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CONTENTS

TOPIC OF INTEREST - ENDOCRINOLOGY

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Gurgaon

49th Annual National Conference of IAP

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ENDOCRINOLOGY

CHILDHOOD METABOLIC SYNDROME AND POLYCYSTIC OVARIAN DISEASE

Nalini S Shah

Abstract: *Obesity in youth is a worldwide public health problem. Childhood obesity results in clinical conditions such as metabolic syndrome, early atherosclerosis, dyslipidemia, hyper tension, fatty liver and type 2 diabetes. Central obesity is directly linked to insulin resistance and metabolic syndrome. Ethnicity, intrauterine environment, low birth weight, excess diet and poor physical activity are the etiopathogenetic factors which work synergistically. With the foresight that metabolic syndrome tracks into adulthood, it should be recognized and intervened early for the prevention of diabetes and coronary heart disease. The treatment of obesity during childhood and adolescent period is mainly non pharmacological and aims at promoting lifestyle modification.*

Polycystic ovarian syndrome is a strong clinical correlate of metabolic syndrome relevant to adolescent girls. Diagnostic criteria and treatment for adolescent PCOS are not clearly defined yet. Lifestyle modification forms the basis of preventive and therapeutic strategy of the epidemic of obesity and metabolic syndrome.

Keywords : *Metabolic syndrome, Polycystic ovarian disease.*

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The "metabolic syndrome" (MS) is a term used to describe the clustering of metabolic risk factors for type 2 diabetes and atherosclerotic cardiovascular disease in adults, namely: abdominal obesity, hyperglycemia, dyslipidemia and hypertension. The prevalence and magnitude of childhood obesity are increasing dramatically. It is also clear that insulin resistance is significantly related to obesity and cardio-metabolic risk in children. Importantly childhood metabolic syndrome likely tracks into adulthood and so early identification may help target interventions to improve future cardiovascular risk.[1]

Definition and prevalence

Single definition, with gender and ethnicity-specific cutoff points is applicable for adults, but using a single definition in children and adolescents is difficult. Blood pressure, lipid levels, and anthropometric variables change with age and pubertal development.[2] To overcome this limitation values above the 90th, 95th or 97th percentile for gender and age are used to define abnormalities in children.

Duncan, et al. studied 991 adolescents (aged 12-19 yr) from National Health and Nutrition Examination Study (NHANES) in 1999-2000 and used the Adult treatment panel III (ATP III) definition modified for age. The overall prevalence of a metabolic syndrome (MS) phenotype among US adolescents increased from 4.2% in NHANES III (1988-1992) to 6.4% in NHANES 1999-2000.[1]

In a sample of obese youth, Weiss, et al showed that 39% of moderately obese and

50% of severely obese youth had >3 components of the metabolic syndrome. BMI > 97th percentile for age and sex was used to define obesity instead of waist circumference.[3]

Vikram, et al applied NCEP, ATP III criteria with appropriate percentile cutoff points for Indian adolescents and reported MS prevalence was only 0.8%. Inclusion of BMI in the MS definition increased its prevalence to 4.3%. Further, adding fasting hyperinsulinemia as a criterion, the prevalence increased up to 10.2%.[4]

Among obese children, the prevalence of the metabolic syndrome is high and increases with worsening obesity. This was illustrated by study in chinese adolescents where MS prevalence was reported to be 3.7%; however, the prevalence was 35.2, 23.4, and 2.3% among adolescents who were overweight (BMI >95th percentile), at risk of overweight (BMI between 85th and 95th percentile), and normal weight (BMI below the 85th percentile), respectively.[5]

As noted above the prevalence rates of MS in childhood vary depending on diverse criteria used.

In 2007, International Diabetes Federation (IDF) provided a unified definition for identifying those at risk, with abdominal obesity as defined by waist circumference as the 'sine qua non' criteria (Table I).[6]

The IDF definition of metabolic syndrome in children 10 to 16 years old is similar to that used by the IDF for adults, except that the definition for adolescents uses ethnic-specific waist circumference percentiles and single cutoff level for HDL for both sexes. For children 16 years and older, the adult criteria can be used. For children younger than 10 years of age, metabolic syndrome cannot be diagnosed, but vigilance is recommended if the waist circumference is >90 percentile. For those of South and South-East Asian, Japanese, and ethnic South and Central American origin, the waist

Table I. International Diabetes Federation criteria for metabolic syndrome in children

Age Group (years)	Waist circumference*	TG (mg/dl)	HDL (mg/dl)	Blood Pressure (mmHg)	Glucose (mg/dl)
6 -10	> 90th Percentile				
10 - 16	> 90th Percentile	> 150	< 40	Systolic BP > 130 or diastolic BP > 85	FPG > 100 or T2D
> 16 Adult Criteria	>94 cm (males) > 80 cm (females)	> 150	< 40 (males) < 50 (females)	Systolic BP > 130 or diastolic BP > 85	FPG > 100 or T2D

(Diagnosis of MS requires the presence of central obesity plus any two of other criteria)

BP-Blood pressure; FPG-Fasting plasma glucose; T2D-Type 2 diabetes; TG-Triglycerides

* Waist circumference is measured midway between lower rib and iliac crest with both legs close together

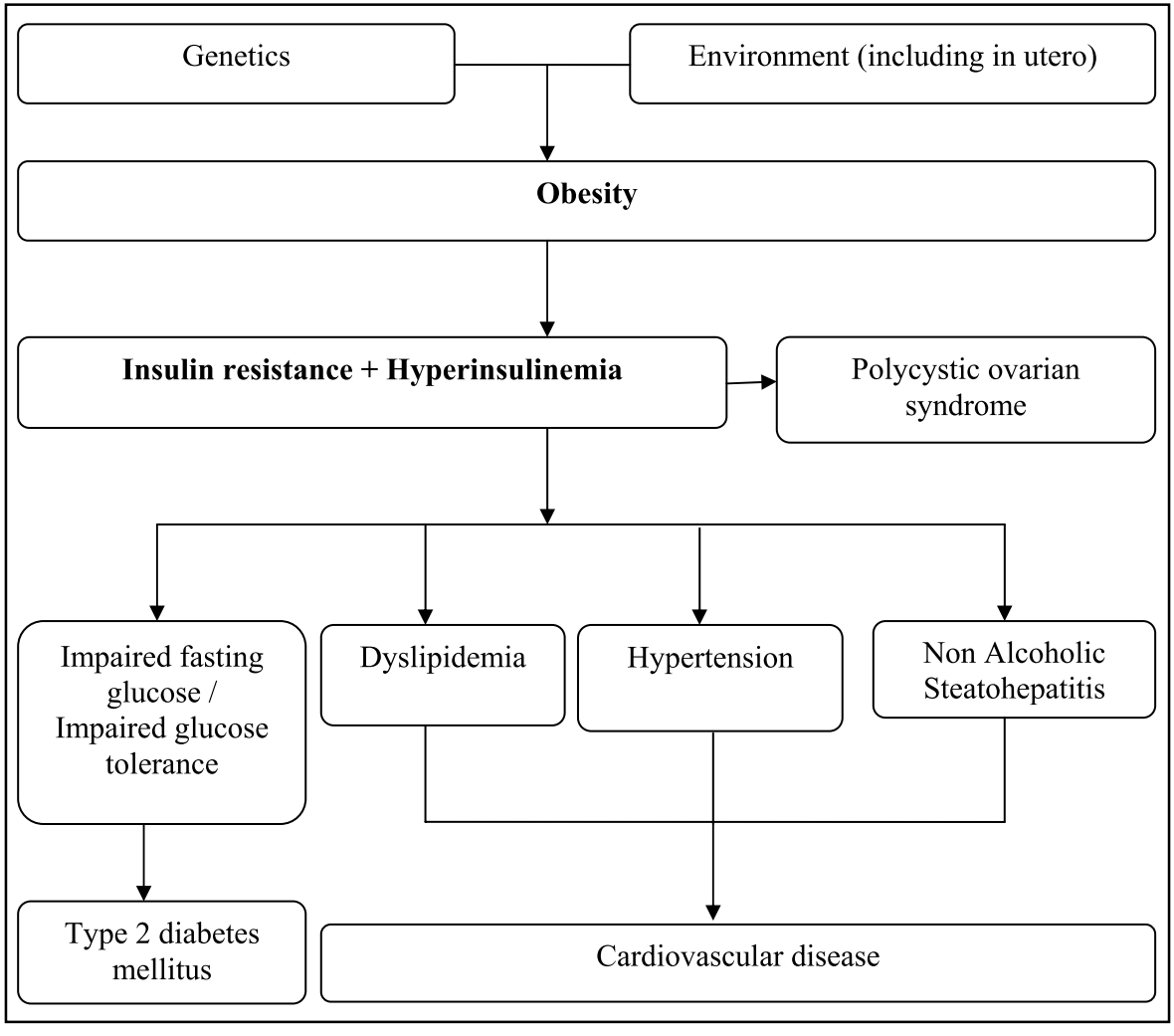

Fig.1.Components of metabolic syndrome and their association

circumference cutoffs should be >90 cm for men, and >80 cm for women.

Pathophysiology

A key factor in the pathogenesis of MS is insulin resistance, a phenomenon occurring mainly in obese subjects. Hypertension, dyslipidemia, and subclinical inflammation are likely to be the products of insulin resistance (Fig.1). The pattern of fat distribution is important as excess visceral fat is strongly associated with MS in childhood and Coronary artery disease (CAD) later in life.[7] Genetics and ethnicity play a role in the pathogenesis of MS. In fact, heritability for obesity ranges from 60% to 80% and it varies from 11% to 37% and 43% to 54% for blood pressure and lipid levels respectively.[8]

Indians tend to develop severe insulin resistance even in the presence of mild increase of BMI or abdominal adiposity[9] and have greater insulin resistance even when BMI is matched

with persons of other ethnic groups.[10] Another difference highlighted as compared to white Caucasians and Blacks is greater truncal subcutaneous adipose tissue in Indian children.[11]

External factors such as poor nutrition in a pregnant woman leading to low birth weight and "catch-up" childhood obesity adversely affects body composition.[12] Large-for-gestational-age offspring of diabetic mothers and those born to obese mothers are at an almost twice the significant risk of developing the MS in childhood.[13] Urbanisation, unhealthy diet and sedentary lifestyle are the modifiable external contributors to MS.[14]

The effect of hyperinsulinemia on blood pressure may be ascribed to the effect of insulin on (a) sympathetic nervous system activity (b) sodium retention by kidney and (c) vascular smooth-muscle growth stimulation.[15] In vivo studies showed that hyperinsulinemia causes dyslipidemia by stimulating triglyceride synthesis via transcription of genes for lipogenic enzymes in the liver.[16]

The Bogalusa Heart Study showed that insulin resistance in childhood promotes the development of premature atherosclerosis and significantly increases cardiovascular risk early in life.[17]

Polycystic ovarian syndrome is strongly associated with insulin resistance. South Asian subjects with PCOS are more symptomatic (hirsutism, acne, acanthosis nigricans, and secondary infertility) and have higher fasting insulin concentrations as compared white Caucasians.[18]

Non-alcoholic fatty liver disease (NAFLD) sometimes resulting in non-alcoholic steatohepatitis (NASH), has been shown to be the new and important hepatic correlate of insulin resistance and the metabolic syndrome. NAFLD probably is the most common form of liver disease in children. Early development of fatty liver in non-obese prepubertal children suggests that accumulation of fat in the liver may be the crucial step in the development of insulin resistance in these subjects and often NASH may be the first clinical indication of insulin resistance.[19]

Diagnostic approach

Approach to diagnosis of insulin resistance and MS in a child

Detailed clinical history, clinical examination and relevant investigations are required for the diagnosis of metabolic syndrome. History should include family history of obesity and diabetes, small for gestational age with catch up childhood obesity, large for gestational age and maternal diabetes, diet and physical activity. Clinical examination should include anthropometric measurements like weight, height, BMI and waist circumference, blood pressure recording, skin examination for ancanthosis nigricans and sexual maturity rating. Rare genetic lipodystrophies can present as severe insulin resistance in childhood.

