrogen can be started in children with TS from 5 years of age; estrogen replacement for pubertal induction should be started by 12 years instead of the conventional 15 years of age.
- Turner girls with heart disease, especially with aortic root dilatation, should be counselled against pregnancy as there is an increased risk of aortic root dissection and death. Fertility potentiation through oocyte preservation, though experimental, can be tried.
- Cardiac monitoring is essential and risk categorisation helps. Measuring BP in each clinic visit is mandatory. Cardiac MRI is not essential in all cases.

Academic Activities by Dr Anurag Bajpai

Dr Bajpai conducted a Growth workshop in association with IAP Faridabad, on 28.02.2015, a thyroid workshop in association with IAP Gurgaon on 12.04.2015, a puberty workshop in association with Gurgaon Obs & Gynae Society on 13.04.2015, a growth workshop in association with IAP Moradabad on 02.05.2015, a diabetes workshop in association with IAP Meerut on 03.05.2015 and a thyroid workshop in association with IAP Kanpur on 25.05.2015.

Dr Bajpai delivered lectures on 'Cushing syndrome' at Pedicon, New Delhi in January 2015, on 'Childhood Obesity' and 'Thyroid disorders in children' at an Endocrinology Update organized by IAP Ahmedabad on 13.03.2015, on 'Diabetic Ketoacidosis: what's new?' at an Endocrinology Update organized at Vivekanand Polyclinic, Lucknow on 12.04.2015, and on 'Toddlers falling off the growth curve: which investigations and why?' at IPEDIA organized at Goa on 10.05.2015.

He organized the release of the book 'Pediatric Endocrinology Protocols', published by GROW India, by Dr Murali Manohar Joshi on the occasion of II GROW India day, April 21 2015. The book covers the entire range of pediatric endocrine disorders, with special emphasis on common conditions presenting to the pediatricians. It is divided into six modules corresponding to the GROW Society training modules, developed with the aim of providing a practical approach for assessment and management of the disorders. Clinical assessment has been given due importance with the aim of minimizing investigations. The book is targeted at postgraduate trainees and practicing pediatricians, and can be obtained from Dr Bajpai (Email: *dranuragbajpai@yahoo.com*)



Pediatric Endocrine CME at Vydehi Institute of Medical Sciences and Research Center, Bangalore

The Department of Pediatrics and the Department of Endocrinology, Vydehi Institute of Medical Sciences and Research Center, organised a one day 'Pediatric Endocrine CME' on 3rd July 2015. It was attended by 350 members, predominantly pediatricians and gynecologists from all over Karnataka. Dr Vijaya Sarathi (Approach to a child with short stature), Dr Shivaprasad C (Growth hormone deficiency in children), Dr Anjana Hulse (Vitamin D nonresponsive rickets, Diabetic ketoacidosis), Dr Prasanna Kumar KM (Domiciliary management of T1DM), Dr Belinda George (Congenital hypothyroidism, Childhood obesity) and Dr Vageesh Ayyar (Delayed puberty) delivered lectures in the CME. A panel discussion was conducted on disorders of sex development.

Academic Activities by Dr Hemchand K Prasad

Dr Hemchand K Prasad (Mehta Children's Hospital, Chennai) organized guest lectures on "Diabetes in youth: lessons from the TODAY study" by Prof Stephen Greene from University of Dundee and on "Engaging the patient, family and community" by Dr Alexandra Greene, on 20.01.2015; and another guest lecture on "Type 1 Diabetes mellitus in a toddler" by Dr Ragnar Hanas from Uddevalla Hospital, Sweden on 13.01.2015 at the Mehta Children's Hospital Auditorium.

Academic activities by Dr Ravindra Kumar

World Thyroid Day was celebrated on 28th May 2015 by the Department of Pediatrics at Hindu Rao Hospital, Delhi. Dr Ravindra Kumar delivered a lecture on 'Congenital hypothyroidism' and Dr Rajesh Khadgawat highlighted 'Thyroid disorders in childhood'.