Investigations should include fasting plasma glucose, glycosylated hemoglobin, lipid profile, and serum aminotransferases. Secondary causes of obesity (eg. Cushing's syndrome, craniopharyngioma, hypothyroidism, etc) should be ruled out with relevant tests in cases of suspicion. If PCOS is suspected then additional hormonal profile and ovarian ultrasonography may be obtained.

It is important to note that fasting insulin is a poor measure of insulin sensitivity in an individual child, and it should not be used for clinical decision making in day to day clinical practice.[20] Ultrasonography to look for fatty liver is optional.

PCOS in adolescents

PCOS is defined as otherwise unexplained hyperandrogenism (hirsutism, severe acne, androgenic pattern alopecia), and ovarian dysfunction that manifests as either menstrual irregularity (oligo - or amenorrhea, irregular bleeding) or polycystic ovaries. The Rotterdam criteria define PCOS when two of the three primary features are present: unexplained clinical or biochemical signs of hyperandrogenism, oligo-anovulation, and/or polycystic ovaries. Androgen excess society 2006 has made hyperandrogenism as an essential criterion for the diagnosis of PCOS. There are no formal diagnostic criteria for PCOS in adolescents because of the inherent difficulties. Distinction between PCOS and physiologic anovulation is difficult especially during the first two years of postmenarcheal period.[21] Transabdominal ultrasound can miss polycystic ovaries specifically in obese adolescents where transvaginal route is routinely avoided. Hyperandrogenism still can be used as specific diagnostic feature of adolescent PCOS. Serum total and free testosterone are best assessed in the early morning, on days 4 through 10 of the menstrual cycle in regularly cycling girls. Secondary causes like hyperprolactinemia, Cushing's syndrome, acromegaly, hypo-thyroidism, congenital adrenal hyperplasia, drugs like valproate and virilising tumors should be considered and ruled out.

Polycystic ovary syndrome (PCOS), independent of weight, is characterized by insulin resistance in childhood. Insulin-resistant hyperinsulinism is an important extrinsic factor in the steroidogenic dysregulation of PCOS. The prevalence of metabolic syndrome in adolescents with PCOS was 25% which was three times greater than expected for age, ethnicity, or body mass index. In most series of patients with PCOS, the prevalence of obesity varies from 30% to 75%.[22] Once the diagnosis of PCOS has been established, it is important to identify and monitor for abnormal glucose tolerance and other features of the metabolic syndrome, because PCOS is a risk factor for the early development of type 2 diabetes mellitus and metabolic syndrome and their associated morbidity.

Treatment

Dietary modification

In adolescents receiving either a high-fiber[23] or low glycemic load diet[24] weight loss was observed with improved insulin sensitivity. DASH diet comprising of fruits, vegetables, and low-fat dairy products and avoiding salted and processed food products was found to be beneficial for children and adolescents with labile or mild hypertension.[25] Excess calories, high-carbohydrate, saturated fats with sweetened beverages should be avoided.

Physical exercise

Allen, et al have shown that fitness may play a more important role than body mass index reduction on improvement in insulin sensitivity in obese adolescents.[26] However, there is inadequate evidence about the optimal form of exercise i.e., aerobic, resistance or combination types.

Pharmacologic treatment

Metformin has been shown to improve insulin sensitivity in adolescents with type 2 diabetes[27] and girls with obese PCOS.[28] Metformin treatment has not been approved for treatment of children with insulin resistance alone, as data from controlled trials is lacking.[20] Orlistat[29] improve insulin sensitivity with weight loss of approximately 0.6 SD in children and adolescents. The antiobesity drugs should be conservatively used as long term safety of these drugs in children is not known.

Behavioral modification

Life style disorders are to be dealt with behavioral changes to have sustainable effects.

Importantly, other therapeutic modifications are liable to fail without proper behavioral modification.

Prevention

Targeting factors affecting fetal growth such as maternal obesity, gestational diabetes, maternal undernutrition, and smoking during pregnancy could prevent childhood MS.[20]

Identifying high risk groups for MS (eg. small for gestational age with catch up growth) and instituting adequate diet and exercise plans at the earliest.[30] Promotion of healthy dietary habits starting from promotion of breast feeding and proper diet during infancy and childhood has shown long term beneficial impacts.[31] Physical activity among children should be promoted at all age groups.

Points to Remember

- ***Metabolic syndrome (MS) is characterized by the presence of abdominal obesity, hypertension, hyperglycemia and hyperlipidemia.***
- ***Insulin resistance is the key factor that leads to development of all the features of MS.***
- ***Polycyctic ovary syndrome (PCOS) is a strong risk factor for type 2 Diabetes Mellitus and MS.***
- ***Life style modification that includes proper diet and physical exercise and drugs therapy improve insulin resistance.***

References

1. Duncan GE, Li SM, Zhou XH. Prevalence and trends of a metabolic syndrome phenotype among U.S. Adolescents, 1999–2000. Diabetes Care 2004;27:2438-2443.
2. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. Circulation 2007; 115:2316.
3. Weiss R, Dziura J, Burgert T, Tamborlane W, Taksali S, Yeckel C, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004;350 :2362-2374.
4. Vikram NK, Misra A, Pandey RM, Luthra K, Wasir JS, Dhingra V. Heterogeneous phenotypes of insulin resistance and its implications for defining metabolic syndrome in Asian Indian adolescents. Atherosclerosis 2006;186 :193-199.
5. Li Y, Yang X, Zhai F, Kok FJ, Zhao W, Piao J, Zhang J, Cui Z, Ma G 2008; Prevalence of the metabolic syndrome in Chinese adolescents. Br J Nutr 2008;99: 565-570.
6. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. Lancet 2007; 369:2059.
7. Janssen I, Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C, et al. Combined influence of body mass index and waist circumference on coronary artery disease risk factors among children and adolescents. Pediatrics 2005;115:1623-1630.
8. Ter_an-Garc_ýa M, Bouchard C. Genetics of metabolic syndrome. Appl Physiol Nutr Metab 2007;32:89-114.
9. Vikram NK, Pandey RM, Misra A, Sharma R, Devi JR, Khanna N. Non-obese (body mass index _ 25 kg/m2) Asian Indians with normal waist circumference have high cardiovascular risk. Nutrition 2003;19:503-509.
10. Chandalia M, Abate N, Garg A, Stray-Gundersen J, Grundy SM. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. J Clin Endocrinol Metab 1999;84: 2329-2335.
11. Misra A. Impact of ethnicity on body fat patterning in Asian Indians and Blacks: relationship with insulin resistance. Nutrition 2003;19: 815-816.
12. Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350:865-875.
13. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association

with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115:e290-296.

14. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415-1428.
15. Landsberg L. Hyperinsulinemia: possible role in obesity-induced hypertension. Hypertension 1992;19:I61-166.
16. Assimacopoulos-Jeannet F, Brichard S, Rencurel F, Cusin I, Jeanrenaud B. In vivo effects of hyperinsulinemia on lipogenic enzymes and glucose transporter expression in rat liver and adipose tissues. Metabolism 1995;44:228-233.
17. Tzou WS, Douglas PS, Srinivasan SR, Bond MG, Tang R, Chen W, et al. Increased subclinical atherosclerosis in young adults with metabolic syndrome: the Bogalusa Heart Study. J Am Coll Cardiol 2005;46:457-463.
18. Wijeyaratne CN, Balen AH, Barth JH, Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among South Asians and Caucasians: is there a difference? Clin Endocrinol (Oxf) 2002;57:343-350.
19. Mandato C, Lucariello S, Licenziati MR, FranzeseA, Spagnuolo MI, Ficarella R, et al. Metabolic, hormonal, oxidative, and inflammatory factors in pediatric obesity-related liver disease. J Pediatr 2005;147:62-66.
20. Insulin Resistance in Children: Consensus, Perspective, and Future Directions Claire Levy-Marchal, Silva Arslanian, Wayne Cutfield, et al. J Clin Endocrinol Metab 95: 2010 (ahead of publication)
21. Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Pediatrics. 2006 ;118 :2245-2250.
22. Ehrmann, DA. Polycystic ovary syndrome. N Engl J Med 2005; 352:1223.
23. Steffen LM, Jacobs Jr DR, Murtaugh MA, Moran A, Steinberger J, Hong CP, Sinaiko AR. Whole grain intake is associated with lower body mass and greater insulin sensitivity among adolescents. Am J Epidemiol 2003;158: 243-250.
24. Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced-glycemic load diet in the treatment of adolescent obesity. Arch Pediatr Adolesc Med 2003;157:773-779.
25. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336:1117-1124.
26. Allen DB, Nemeth BA, Clark RR, Peterson SE, Eickhoff J, Carrel AL. Fitness is a stronger predictor of fasting insulin levels than fatness in overweight male middle-school children. J Pediatr 2007;150:383-387.
27. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes:a randomized controlled trial. Diabetes Care 2002;25:89-94.
28. Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 2002;87:1555-1559.
29. McDuffie JR, Calis KA, Uwaifo GI, SebringNG, FallonEM, Frazer TE, et al. Efficacy of orlistat as an adjunct to behavioral treatment in overweight African American and Caucasian adolescents with obesity-related co-morbid conditions. J Pediatr Endocrinol Metab 2004;17:307-319.
30. Harder T, Bergmann R, Kallischnigg G, Plagemann A. Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol 2005;162:397-403.
31. Kaitosaari T, Ro¨nnemaa T, Viikari J, Raitakari O, Arffman M, Marniemi J, et al. Low saturated fat dietary counseling starting in infancy improves insulin sensitivity in 9-year-old healthy children: the Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study. Diabetes Care 2006;29:781-785.

ENDOCRINOLOGY

ENDOCRINE EMERGENCIES IN CHILDREN

** Ravikumar KG*

Abstract: *Endocrine disorders often present as emergency and are an important cause of morbidity and mortality in children. One of the common endocrine disorder in pediatric clinical practice is probably diabetes which can present as diabetic ketoacidosis. Diabetic children can also have hyperosmolar coma and hypoglycaemia which needs to be promptly recognised and treated to prevent long-term sequelae. One of the subtle ways some endocrine disorders present is by causing electrolyte imbalance and acid-base disorder. It is important to remember hormonal causes in the differential diagnosis of these patients and investigated accordingly.*

Keywords: *Endocrine emergencies, Diabetes, Ketoacidosis, Hypoglycemia.*

Endocrine conditions often present in a subtle manner and a high index of suspicion needs to be kept to diagnose them during emergencies. Prompt and aggressive treatment is required to prevent morbidity and mortality. Diabetic ketoacidosis (DKA) is the commonest pediatric endocrine emergency seen in clinical practice followed by hypoglycemia and hypocalcemia especially in sick neonates.[1] Other less common endocrine emergencies are adrenal insufficiency, thyroid storm, hypertension, pheochromocytoma and diabetes insipidus. Early clinical and biochemical pointers to the possibility of underlying endocrine disorder is listed in Table I.

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Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counter-regulatory hormones: catecholamines, glucagon, cortisol and growth hormone. DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments. The biochemical criteria for the diagnosis of DKA are 1) hyperglycemia with a blood glucose more than 200 mg/dL, 2) venous pH less than 7.3 or bicarbonate less than 15 mmol/L and 3) Ketonemia and ketonuria.

Clinical manifestations of diabetic ketoacidosis are variable and include dehydration, rapid, deep, sighing respiration (Kussmaul respiration), nausea, vomiting and abdominal pain mimicking an acute abdomen and progressive obtundation and loss of consciousness. Fever may be present when there is associated infection. Investigations often show increased leukocyte count with shift to the left and non-specific elevation of serum amylase.

The severity of DKA is categorized by the degree of acidosis and is listed in Table II.[2] The management algorithm is described in Fig.1.