Endocrinology workshop, 14th Aug 2015 at Adolescon 2015, Mangalore

The workshop aimed to provide comprehensive approach to management of endocrine disorders in adolescence:plot and interpret growth charts, read bone age X rays, perform sexual maturity rating, plan appropriate assessment and suggest management to an adolescent with endocrine disorders. It was organized by Dr Preeti Galagali, Secretary, Adolescent Health Academy, *secretary@ahaiap.org.*

Activities by ISPAE in PEDICON 2015

Issue of certificates by Dr Vaman Khadilkar to ISPAE Observership Award winners Dr Abraham Paulose (SGPGI, Lucknow) and Dr Vishnu Agarwal (BJ Wadia Hospital, Mumbai) at PEDICON 2015.

Charitable Activities by ISPAE Members

Activities by GROW INDIA

Web Awareness initiatives related to pediatric endocrinology launched by GROW India

1. Type 1 DM from problem to solution-The informational video traces the lives of five children with Type 1 DM to identify and rectify their day to day problems: *https://www.youtube.com/watch?v=ZWB5PjW-FxE*
2. Celiac disease- The video provides practical information to families dealing with celiac disease: *https://www.youtube.com/watch?v=ZCBSEuBCncE*
3. Think thyroid- Awareness about childhood thyroid disorders: *https://www.youtube.com/watch?v=H3TxRD1VcOI*
4. Road to growth- Awareness video on growth disorders: *https://www.youtube.com/watch?v=EY2l8QxsRQg*
5. Website for children with diabetes*: www.diaboworld .com*

II GROW India Day, April 21 2015

II GROW India day was organized at Ragendra Swarup Auditorium, Kanpur and attended by 100 teachers, 300 children with hormonal disorders including type 1 DM, doctors and members of social groups. The thrust area of this year's program was Type 1 DM. Key events included release of Type 1 DM documentary, release of Pediatric Endocrinology protocols, declaration of "Road to Growth" results, growth exhibition and submission of "Memorandum of Demands" of children with diabetes to the chief guest of the event, Dr Murali Manohar Joshi. Dr Joshi highlighted the key role of lifestyle in preventing chronic disorders.

Patient Activities by Dr Hemchand K Prasad, Chennai

"Grow day" was celebrated on 01.05.2015 at Mehta Children's Hospital auditorium: attended by 25 children with GHD and their families. Families shared their experiences on GH therapy and how they have benefitted from it. The program was followed by cultural events.

"Diabetic get together" was held of families with type 1 diabetes at a theme park called Queensland in Chennai on 17th May 2015. The families assembled and were taken to Queensland. Children enjoyed participating in the events and had an education session on 'Diet' and 'Management on days of Outings'. The program was highly appreciated by all.

Report of charity activity done during Kashmir floods in September 2014

Dr Shafi Kuchay, Dr Ganesh Jevalikar, Division of Endocrinology, Medanta, The Medicity, Gurgaon

In September 2014, the state of Jammu and Kashmir faced the worst floods in history. There was acute shortage of medical facilities and personnel during this natural disaster. Dr Shafi Kuchay, ISPAE member, volunteered for relief work during this disaster, which included medical camps, distribution of antibiotics and other medications, and administration of intravenous fluids.

Since there was acute shortage of insulin and blood sugar strips, many diabetic patients had hyperglycemia and some had ketoacidosis. In addition to acute medical problems like respiratory infections, fever and GI infections, about 20-30 diabetic patients were seen per day in different medical camps in Budgam district (Humhama, Peerbagh, Hyderpora and Baghat). These patients were provided with free blood glucose testing, oral antidiabetic medications and insulin. About 10-15 patients with hyperglycemic emergencies were managed at medical camps.

All consultants of the Division of Endocrinology and Diabetes, Medanta Medicity Hospital, including Dr Khalid Farooqui, Dr Ganesh Jevalikar, Dr Parjeet Kaur, Dr Beena Bansal, Dr Ambrish Mithal, Dr Harmandeep Gill (all ISPAE members), Dr Jasjeet Wasir and Dr Sunil Mishra, collectively contributed to purchase insulin, blood glucose testing strips, insulin syringes and glucometers, which were sent to Dr Shafi Kuchay at Srinagar by Spicejet cargo.