Diabetic ketoacidosis can be differentiated from another diabetic emergency known as

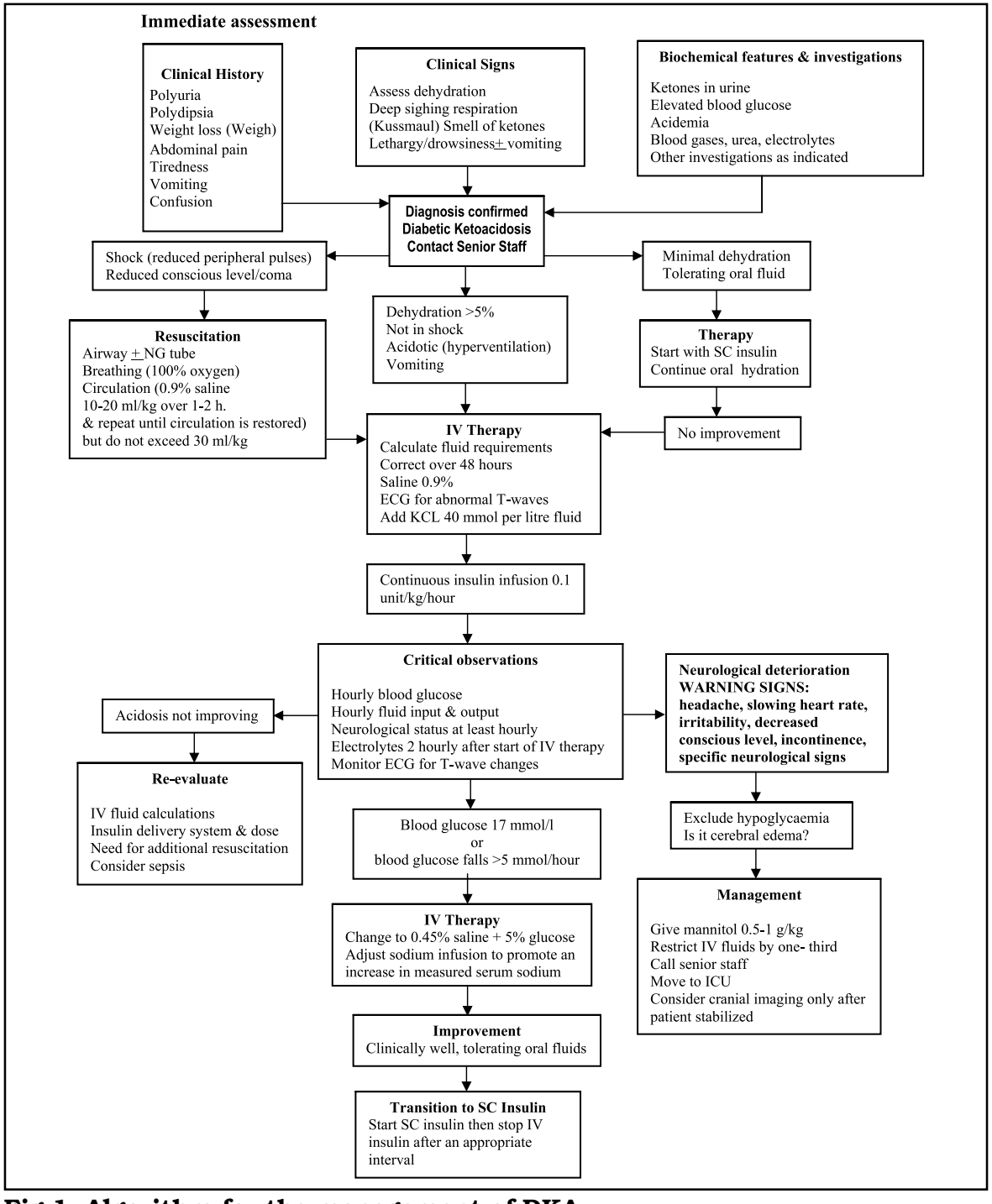

Fig.1. Algorithm for the management of DKA

(NG-nasogastric, SC-subcutaneous)

Source: Adapted from Dunger et al. Karger Publ. 1999

Table I. Pointers to the possibility of endocrine emergency

Clinical:	**Laboratory:**
Tall or short stature	*Electrolyte Imbalances:*
Obesity	Hyponatremia, Hypernatremia,
Hypertension	Hypokalemia, Hyperkalemia,
Goitre	Hypocalcemia
Genital anomalies	*Glucose imbalances*: Hypoglycemia,
Hypo or hyerpigmentation	Hyperglycemia
Polyuria	*Acid-Base disorders*: Metabolic acidosis
Dysmorphic features/ Midline anomalies	with wide anion gap, metabolic alkalosis

Table II. Severity of DKA

Category	*Venous PH*	*Bicarbonate in mmol/L*
Mild	Less than 7.3	Less than 15
Moderate	Less than 7.2	Less than 10
Severe	Less than 7.1	Less than 5

hyperglycemic hyperosmolar state (HHS) by the presence of plasma glucose concentration of more than 600 mg/dL with an arterial pH more than 7.30 and serum bicarbonate more than 15 mmol/L. HHS may also have mild ketonuria, absent to mild ketonemia and effective serum osmolality more than 320 mOsm/kg in the presence of stupor or coma.

Management of DKA

Emergency Assessment

Initial clinical evaluation in the emergency room is mandatory to confirm the diagnosis and determine its cause.[3] The clinician should then assess the clinical severity of dehydration. Atleast 5% dehydration is present when there are clinical signs such as prolonged capillary refill time, abnormal skin turgor and hyperpnea. The child may have more than 10% dehydration if peripheral pulses are weak or impalpable, hypotension and oliguria. The level of consciousness should be assessed at the time of admission.

Biochemical assessment

Initial investigations should include plasma glucose, electrolytes, urea, creatinine, osmolality, venous (or arterial in critically ill patient) pH, pCO_2, calcium, phosphorus and magnesium concentrations, HbA1c, hemoglobin and hematocrit or complete blood count. Urinalysis for ketones and glucose should be done. Culture of blood, urine, throat would be useful if there is evidence of infection.

Supportive measures

Children with DKA often have altered consciousness and it is important to ensure

a secure airway. Continuous nasogastric suction is also required to prevent pulmonary aspiration in these cases. Two peripheral intravenous (IV) catheter should be inserted for insulin infusion and IV fluids separately. Arterial catheter is useful for monitoring of invasive blood pressure and for frequent sampling. Child should be connected to cardiac monitor for continuous electro cardiographic monitoring to assess T-waves. Oxygen is required for patients with severe circulatory impairment or shock. Antibiotics should be given to febrile patients after obtaining appropriate cultures of body fluids. Children who are unconscious need bladder catheterisation to monitor urine output. Subsequent clinical and biochemical monitoring are done as listed in Table III.

Principles of water and salt replacement

Despite much effort to identify the cause of cerebral edema its pathogenesis is incompletely understood. The Milwaukee protocol which has been widely used suggests correcting fluid deficit over 24 hour period and switching over to low sodium containing fluids after the initial 2 hours of resuscitation.[4] However, more recent recommendations from British Society of Pediatric Endocrinology and Diabetes (BSPED) and Inernational Society for Pediatric Adolescent Diabetes (ISPAD) suggest more slower correction to reduce the incidence of cerebral edema.[2,5,6]

Initial fluids: For children with DKA who present with shock, it is recommended that circulatory volume is rapidly restored with isotonic saline (or Ringer's lactate) in 20 mL/kg boluses infused as quickly as possible. Colloids are not advisable for this purpose. For those in severe volume depletion but not in shock, volume expansion with 0.9 % saline at a rate of 10 ml/kg/hour is recommended.

Subsequent fluid management: Use 0.9% saline with potassium chloride for atleast 4-6 hours, preferably up to 12 hours. Thereafter, the replacement should be with 0.45% saline with potassium chloride. Urinary losses should not be routinely added to the calculation of replacement fluid.

Fluid calculations

The required amount of fluid given in DKA is calculated according to the formulae in Table IV. The total fluid requirement is calculated by adding maintenance fluid and deficit after deducting the fluids that have already been given.

Table III. Clinical and biochemical monitoring in DKA

Parameter	*Frequency of monitoring*
Vital signs (heart rate, respiratory rate, blood pressure)	Hourly
Neurological observations (Glasgow coma score) for warning signs and symptoms of cerebral edema	Hourly
Fluid input and output.	Hourly
Capillary blood glucose	Hourly
Laboratory tests: serum electrolytes, glucose, urea, calcium, magnesium, phosphorus, hematocrit and blood gases	2-hourly for the first 12 hours and then as required
Urine ketones	6 hourly

Table IV. Calculations used in management of DKA

Calculation	*Formula*
Fluid Requirement	Maintenance + Deficit – fluid already given
Maintenance fluid requirement	<10 kg : 100 mL/kg/24 hr; 11–20 kg: 1000 mL + 50 mL/kg/24 hr for each kg from 11–20 >20 kg: 1500 mL + 20 mL/kg/24 hr for each kg >20
Deficit (litres)	% dehydration x body weight (kg)
Hourly rate	(48 hr maintenance + deficit – resuscitation fluid already given) divided by 48
Anion gap	Na - (Cl + HCO3) Normal is 12 ± 2 (mmol/L). In DKA the anion gap is typically 20–30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis
Corrected sodium	measured Na + 2 ([plasma glucose >5.6]/5.6) (mmol/L)
Effective osmolality (mOsm/kg)	2 x (Na + K) + glucose (mmol/L)

The hourly rate is calculated by dividing the total requirement by 48 in order to correct the fluid deficit over 48 hours.

The sodium content of the fluid may need to be increased if measured serum sodium is low and does not rise appropriately as the plasma glucose concentration falls. Corrected sodium levels can be calculated according to the formula given in Table IV. Corrected sodium levels should rise as blood glucose levels fall during treatment. If they do not, then continue with normal saline and do not change to 0.45% saline. Once the blood glucose has fallen to 250 mg/dL or if the glucose fall is more than 90 mg/dL per hour add glucose to the fluid.

Insulin therapy

Insulin should be started one hour after starting fluid replacement. The initial dose of insulin is 0.1 unit/kg/hour. This can be prepared by diluting 50 units of regular (soluble) insulin in 50 mL of normal saline to make the final solution of 1 unit in 1 mL. An IV bolus is unnecessary and may increase the risk of cerebral edema. The dose of insulin should usually remain at 0.1 unit/kg/hour at least until resolution of DKA (pH >7.30, bicarbonate >15 mmol/L). In younger children or those with marked sensitivity to insulin, the dose may be decreased to 0.05 unit/kg/hour.

Potassium replacement

Children with DKA suffer total body potassium deficits of the order of 3 to 6 mmol/kg. The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias. Therefore, replacement therapy is required regardless of the serum potassium concentration.

If the patient is hypokalemic, start potassium replacement at the time of initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium after initial volume expansion concurrent with insulin therapy. If the patient is hyperkalemic, defer potassium replacement therapy until urine output is documented.

The starting potassium concentration in the infusate should be 40 mmol/L. Potassium replacement should be continued throughout the IV fluid therapy. The maximum recommended rate of intravenous potassium replacement is usually 0.5mmol/kg/hr.

If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

Acidosis

Severe acidosis is reversible by fluid and insulin replacement. Bicarbonate therapy has shown no clinical benefit and may cause paradoxical CNS acidosis. However, bicarbonate may be indicated in patients with severe acidemia (arterial pH <6.9) where decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion with life-threatening hyperkalemia.

Transition to Subcutaneous(SC) Insulin

Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present). When oral fluid is tolerated, IV fluid should be reduced. When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, the most convenient time to change to SC insulin is just before a mealtime. To prevent rebound hyperglycemia the first SC injection should be given 15–30 minutes (with rapid acting insulin) or 1–2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed.

Complications during treatment of DKA

The mortality rate from DKA in children is 0.15% to 0.30%. Cerebral edema accounts for 60% to 90% of all DKA deaths. Other rare complications include hypokalemia, hyperkalemia, severe hypophos phatemia, hypoglycemia, central nervous system complications (disseminated intravascular coagulation, dural sinus thrombosis, basilar artery thrombosis), peripheral venous thrombosis, sepsis, rhinocerebral or pulmonary mucormycosis, aspiration pneumonia, pulmonary edema, adult respiratory distress syndrome (ARDS), pneumothorax, pneumomediastinum and subcutaneous emphysema, rhabdomyolysis, acute renal failure and acute pancreatitis.

Cerebral edema

The incidence varies from 0.5 % up to 6 % in different countries with mortality up to 25 %. Potential risk factors for cerebral edema are presence of severe hypocapnia at presentation after adjusting for degree of acidosis, increased blood urea at presentation, severe acidosis at presentation, bicarbonate treatment for correction of acidosis, an attenuated rise in measured serum sodium concentration during therapy, high volumes of fluid given in the first 4 hours and administration of insulin in the first hour of fluid treatment.

Clinically significant cerebral edema usually develops 4-12 hours after treatment has been started, although it may rarely develop as late as 24-48 hours after the start of treatment. Warning signs and symptoms of cerebral edema include headache and slowing of heart rate, change in neurological status (restlessness,

irritability, increased drowsiness, incontinence), specific neurological signs (e.g., cranial nerve palsies), rising blood pressure and decreased O_2 saturation. Clinical diagnosis is made based on the criteria mentioned in Table V. One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%.

Treatment of cerebral edema

Treatment should be initiated as soon as the condition is suspected. Elevate the head of the bed. Reduce the rate of fluid administration by one-third. Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours. Hypertonic saline (3%), 5–10 mL/kg over 30 minutes, may be an alternative to mannitol or a second line of therapy if there is no initial response to mannitol. Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation [(to a pCO_2 <2.9 kPa (22 mm Hg)] has been associated with poor outcome and is not recommended. After treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration (hemorrhage<10% of cases), especially thrombosis or hemorrhage, which may benefit from specific therapy.

Adrenal Crisis

Adrenal insufficiency due to any cause can lead to adrenal crisis where patient may suddenly present with vomiting, lethargy, anorexia and dehydration. Circulatory collapse may be fatal.[7] The patient suddenly becomes cyanotic, the skin is cold, and the pulse is weak and rapid. The blood pressure falls, and respirations are rapid and laboured. In the absence of immediate and intensive therapy, the course can be fatal. Causes of adrenal insufficiency are listed in Table VI.

Table V. Diagnosis of cerebral edema

Diagnostic criteria	1) Abnormal motor or verbal response to pain 2) Decorticate or decerebrate posture 3) Cranial nerve palsy (especially III, IV, and VI) 4) Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)
Major criteria	1) Altered mentation/fluctuating level of consciousness 2) Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state 3) Age-inappropriate incontinence
Minor criteria	1) Vomiting 2) Headache 3) Lethargy or not easily arousable 4) Diastolic blood pressure >90 mm Hg 5) Age <5 years

Table VI. Causes of adrenal insufficiency

Low ACTH	CNS Infection, haemorrhage, infarction Congential hypopituitarism, Iatrogenic chronic adrenal suppression
High ACTH	Addisons disease CAH AHC (adrenal hypoplasia congenita) Adreno-leuco-dystrophy, Wolman disease

Clinical signs such as hyperpigmentation or hypopigmented patches, ambiguous genitalia, asthenic appearance, muscular hypertrophy (in X linked 21p deletions), midline craniofacial defects and achalasia, alacrimia (in case of triple A syndrome) should increase the suspicion of adrenal insufficiency in an acutely ill child.

Immediate investigations for suspected adrenal insufficiency include electrolytes (to look for hyponatremia, hyperkalemia), plasma cortisol, ACTH and sometimes renin, aldosterone and 17 hydroxyprogesterone. Plain x-ray of the abdomen may show calcified adrenals in case of adrenal hemorrhage. CT scan and MRI may be helpful. ECG monitoring is useful to look for changes of hyperkalemia.

Treatment should be started immediately after diagnosis and consist of hydration with normal saline, correction of hyperkalemia (2-3 mEq/Kg of sodium bicarbonate IV, Regular insulin 0.1 U/kg IV with 25% dextrose as 2 mL/Kg over 30 minutes which can be repeated and Kayexalate) and glucocorticoid administration (100 mg/ m^2 of hydrocortisone). Dexamethasone at a dose of 4mg/ m^2 can also be given as it does not interfere with cortisol measurement with ACTH stimulation test. Mineralocorticoid (Fludrocortisone, 0.1-0.2 mg PO daily) may be required in primary adrenal insufficiency.

Taper the glucocorticoid dose if illness improves to physiological maintenance (10 mg/ m^2/d in 3-4 doses in non-CAH patients and 12-15 mg/ m^2/d in 3-4 doses in CAH patients) over 1-3 days. In children who are on long term steroid replacement it is important to increase the dose of hydrocortisone to 30 mg/m^2/d in 3-4 divided doses in febrile and minor illness and to 50-100 mg/ m^2/d in 4 divided doses in major stress.

Pheochromocytoma

Pheochromocytoma is rare in children and usually appears after age 14. It is often bilateral with extra-adrenal tumors. Noradrenaline is the predominant product.

Hypertensive crisis in pediatric intensive care unit can be caused by pheochromocytoma. Other symptoms include tachycardia, sweating, headache, nausea and vomiting, change in vision, orthostatic hypotension, abdominal pain, polyuria and polydypsia. Hypertension that responds to alpha blockade and not to other antihypertensives is likely to be due to pheochromocytoma. The treatment consists of removal of the tumour but hypertension should be controlled preoperatively as well as intra and post-operatively. Alpha blocking agents such as phenoxybenzamine and prazosin are used initially preoperatively followed by beta blockers such as propanolol. Use of beta blockers without alpha blockade will lead to severe hypertension. Intra operatively blood pressure needs to be controlled using sodium nitroprusside.

Hydrocortisone may be required if bilateral adrenals are involved and had to be removed.

Thyroid storm

Thyroid storm is rare in children. It is an acute, potentially life threatening syndrome of thyroid hormone excess which is often precipitated by stress such as infection or surgery. There is hypercatabolic and hyperdynamic state characterized by vasodilatation, increased cardiac output, heart failure, arrhythmia, diarrhoea, nausea, vomiting, abdominal pain, hyperthermia and CNS disturbances. Differential diagnosis includes sepsis, malignant hyperthermia, pheochromocytoma, cocaine intoxication and pancreatitis.

Management is by control of hyperthermia with paracetamol, cooling and fluids. Start propylthiouracil 20 mg/kg/day and Lugol's iodine 5-10 drops 8 hourly 2 hours after propylthiouracil. Beta blockers such as propranolol 1-2 mg/kg/d can be used. Corticosteroids also have a role in preventing conversion of T4 to T3.

Diabetes insipidus

Diabetes Insipidus (DI) can be congenital or acquired, central or nephrogenic, dipsic or adipsic. CNS tumours like craniopharyngioma, traumatic brain injury, encephalitis can all lead to DI. Brain tumour surgery especially in the area of pituitary and hypothalamus can lead to diabetes insipidus in the perioperative and postoperative period.[8]

As cortisol has a permissive role on water clearance, DI often manifests only after adequate cortisol replacement is done. DI usually manifests within 6-12 hours of surgery, lasts for 1-2 days and then recovers for 1-2 days only to return in the majority of patients in 3-5 days (Triphasic response). The transient recovery is due to lysis and release of antidiuretic hormone (ADH) stored in neuronal cells containing ADH. This triphasic response needs effective management by meticulous assessment of fluid input and output, and regular monitoring of electrolytes. In the immediate postoperative period, hourly urine output should not exceed 100-150 ml/ m^2. The urine output can be controlled by using DDAVP. In some patients, due to injury to the hypothalamus a permanent state of adipsic DI leading to chronic hypernatremia and hyperosmolality may develop, which is difficult to manage. As the patient has no thirst, a fixed schedule of replacement of water and a flexible schedule for DDAVP varying according to the environmental temperature is needed.

Hypoglycemia in newborn and children

Hypoglycemia is very commonly seen in newborn babies. It is also seen in infants and children especially during illness and starvation or in children with diabetes mellitus who take insulin. In children, hypoglycemia is defined as plasma glucose values of less than 50 mg/dL whereas in newborn period glucose values of less than 47 mg/dl can be associated with poor neurological outcome. It can be symptomatic or asymptomatic. The serum or plasma level of blood glucose tends to be 12-15 percent higher than the whole blood glucose. Asymptomatic hypoglycemia is as serious as symptomatic type and needs prompt treatment.[9]

Hypoglycemia in newborn

Signs and symptoms of hypoglycemia in newborn include apnea, bradycardia, cyanosis, tachypnea, abnormal cry, hypothermia, hypotonia, lethargy, apathy, jitteriness and seizures.

Causes of hypoglycemia in Newborn

1) Prematurity
2) IUGR, SGA,LGA, Postmature

3) Perinatal stress/hypoxia, cold, stress, sepsis, congestive heart failure

4) Infant of diabetic mother, Rh Incompatibility, nesidioblastosis, Beta- blockers

5) Beckwith-Wiedemann, Inborn errors of metabolism

6) Endocrine: Hypopituitarism, GH deficiency, cortisol deficiency, glucagon deficiency

Evaluation

A detailed maternal history and thorough physical examination are required to determine the probable cause of neonatal hypoglycaemia. Family history of diabetes or glucose intolerance, drug ingestion (chlorpropamide, thiazides, salicylates), blood group incompatibility, pre-eclampsia and the rate of dextrose administered to the mother during labour should be elicited. Physical examination will conclude whether the child is AGA, SGA or LGA as well as gestational age. Dysmorphic features suggestive of Beckwith- Wiedemann include protruberant tongue, umbilical hernia and macrosomia. Prolonged jaundice, cataract and urinary reducing substances are suggestive of galactosemia. Unexplained hepatomegaly may indicate glycogen storage disease. Midline defects, micropenis, cleft lip and palate may indicate hypopituitarism.

Laboratory investigations include glucose, insulin, growth hormone, cortisol, thyroid function, PH, lactate, pyruvate and urinary ketones at the time of hypoglycaemia or following a fast of 3-4 hours.

Treatment

In mild asymptomatic hypoglycaemia in newborn, oral feeding can be administered if the baby is able to tolerate feeds. In moderate hypoglycaemia or symptomatic hypoglycaemia, intravenous treatment with a constant infusion pump is recommended. The administration of glucose bolus is controversial as there can be rebound hypoglycaemia after this. There is no place for large bolus (> 500 mg/kg) but a small bolus (200 mg/kg, 2 ml/kg of 10 % dextrose over 1 min) can be given. This should be followed by a continuous infusion of 6-8 mg/kg/min which can be gradually increased to achieve euglycemia. Concentration greater than 12.5% should only be given through central route and rates more than 25 mg/kg/min should never be given. Glucose values should be estimated atleast every hourly.

In refractory hypoglycaemia where the glucose administration exceeds 15 mg/kg/min, other agents can be used. Hydrocortisone at a dose of 5 mg/kg/day or prednisolone 2 mg/kg/day act by gluconeogenesis from non-carbohydrate sources and by decreasing peripheral glucose utilisation.

Glucagon (dose 30 mg/kg up to 300 mg/kg followed by infusion) and epinephrine subcutaneously have also been used. In persistant hyperinsulinism drugs like diazoxide, octreotide and calcium channel blockers are used and in refractory cases subtotal pancreatectomy may be required.

Hypoglycemia in children

Signs and symptoms of hypoglycemia in children include autonomic symptoms like sweating, hunger, paresthesia, tremors, pallor, anxiety, nausea, palpitations and neuroglycopenic symptoms like warmth, fatigue, weakness, dizziness, headache, inability to concentrate, drowsiness, blurred vision, difficulty speaking, confusion, bizarre behaviour, loss of coordination, difficulty walking, coma and seizures. The examination findings and the likely cause of hypoglycemia is listed in Table VII.