Hearty Welcome to New ISPAE Members

Kartheek Nalluri	Ranjuraj Rajendran	Neeraj Kumar Agarwal
Vishal Mahajan	Arun Mukka	Praveen K Ganji
K Sudeep	Deepty Kumar	Ashok Venkatanarasu
Swati Dublish	Garima Chawla	Bharath Bhachimanchi
Anbezhil Subbarayan	Aniket Kumbhojkar	Thangawelu Sangaralingam
Prashant Patil	Ruchi Mishra	Parvatham Venkateshwarlu
Anurag Katiyar	Dalal Lopa Kanhaiyalal	Shalini Patlolla
Sailaja Anantarapu		

Upcoming Events by ISPAE Members

Pediatric Endocrine CME at Bangalore on 23rd Aug 2015

Manipal Advanced Children Center (MACC) and Sushruta Diabetes and Endocrinology Research Trust have organised a one day CME on 'Pediatric Endocrinology (Endocrinology made easy)' at 'My Fortune Bengaluru' on 23rd August 2015. The CME is entitled with 2 KMC credit hours. For registration contact Dr Latha R (Mobile: 9886740450).

PAED ENDO 2015 at Chennai on 30th Aug 2015

The Department of Pediatrics, Sri Ramachandra Medical College and Research Institute, and the Institute of Child Health and Hospital for Children, have organised a one day CME 'PAED ENDO 2015 (Conference on Paediatric and Adolescent Endocrinology for Postgraduates and Paediatricians)' on 30th August 2015, at Hotel Ramada, Egmore, Chennai. For registrations contact Dr J Dhivyalakshmi (Mobile: 9841184748, Email: *dhivya8@yahoo.co.in*).

ISPAE 2015 and ISPAE PET 2015

Dr Ganesh Jevalikar, Organizing Secretary, ISPAE 2015

The millennium city, Gurgaon, is getting ready to welcome delegates for ISPAE 2015 and ISPAE PET 2015. The 4th biennial meeting of ISPAE will be held between 27-29 November 2015 at The Epicentre, in Gurgaon. The scientific program is ready, with topics of interest to paediatricians, endocrinologists, and pediatric endocrinologists. It has been uploaded on the conference website www.ispae2015.com. We have received several abstracts for oral as well as poster presentations. The deadline for abstract submission is 31st August 2015: through CAPE NEWS, I once again request all ISPAE members to display their huge clinical work to the national and international community, which looks forward to ISPAE as a promising organization.

The Fellows' program, ISPAE PET 2015, has received several applications which will be scrutinized and the names of selected candidates displayed on the website by August end. The eminent international and national faculty includes Drs Margaret Zacharin, Paul Hoffman, Matthew Sabin, Craig Munns, Olaf Hiort, Jean Claude Carel, P Raghupathy, PSN Menon, V Bhatia, Preeti Dabadghao, Sudha Rao, Nalini Shah, Vandana Jain, and Rajesh Khadgawat. The venue of the meeting is Savoy Suites, in Manesar, on the outskirts of Gurgaon. It is supported by a financial grant from Novo Nordisk India.

Looking forward to welcome you all in Gurgaon this winter!!

4th Biennial Meeting of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)

27th - 29th November, 2015

Epicentre, Gurgaon

ISPAE 2015- International Faculty

Dr. Craig Munns | Dr. Jean-Claude Carel | Dr. Margaret Zacharin

Dr. Matthew Sabin | Dr. Olaf Hiort | Dr. Paul Hoffman

Registration Fees

Category	Till 30th September 2015	1st October 2015 Onwards
General	INR 5000	INR 6000
ISPAE Member	INR 4000	INR 5000
Post Graduate (Student)	INR 3500	INR 4500
Accompanying Person	INR 3000	INR 3000
Foreign Delegates	INR 6000	

Multicity Bank Cheque / Demand Drafts (payable at Gurgaon) are to be made in favour of: ISPAE 2015

To Register, Contact Mr. Davesh Sharma (+91-9560493999)

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Answer to Photo Quiz

1. Figure 1A shows squint in an obese child (child also had nystagmus) and figure 1B shows thinning of corpus callosum (child also had absent septum pellucidum, not shown in figure). The features are diagnostic of Septo-optic dysplasia (De-Morsier syndrome). The most common hormonal deficiency in Septo-optic dysplasia in growth hormone deficiency.

2. Figure 2A shows an obese girl with searching look and figure 2B shows postaxial polydactyly. The features are suggestive of Bardet-Beidl syndrome. The syndrome that mimics Bardet-Beidl syndrome closely is Alstrom syndrome.