The diagnosis can be made following the algorithm as in Fig.2.

Lab Investigations at the time of hypoglycemia are as follows:

1) Metabolites: Glucose, lactate, pyruvate, aminoacids (alanine), uric acid, serum electrolytes, anion gap, pH, bicarbonate, AST, ALT, CK.
2) Insulin secretion: Insulin, C-peptide, Proinsulin.
3) Counter regulation: GH, cortisol, glucagon
4) Fatty acid oxidation: FFA, fatty acid profile, β hydroxy butyrate, acetoacetate, carnitine, acylcarnitine.
5) Urine: ketones, reducing sugars, organic acids, acylglycines.

Table VII. Findings on physical examination in a child with hypoglycemia

Examination	*Possible causes*
Short stature; growth failure	GH deficiency, hypopituitarism
Microphallus	GH deficiency, hypopituitarism
Midline facial defects Cleft lip and palate Single central incisor Optic nerve hypoplasia	GH deficiency, hypopituitarism
Abnormal skin pigmentation	Addison's disease
Large liver	Glycogen storage disease Disorder of gluconeogenesis Galactosemia Disorder of fatty acid β- oxidation Disorder of carnitine metabolism Tyrosinemia type I
Macrosomia Large tongue Omphalocele/umbilical hernia Visceromegaly Horizontal grooves on ear lobes	Beckwith-Wiedemann syndrome
Hyperventilation	Metabolic acidosis, hyperammonemia
Odour	Maple syrup urine disease, isovaleric acidemia, 3-methylcrotonyl CoA carboxylase deficiency, multiple acyl CoA dehydrogenase deficiency (glutaric acidemia type II)
Heart Gallop or murmur Cardiomyopathy	Disorder of fatty acid β-oxidation Disorder of carnitine transport or metabolism

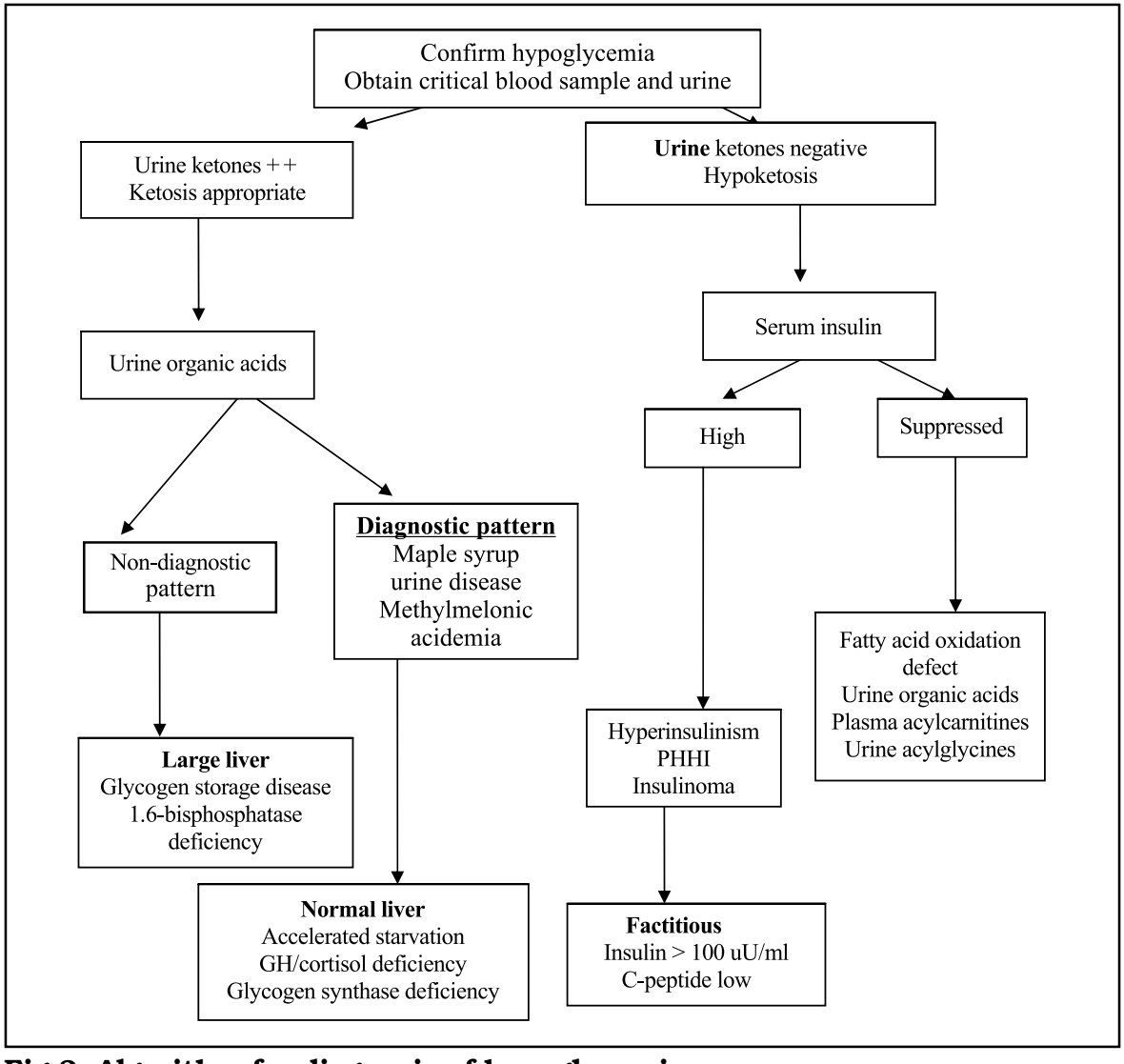

Fig.2. Algorithm for diagnosis of hypoglycemia

(PHHI - persistent hypoglycemia with hyperinsulinism)

Immediate management of hypoglycemia in children is 2-4 ml/kg of 10% dextrose. Further specific management will be according to the diagnosis.

Points to Remember

- ***A high index of suspicion is necessary to diagnose endocrine problems in a sick child.***
- ***Cerebral edema is the most important cause of mortality in diabetic ketoacidosis and preventive measures should be taken during treatment.***
- ***Avoid excessive fluid administration and hyponatremia in diabetic ketoacidosis.***
- ***Prompt recognition and management is life saving in a child with adrenal insufficiency.***

- ***In children presenting with hypoglycaemia, ensure 'critical sample' is taken for investigations at the time of hypoglycaemia.***

References

1. Charles G D Brook, Rosalind Brown. The endocrine problems of Infancy. In: Handbook of clinical pediatric Endocrinology; Blackwell publishing, UK; first edition 2008; pp202-207.
2. Wolfsdorf J, Craig ME, Daneman D, Dunger D, Edge J, Lee W et al. Diabetic ketoacidosis in children and adolescents with diabetes. Pediatric Diabetes 2009; 10 (Suppl. 12): 118–133.
3. Wolfsdorf MB, Glaser N, Sperling MA. Diabetic Ketoacidosis in infants, children and adolescents. Diabetes Care 2006; 29: 1150-1159.
4. Alemzadeh R, Wyatt DT, Diabetes mellitus; In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, Eds, Nelson textbook of pediatrics, 18th Edn; Elsevier publications, India 2008; pp2405-2424.
5. Cooke DW, Plotnick L. Management of diabetic ketoacidosis in children and adolescents. Pediatr Rev 2008; 29:431-435.
6. Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, Danne TPA, et al. ESPE/ LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis child 2004; 89:188-203.
7. Sperling M A. 14, The adrenal cortex. In: Pediatric Endocrinology 2nd Eds, Saunders publications, USA, 2002; pp385-434.
8. DeVile CJ, Grant DB, Hayward RD, Stanhope R. Growth and endocrine sequelae of craniopharyngioma. Arch Dis Child 1996; 75: 1-7.
9. Wolfsdorf et al; Hypoglycemia in children. In: Pediatric endocrinology; 5th edn; edited by Fima Lifshitz; Marcel Dekker publications, USA 2006; pp575-603.

CLIPPINGS

Phalguni Dutta, Utpala Mitra, Shanta Dutta, Trailokya Nath Naik, Krishnan Rajendran, Mrinal Kanti Chatterjee. Zinc, Vitamin A, and Micronutrient Supplementation in Children with Diarrhea: A Randomized Controlled Clinical Trial of Combination Therapy versus Monotherapy. The Journal of Pediatrics May 20.

This study was done to compare the clinical efficacy of supplementation of zinc, zinc plus vitamin A, and zinc plus combination of micronutrients and vitamins (iron, copper, selenium, vitamin B_{12}, folate, and vitamin A) on acute diarrhea in children.

This was a double-blind, randomized, placebo-controlled trial. Children aged 6 to 24 months with diarrhea and moderate dehydration were randomized to receive zinc plus placebo vitamin A (group 1), zinc plus other micronutrients plus vitamin A (group 2), zinc plus vitamin A (group 3), or placebo (group 4) as an adjunct to oral rehydration solution. Duration, volume of diarrhea, and consumption of oral rehydration solution were compared as outcome variables within the supplemented groups and with the placebo group.

Supplementation with a combination of micronutrients and vitamins was not superior to zinc alone, confirming the clinical benefit of zinc in children with diarrhea.

ENDOCRINOLOGY

THYROID DYSFUNCTION AND MANAGEMENT

**** Anju Virmani***

Abstract: *Thyroid disorders are prevalent, easy to diagnose and treat. Ultrasensitive TSH is usually sufficient for screening for thyroid dysfunction and monitoring therapy. During pregnancy, with TSH, free T4 should be tested, not total T4, and replacement started early if hypothyroidism is detected. Screening for congenital hypothyroidism is highly cost effective and must be done in all newborns. It can be done by testing TSH in cord blood or on day 4-5 of life. Day specific normal values should be used as cut offs. After repeat testing for confirmation, thyroxin replacement, given as a single morning dose, must be started early, preferably in the first week of life, in adequate doses. At age 3 years, replacement should be interrupted for 5-6 weeks, and T4, TSH, and technetium scan done to confirm permanent congenital hypothyroidism. In childhood, thyroid dysfunction usually has an autoimmune basis. Primary hypothyroidism is characterized by slow height velocity (other symptoms/ signs are variable), raised TSH and low T4. Adequacy of thyroxin replacement is monitored with growth and TSH (at intervals of 3-6 months). In central hypothyroidism, T4 is low, but TSH can be low, normal, or slightly raised; monitor with T4 levels. Need for thyroxin in subclinical hypothyroidism continues to be controversial. Hyperthyroidism is characterized by low TSH, high T4 and T3. A thyroid scan helps distinguish Graves' disease (increased uptake, needs neomercazole therapy), from thyroiditis (decreased uptake, needs symptomatic relief with propranolol) or toxic solitary nodule (needs surgery). In Graves' disease, alternative modes of treatment are radioiodine ablation or surgery.*

Keywords: *Thyroid dysfunction, Ultrasensitive TSH, Congenital hypothyroidism screening, Primary hypothyroidism, Central hypothyroidism, Subclinical hypothyroidism, Hyperthyroidism.*

Thyroid hormones can now be easily, reliably and inexpensively tested across the country, and therefore thyroid dysfunction can now be diagnosed conveniently, usually with a single, simple blood test. Thyroid dysfunction, especially hypothyroidism, is relatively easy and inexpensive to treat. These factors, and the fact that thyroid dysfunction is common in the general population, has translated into a great deal of misdiagnosis and misuse of thyroid treatment. As physicians, it therefore behoves us to know in detail about various aspects of thyroid dysfunction. Among the basic thyroid hormone (TH) tests, an ultrasensitive TSH is usually sufficient for screening for thyroid dysfunction and for monitoring therapy. However, in most circumstances, T4 can be added and can sometimes provide useful additional information. Serum T3 is hardly ever useful, and may confuse matters. The conversion (deiodination) of T4 to T3 increases with rising TSH and falling T4, hence in very early hypothyroidism or in iodine

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deficiency, serum T3 may be high rather than low as a compensatory mechanism. One situation where T3 is important is suspected thyrotoxicosis with suppressed TSH but normal T4: here the high T3 will help make the diagnosis of T3 toxicosis.

It is well known that a woman with iodine deficiency, with or without hypothyroidism, is less likely to get pregnant. When she does, there is a high risk of cretinism, because of the critical role iodine and thyroxine play in the development of the embryonic brain and ear. In the first trimester, since the embryo has not yet developed its thyroid gland, all the thyroid hormone comes from the mother. Moreover, the need for thyroid hormone rises early in pregnancy. Fortunately, iodine deficiency has significantly reduced with iodization of salt, and the incidence of cretinism has come down sharply. However, it is important to make sure that the mother does not have hypothyroidism. When a woman goes for a pre-pregnancy test, or is known to have pre-existing hypothyroidism, her serum TSH should be checked to ensure she is euthyroid before she conceives, and as soon as she is known to have conceived.

Many gynecologists will order thyroid function when a woman comes with early or suspected pregnancy. During pregnancy it is very important to remember to ask for both free T4 and TSH levels. In pregnancy, the rise in sex hormone binding globulins leads to a rise in total T4 level, while free T4 continues to be normal. Moreover, TSH levels may be low, and the combination of apparently high T4 and low TSH lead to a false impression of hyperthyroidism in the mother. This mistaken diagnosis and consequent treatment with anti-thyroid drugs can play havoc with fetal development, leading to possible iatrogenic cretinism. Thus, if the TSH is low, but free T4 level is normal, one need not worry. Conversely, if the TSH is high, thyroid replacement should be started or increased, and its adequacy monitored with regular checking of free T4 and TSH levels.

Birth: Screening for congenital hypothyroidism (CH) is done in all newborns in developed countries since the 1970s, because of its undoubted cost effectiveness. CH occurs in one in 2,500- 4,000 newborns in most populations, but there is some evidence to suggest that our incidence may be closer to one in 1,100-1,200 newborns. Ninety-five percent of the affected infants appear clinically normal at birth, but will end up with irreversible brain damage and therefore permanent mental retardation because of delayed diagnosis. Therefore we should be practicing universal screening, i.e. screening every single newborn, rather than screening only selected groups like infants of hypothyroid mothers. Each country or region has its own policy. While we in India do not as yet have a formal policy, the simplest way to screen is by testing TSH in cord blood (sample should be taken from the placental end). If the level is above 25-30 mIU/ L, the newborn should be re-tested for serum T4 and TSH as soon as possible, preferably by day 5 of life, for confirmation of the diagnosis. If the TSH is raised, and if it is conveniently possible, a technetium thyroid scan and/ or ultrasound should be done to look for an etiological diagnosis. If a scan cannot be easily done, it is not critical. What is critical is that thyroxine replacement must be started as soon as the diagnosis of hypothyroidism is made, preferably within the first week of life, but definitely before the age of two weeks.

There is a sharp thyroid surge at birth. The TSH rises rapidly within 30 minutes of birth, peaking at 24 hours, then gradually declining to below 10 mIU/ ml by 72 hours of life. The normal infant may have levels up to 10 mIU/ ml for the initial 2-3 months of life. The TSH surge results

in a peaking of T4 by 24-36 hours of age, followed by a gradual decline to baseline by about 96 hours. Preterm infants follow the same time pattern, but the peaks achieved may be somewhat lower. Therefore, if the sample for TSH is taken from the baby and not from the cord, the effect of this thyroid surge should be taken into account, and day-of-life specific norms should be used as cutoffs. For example, the TSH may be as high as 50 mIU/ L in normal newborns on day 1 of life.

Some centers prefer to combine thyroid screening, with that for other disorders which cannot be done in cord blood. They then offer heel prick sampling and collection on filter paper, on day 4-5 of life. Filter paper collection and testing are technically challenging, and prone to error, so care should be taken to adequately train nursing staff and lab staff for proper collection for testing. High levels of TSH should be confirmed by a venous sample for TSH and T4.

Replacement should be started as early as possible. A high starting dose of 10-15 mcg/kg/day is recommended to ensure quick normalization. Subsequent doses depend on the infant's serum T4 and TSH levels. Monitoring should be done by testing serum T4 level after 2 weeks, and T4 and TSH levels after 4-5 weeks to make sure the dose is adequate. Thereafter, monitoring of T4, TSH and growth should be done every 2-3 months in the first 2 years of life. The target for T4 is in the upper half of the normal range, and TSH is 1-3 mIU/ml, with normal growth velocity (both length and weight gain). It is not necessary to give thyroxine in the fasting state; what is important is the timing should be consistent. Care should be taken not to give iron, soya or calcium, within 4 hours of administering thyroxin, as its absorption may be affected.

Two thirds of permanent CH cases are due to dysgenesis (agenesis, hypoplasia or lingual gland), while one third are due to dyshormonogenesis. The thyroid scan would give a diagnosis of dysgenesis (Fig.1); dyshormonogenesis may be suspected if the gland is enlarged or has a high uptake. Where the diagnosis is evident, e.g. an absent or lingual gland, the parents can be told that replacement must be lifelong. It is important to assure them that the mental and physical growth and development would be normal if replacement is adequate and regular. This is a must to allay their fears, because they are likely to be confused by myths about hypothyroidism, and also to emphasize the need for compliance with medication and monitoring.

About 10-50% of CH may be transient. Therefore, where etiology is not clear from the thyroid scan, or if the thyroid scan could not be done at birth, then treatment should be interrupted for 5-6 weeks at the age of 3 years (when brain myelination is complete). After stopping thyroxine for this duration (5-6 weeks), T4 and TSH as well as a technetium scan and ultrasound should be performed. Suspected agenesis can be confirmed by thyroglobulin levels, if easily available. If the TSH remains normal, treatment need not be restarted. Care should be taken not to test too early, as it takes at least 4 weeks for the TSH level to change fully.

It is important to remember that thyroxin replacement should be started as early as possible to ensure normal brain development. Each month of delay can mean a 5 point decrease in IQ. Several large urban hospitals are now screening either cord blood or by heel prick and filter paper on day 3-5 of life. Cord blood screening is feasible in almost all hospital deliveries, and should be done in all newborns. If screening was not done at birth, the pediatrician should ask for thyroid hormone tests on an urgent basis whenever the baby is first seen, e.g. for vaccination. One must also remember that till 3 months of life, normal TSH level can be up to

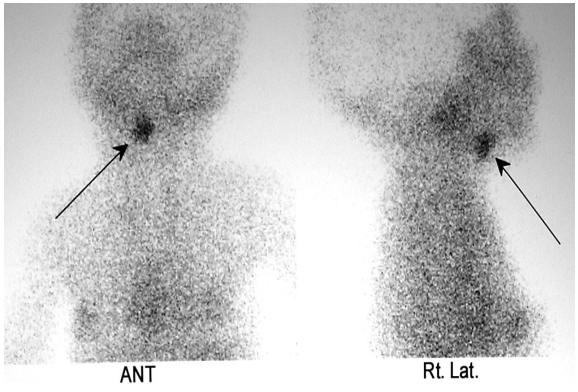

Fig.1.Lingual Thyroid

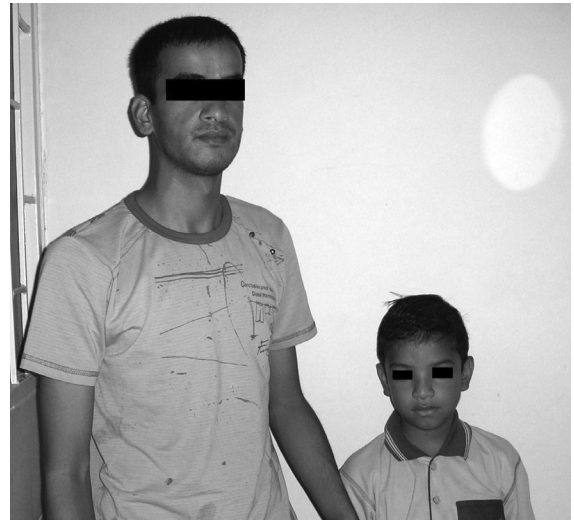

Fig.2.Congenital hypothyroidism 14 year old with 17 year old normal brother

10 mIU/L. Therefore, thyroxin should not be started for borderline high levels of TSH (< 10) unless T4 level is subnormal.

Childhood: Because of the absence of universal neonatal thyroid screening, and the frequent absence of routine growth monitoring in India, congenital hypothyroidism may be detected very late (Fig.2). However, after infancy, thyroid dysfunction almost always has an autoimmune basis (e.g. chronic lymphocytic thyroiditis [CLT]); very rarely it could be due to radiation, surgery, or drugs.

Primary hypothyroidism is far more common, and may be overt or subclinical. Thyroid function should be tested in all children presenting with slow height gain, delayed puberty, chronic anemia, chronic constipation, poor scholastic performance, irregular periods or menorrhagia, weight gain, goiter, lipid abnormalities, hyperprolactinemia, etc. In children with autoimmune diseases like type 1 diabetes, vitiligo, celiac disease, pernicious anemia; polyendocrine failure syndromes (type 1 and 2); family history of thyroid disorders; certain medications (see Subclinical Hypothyroidism below); or conditions such as Down syndrome, thyroid function should be tested periodically.

On examination, these children are short, often look sallow and puffy; they may have a hoarse voice, dry cool skin, slow deep tendon reflexes, with or without goiter. Overweight children who are tall for age (and midparental height: MPH) are unlikely to be hypothyroid.

In overt primary hypothyroidism, the classic lab presentation is low T4 and raised TSH. Thyroid peroxidase antibodies may be present, but the test is expensive, and in overt hypothyroidism usually does not change management, since antibodies being negative does not mean the cause is not autoimmune. There is little reason to repeat the test. Even if strongly positive, there is no role for corticosteroid therapy. However, antibodies may be useful in subclinical hypothyroidism, discussed below. In central hypothyroidism,

TSH can be low, normal, or even slightly raised (bioinactive TSH), while T4 is low.

The child should be started on thyroxine replacement, as a single early morning dose. From the high requirement in the neonatal period, thyroxine requirement comes down with age, with the older child (and adult) needing just 1-4 mcg/ kg/ day. Adequacy of the dose should be monitored by doing TSH and T4 after 4-8 weeks. Testing earlier than 4 weeks could confuse matters as the TSH would not have had sufficient time to change. The aim should be to maintain TSH in the middle of the normal range. Most people (children and adults alike) need 50-125 mcg of thyroxin daily. Iron, soy, calcium and antacids should be given 4 hours away from thyroxine. Drugs such as carbemazepine, phenytoin, rifamipicin, estrogen, may increase the metabolism and thus the dose of thyroxin. Otherwise, higher doses should raise concerns about compliance, medicine quality, and lab errors.

On therapy, a common source of confusion is encountering a high TSH along with a high T4. This often happens if the medication has been missed in the preceding weeks, and just before the test a larger dose than advised is given to the child. While the high dose raises the T4, there was not enough time for the TSH to normalize. In this situation, the dose should not be increased; rather the need for better compliance should be stressed. Once stabilized, the dose can be monitored by checking TSH, height, weight and pubertal status every 6 months; bone age can be done annually. There is no role of restricting the intake of "goitrogenic foods" like cabbage, etc. School performance may improve, but occasionally may drop a little with adequate replacement, as the children become normally naughty.

If multiple endocrine deficiencies exist together, it is important to replace cortisol before starting thyroxin, otherwise an adrenal crisis can be precipitated.

Subclinical hypothyroidism - Raised TSH with normal T4 - is a frequent source of confusion. The need for treatment in otherwise asymptomatic children is very controversial, with studies in children showing varying outcomes. Most experts agree that if the child is asymptomatic, height is appropriate for age and MPH, TSH is < 10 mIU/L, and antibody levels are negative, replacement need not be started. Instead, a period of follow up, with monitoring of growth velocity and a repeat thyroid TSH and T4 after 3-6 months can be advised. This is particularly true in obese and tall children, in whom the TSH may normalize with weight loss. In general, children are less likely to progress to overt hypothyroidism than adults, particularly if antibodies are negative. Several drugs can cause increased TSH - iodine administration or iodine containing compounds (amiodarone, topical antiseptics, contrast agents, expectorants), anti-epileptic drugs (e.g. valproate), lithium, interferon, sulfonamides, sulfonylureas – which may be transient or go onto overt hypothyroidism. External radiotherapy of head and neck (lymphoma, leukemia, other malignancies) and bone marrow transplantation may also be associated with slight increases in TSH.

Central hypothyroidism characterized by low serum free T4 and normal or low TSH - is exceedingly rare by itself, but may be seen in the setting of pituitary dysfunction, e.g. in craniophyrangioma, pituitary adenoma or other intracranial tumors, especially after they are operated upon; or after pituitary radiation or trauma. Evidence of other hormones being abnormal is therefore often present. Replacement and monitoring is on the same lines, except of course that TSH testing is useless for monitoring. Low T4 and low TSH can also be seen in severe non-thyroidal illness.

Hyperthyroidism is uncommon in children, usually occurs in adolescents, and is almost always associated with goiter. The most frequent etiology is Graves' disease, less often the cause is Hashimoto thyroiditis (increased release of preformed hormone rather than increased formation of hormone), or very rarely toxic nodule, McCune Albright syndrome, familial non-autoimmune hyperthyroidism (FNH), or exogenous administration. Behavior changes and poor school performance may be the earliest signs; weight loss in spite of increased hunger, tiredness, palpitations, irritability, sweating, increased stool frequency, proximal muscle weakness (child may not be able to get up from the toilet), poor sleep, eye abnormalities and neck swelling may also be present. On examination, goiter is almost invariable, and may be smooth or nodular; there may be tachycardia, tremors, eye signs, and/ or proximal muscle weakness. The child is usually thin (weight for height is low), fidgety and irritable. The classic lab picture is suppressed TSH, with high T4 and T3. A thyroid scan would show a uniformly enlarged gland with increased uptake (Graves' disease) (Fig.3), patchy and decreased uptake (thyroiditis), or toxic solitary nodule.

In thyroiditis, the high T4 and T3 are due to release of pre-formed hormone, so thyroid suppression is not required and just symptomatic relief with beta blockers is sufficient. In Graves' disease, therapy is with 0.5-1 mg/ kg/ day neomercazole (NMZ) given initially in 3 divided doses, along with a beta-blocker for symptomatic relief. Once control has been achieved, NMZ can be given in 2 or even 1 dose per day. Definitive therapy i.e. ablation with radioiodine or rarely surgery can also be considered, especially if NMZ is not tolerated, or relapses occur frequently. Propylthiouracil (PTU) is the other major anti-thyroid drug, used in doses of 5-10 mg/kg/day, in 3-4 divided doses. Recently, it has fallen into disfavor, with the realization that the risk of liver

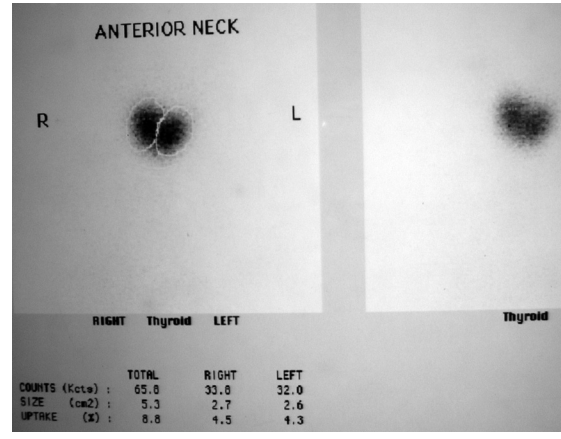

Fig.3. Thyroid scan typical of hyperthyroidism

cell failure is higher with PTU than with NMZ. Monitoring should be clinical (pulse rate, weight, height, BP, eye exam) and lab (T4 every 4-8 weeks after a dose change, and every 4-8 months if stable). Dose adjustment should be done till euthyroid, then the dose and frequency reduced gradually. T3 levels may be needed if clinical symptoms are at variance with T4 levels. TSH may continue to be suppressed for several months, and so can be misleading. Major side effects (agranulocytosis, hepatotoxicity, systemic vasculitis) are fortunately very rare.

Since relapse rates are higher in children, some experts recommend radioiodine ablation as the primary form of therapy, aiming for hypothyroidism. Radio iodine ablation is safe and does not decrease fertility or lead to increased risk of cancer or teratogenicity. It is contradicted if the patient is pregnant or breast feeding. After administering radio iodine, TH are monitored regularly. Anti-thyroid drugs may be required for a few weeks to months till the full effect of the iodine occurs. Once hypothyroidism develops, thyroxin is started.

Surgery may rarely be required, in a large or nodular gland. TH are monitored regularly,

and when hypothyroidism develops, thyroxin is started.

Thyroiditis is managed with relief of symptoms using beta blockers, till excessive release subsides. These children often end up eventually with hypothyroidism. A toxic nodule is rare in childhood, and needs surgical removal (preferable, as it also gives the pathology), or radioiodine. FNH is due to a 'gain-in-function' mutation in the TSH receptor gene. It is suspected in the presence of a strong family history, and is important to identify since these children should be offered complete ablation (surgical or radioiodine).

Thyroid storm is very rare in children, but must be kept in mind because of its very high mortality if the diagnosis is missed or delayed. The child may present for the first time with a storm, or have poorly controlled hyperthyroidism. It may be precipitated by infection, surgery or other trauma, missed anti-thyroid medication, or radio iodine therapy. Characteristic features are very high fever, tachycardia out of proportion to fever, restlessness or convulsions, diarrhea or jaundice. Therapy consists of basic resuscitation and supportive care, reducing body temperature, administering beta-blockers, and reducing thyroid hormone levels by using PTU or iodide, and corticosteroids. PTU is preferred here because it is thought to not only reduce T4 and T3 production, but also reduce conversion of T4 to the metabolically active T3. It can be given orally, and if that is not tolerated, rectally, in a dose of 100-200 mg 4-6 hourly, which is later reduced to 5-10 mg/ kg/ day in 3-4 divided doses. Once PTU has been given, potassium iodide can be added (4-6 drops 8 hourly) to rapidly reduce thyroid hormone production still further; it should be discontinued soon, otherwise it can cause rebound hyperthyroidism. The dose of propranolol is 2 mg/ kg/ day given 8 hourly; and of hydrocortisone 1-2 mg/ kg stat dose, followed by 36-48 mg/ m2/ day 6 hourly. Even more rarely, the older adolescent may present with thyrotoxic periodic paralysis, treated similarly, along with cautious potassium administration.

Goiter is most often due to iodine deficiency, autoimmune disease (CLT) [especially Chronic lymphocytic thyroiditis or Graves' disease]. Drugs, dyshormonogenesis, nodules, and malignancies are less common causes. Significant goiter should be investigated with ultrasound, TH levels, and thyroid peroxidase antibodies. Positive antibodies suggest CLT. Low dose thyroxine can be tried even in euthyroid children for 6-12 months to decrease gland size: there may be no response, or there may be recurrence after stopping.

In children, solitary nodules (even hot nodules) are more likely to be malignant than in adults, and so must be investigated for malignancy with ultrasound, fine needle aspiration cytology, T4, TSH, antibody, thyroglobulin, and calcitonin levels. Cystic lesions are less likely to be malignant. Thyroid cancers, otherwise rare in children, occur more often after radiation and so cancer survivors should be carefully followed up. Papillary thyroid cancer (PTC) is the commoner form in children, and seen more often in iodine replete areas. It is often bilateral, and metastasizes early to local lymph nodes. Iodine deficient areas have more follicular (FTC) or anaplastic cancers.

In summary, all newborns should be tested (preferably cord blood) with TSH and if possible, T4, and replacement started latest by age 2 weeks in those deficient. In older children, TH should be tested with a high index of suspicion, as symptoms can be varied. Careful monitoring and proper treatment give excellent outcomes.

Points to Remember

- ***Ultrasensitive TSH is usually sufficient for screening for thyroid dysfunction and for***

monitoring therapy; serum T4 is often useful; T3 is hardly ever needed.

- ***Hypothyroidism during pregnancy should be treated early. Iodine sufficiency during pregnancy is critical for normal fetal brain development.***
- ***Screening for congenital hypothyroidism (CH) must be done in ALL newborns, most simply by testing TSH in cord blood (cut off > 25-30 mIU/ L). Diagnosis should be reconfirmed at 3 years of age.***
- ***Thyroxine replacement must be started as early as possible, preferably within the first week of life, in adequate doses; monitoring therapy is done with T4, TSH and growth, every 2-3 months initially; every 6 months later.***
- ***Overweight children who are tall for age and mid parental height are unlikely to be hypothyroid.***
- ***Primary hypothyroidism can be monitored by TSH alone; central hypothyroidism needs T4 monitoring.***
- ***In hyperthyroidism, a thyroid scan helps distinguish Graves' disease from thyroiditis.***

References

1. Van Vliet G, Polak M. Thyroid disorders in infancy. In: Pediatric Endocrinology. 5th Edn, Fima Lifshitz ed, Informa, New York 2007; pp 391-404.
2. Nair PS, Sobhakumar S, Kailas L. Diagnostic re-evaluation of children with congenital hypothyroidism. Indian Pediatr 2010;47: 757-760.
3. Zeitler P & Solberg P. for the Pharmacy and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Food and levothyroxine administration in infants and children. J Pediatr 2010; 157: 13-14.
4. Ladensen PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association Guidelines for detection of thyroid dysfunction. Arch Intern Med 2000; 160: 1573-1575.
5. Singer PA, Cooper DA, Levy EG, Ladensen PW, Braverman LE, Daniels G, et al.American Thyroid Association Treatment Guidelines for hyperthyroidism and hypothyroidism. JAMA 1995; 273:808-812.
6. Biondi B & Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocrine Reviews 2008; 29: 76-131.
7. O'Grady MJ, Cody D. Subclinical hypothyroidism in childhood. Arch Dis Child 2011(Mar);96(3):280-284. Epub 2010 Apr 22.
8. Svensson J, Ericsson UB, Nilsson P, Olsson C, Jonsson B, Lindberg B, et al. Levothyroxine treatment reduces thyroid size in children and adolescents with chronic autoimmune thyroiditis. J Clin Endocrinol Metab 2006; 91:1729–1734.
9. Reinehr T, de Sousa G, Andler W. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. J Clin Endocrinol Metab 2006; 91: 3088-3091.
10. Lavard L, Jacobsen BB, Perrild H, Vassart G, Parma J, et al. Prevalence of germline mutations in the TSH receptor gene as a cause of juvenile thyrotoxicosis. Acta Paediatr 2004; 93:1192.

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ENDOCRINOLOGY

VITAMIN D AND CALCIUM DEFICIENCY: PREVENTION AND TREATMENT

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*** Vijayalakshmi Bhatia*

Abstract: *Vitamin D and calcium deficiency are being increasingly recognized in India. Poor sunlight exposure and diet are the underlying causes. Rickets is only one component of the spectrum of skeletal effects of vitamin D and/or calcium deficiency. Neonatal hypocalcemia, small for gestational age and low bone density are some others. Besides, newer data reveal the preventive role of vitamin D in infection, autoimmunity, malignancy and cardiovascular diseases. Early identification of the vulnerable groups and implementation of appropriate therapeutic and preventive strategies need to be emphasized.*

Keywords: *Vitamin D, Calcium, Rickets.*

Vitamin D deficiency is emerging as a public health problem in India despite sunshine being an abundant natural resource. Calcium intake is low in economically deprived sections as milk, the main source of calcium is an expensive food. New insights are available regarding the long term consequences of childhood calcium and vitamin D deficiencies including the non-skeletal implications of the latter. This review summarizes the magnitude of the problem in India, implications of vitamin D and calcium deficiencies and discusses the available evidence regarding therapeutic and preventive options and toxicity concerns.

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Sources of vitamin D and calcium

Vitamin D

The major source of vitamin D in humans is from cutaneous synthesis. Solar UVB radiation converts 7-dehydrocholesterol in the skin to pre vitamin D3 which is rapidly converted to vitamin D3 (cholecalciferol). In the liver D3 is metabolized to 25 hydroxy vitamin D3 [25(OH) D]. Circulating 25(OH) D reflects the vitamin D sufficiency status in the body. Further metabolism in the kidneys results in formation of the hormonal form, i.e. 1, 25-dihydroxy vitamin D3 (calcitriol), which enhances intestinal calcium absorption and renal calcium reabsorption. Excess solar radiation converts pre vitamin D3 to inactive photo isomers, thus preventing toxicity.[1,2]

Dietary sources of vitamin D include certain fish, cod liver oil and egg yolk (Table.I). The fishes rich in vitamin D consumed in our country include sardine [mathi/chala (Malayalam), seedai (Tamil), tarlo (Hindi], salmon [kora (Malayalam), vanjiram meen (Tamil), rawas (Hindi)], mackerel [ayila (Malayalam), kanangeluthi (Tamil), bangda (Hindi)], tuna [choora (Malayalam), keerai (Tamil)], hilsa and cod fish [sarghan (Malayalam), panna (Tamil), gobro (Hindi)].

The newborn baby is protected from vitamin D deficiency by transplacentally acquired

Table.I. Vitamin D content in natural dietary sources.[2]

Food Item	Amount	Vitamin D content (IU)
Cod liver oil	1 tea spoon	400 – 1000
Sardine (canned)	96 gm	300
Salmon (cooked)	80 gm	794
Mackerel (cooked)	80 gm	388
Tuna (canned in oil)	80 gm	235
Egg (1 whole)	60 gm	20

Table.II. Food items rich in calcium[30]

Food Item	Calcium content
Cow's milk	120 mg/ 100 ml
Buffalo milk	220 mg/ 100 ml
Cheese	790 mg/100 gm
Ragi	344 mg/100 gm
Rajmah	260 mg/ 100 gm
Soyabean	240 mg/ 100 gm
Agathi (Agasti keerai)	1130 mg/ 100 gm
Amaranth species	200 - 800 mg/ 100 gm
Cauliflower	626 mg/ 100 gm
Curry leaves	830 mg/ 100 gm
Coconut (dry)	400 mg/ 100 gm
Jaggery (date palm)	363 mg/ 100 gm
Gingelly seeds	1450mg/ 100 gm
Cumin seeds	1080 mg/ 100 gm
Ravas Fish	405 mg/ 100 gm
Mackarel	429 mg/ 100 gm

stores. These last for 2 months.[3] Breast milk is a poor source of vitamin D (40 IU/L) if the mother has poor vitamin D status due to dark skin or poor sunlight exposure, exposing the exclusively breast fed babies to greater risk for deficiency. On the other hand studies have shown greatly improved concentrations in breast milk of mothers supplemented with 4000 to 6000 IU of vitamin D3.[4]

Calcium

The chief source of calcium is milk and milk products. Green leafy vegetables and pulses provide moderate amounts of calcium (Table II). Dietary calcium absorption is influenced by the total calcium intake, presence of calcium binders in the gut (phytates and oxalates as in cereals and tomatoes respectively), calcium to phosphorus ratio (>2:1 favours absorption), age (younger the age, better is the absorption) and physiological status (high in pregnancy). Requirements increase with age parallel to bone growth and maturation. Calcium is mainly absorbed from duodenum by 2 pathways - active intracellular vitamin D dependent process when dietary calcium intake is low and paracellular vitamin D independent process when dietary calcium is normal or high.[5]

Definition of vitamin D deficiency

Adequacy of vitamin D levels is expressed in terms of serum levels of 25(OH) D that prevents compensatory rise in parathyroid hormone (PTH). Experts consider serum 25 (OH) D of 20 ng/ml (50 nmol/l) as the level above which no further suppression of PTH occurs. However, since increasing 25(OH)D from 20 to 30 ng/ml does cause some further increase in another biological indicator of vitamin D action, ie, calcium absorption, serum 25(OH) D <20 ng/ml is taken as indicative of vitamin D deficiency and 20-30 ng/ml as indicative of vitamin D insufficiency.[2] In this context it is interesting to note that people who have the benefit of a sun rich environment (such as documented in a study on farmers from Peurto Rico, latitude 18^0 N) have been shown to have 25(OH) D levels of 54-90 ng/ml.

How common is vitamin D deficiency in India?

Studies from different parts of India reveal rampant vitamin D deficiency. In a study from Delhi, 90.8 % of the 404 school girls aged 6-18 years had 25(OH) D <20 ng/ml irrespective of the socioeconomic status.[6] Eighty four percent of 207 pregnant women and 95.7 % of their newborns were found to be similarly deficient in Lucknow.[7] The situation is the same in south India, from Tirupathi at 13^0 N (rural and urban).[8] This high prevalence could be attributed to the custom of modest clothing (shielding the skin from the sun's rays) and less outdoor activity in women, on the background of being a pigmented race. Particularly vulnerable are adolescent girls, women and exclusively breastfed infants. The direct clinical relevance of hypovitaminosis D is shown by the proportion of neonatal seizure cases attributable to this etiology being documented by our pediatricians.[9,10]

What is the status of calcium intake in India?

Recent studies from India have documented dietary calcium intake in underprivileged toddlers, adolescents and pregnant women to be as low as approximately 200 to 300 mg per day due to the high cost of milk.[11,12]

What is the daily requirement of sunshine, vitamin D and calcium?

Races which have brown or black pigmentation need approximately 1.5 to 2 hours of sun exposure to face and forearms to make about 1000 units of vitamin D.[1,13] Since rampant vitamin D deficiency has been documented in adults in rural communities also, particularly women[12], it is to be construed that the necessary exposure is not occurring. Data regarding the dose of optimal vitamin D supplementation in children of tropical / subtropical countries is not yet available. There is no DRI (Dietary Reference Intake) for vitamin D proposed by the Indian Council for Medical Research (ICMR). The American Academy of Pediatrics in 2008 increased their recommendation to 400 IU per day, starting soon after birth, in infants and children who are exclusively / partially breast fed and those who are taking less than 1 L/day of vitamin D fortified formula / milk.[14] Recently the Institute of Medicine of the National Institutes of Health, USA, while maintaining the infant requirements (adequate intake) at 400 IU/day, has revised the RDA to 600 IU/day in ages 1 to 70 years assuming minimal sun exposure.[15] [Note: DRI is the general term for a set of reference values used to plan and assess nutrient intakes of healthy people; RDA (Recommended Dietary Allowance) is the average daily level of intake sufficient to meet the nutrient requirements of nearly all (97-98%) healthy people. RDA is 20 % higher than EAR (estimated average requirement) which is the level that meets the needs of 50% of the population in that age group.

Table.III Dietary reference intake recommendations for calcium by various countries (mg/day)[15,31,32]

Age group	ICMR *(2010)	UK** (1997)	WHO*** (2004)	NIH**** (2010)
Birth to 1 year	500	525	300-400	200-260[a]
1-3 years	600	350	500	700
4-6 years	600	450	600	1000
7-9years	800	500	700	1000
10-18years	800	1000 (boys) 800 (girls)	1300	1300
Pregnancy	1200	700	1200	1000
Lactation	1200	1250	1000	1000

*Indian Council of Medical Research 2010

** UK Department of Health 1997

*** World Health Organisation 2004

**** National Institutes of Health (Institute of Medicine), USA

[a] Adequate intake

Statistically RDA is set at 2 standard deviations of EAR; AI (adequate intake) is the intake level assumed to ensure nutritional adequacy when evidence is insufficient to develop an RDA].

Adequate calcium intake is one which fulfills the physiological requirement while accounting for the daily calcium loss, through urine, feces and insensible loss. This can be obtained from calcium balance studies in various populations to derive the daily dietary calcium intake for that particular population group (Table III).

Implications of vitamin D and calcium deficiency

Skeleton and mineral implications

Rickets is a deforming condition affecting growing bones due to inadequate mineralization of the newly formed bone matrix. Deficiency of either vitamin D or calcium or both can result in rickets in children[16] and osteomalacia in adults. In the first year of life, rickets usually manifests with sweating, seizures, muscle weakness, soft deformed bones, recurrent respiratory infections and dental enamel hypoplasia. After infancy hypocalcemic symptoms are less severe, but waddling gait and deformities are common.

Rickets is only the tip of vitamin D deficiency iceberg. Calcium intake and serum 25(OH) D during pregnancy have been shown to significantly influence bone mineral content in infancy[17] and at 9 years of age.[18] Vitamin D deficiency in pregnancy can result in poor fetal growth and delayed dentition.[19] In addition, dietary calcium deficiency is implicated in the causation of metabolic bone disease of prematurity, low bone mass accrual in childhood

Table.IV. Extra skeletal functions and implications of vitamin D[1]

Extra skeletal function/ role	Clinical implication
Immunomodulation Phagocytosis	Deficiency results in recurrent respiratory tract infections
Intracellular microbial killing	Increased susceptibility to tuberculosis
Cell differentiation, induction of apoptosis, inhibition of angiogenesis	Suppression of cancer cell growth – sufficient levels reduce risk of malignancies of colon, breast, prostate, ovary, pancreas and hematopoietic cells
Glucose tolerance and insulin secretion	Decreased risk of type 1 and type 2 diabetes
Cardiac myocytes, vascular endothelium	Deficiency associated with increased risk for hypertension and cardiac failure
Brain development and mental function	Deficiency linked to schizophrenia and depression
T-cell differentiation, anti inflammatory, immunosuppression	Predilection for auto immune disorders – SLE, multiple sclerosis, IBD, type 1 diabetes
Keratinocytes - antiproliferative role	Therapeutic use in psoriasis and icthyosis

and adolescence and post menopausal and senile osteoporosis.

Implications outside the skeletal system

Vitamin D has recently been shown to have possible roles in the prevention and treatment of many chronic illnesses, autoimmune diseases, cancers, infectious diseases and cardiovascular diseases. Table IV summarizes the expanding functions of vitamin D and their clinical relevance.

Hypovitaminosis D - Investigations

A proper history regarding diet and sunlight exposure gives necessary clues towards nutritional rickets, precluding costly investigations like serum 25(OH) D and PTH. A simple serum alkaline phosphatase (ALP) and plain radiology of the wrist will confirm rickets. During profound undernutrition, ALP may actually be normal in the presence of florid radiological features. In milder vitamin D deficiency not associated with rickets, ALP is normal, serum phosphorus is typically low and PTH is elevated. But in situations of hypocalcemia due to severe vitamin D deficiency, often seen in neonates, serum phosphorus is often temporarily elevated. In the context of rickets, if a nutritional etiology is suspected, the above mentioned simple investigations may be performed. If there is no response in 1 - 2 months, other etiologies should be sought, requiring tests such as creatinine, PTH, and tests for renal tubular acidosis, malabsorption, etc. As regards

preventive supplementation, since vitamin D deficiency is ubiquitous, it is more cost effective to simply prescribe sun exposure and, in vulnerable groups, a safe and effective physiologic dose, rather than to test 25(OH)D or PTH.

Treatment and prevention

In situations with severe vitamin D deficiency presenting as hypocalcemic seizures, parenteral followed by oral calcium replacement along with 1,25 dihydroxy D3 (calcitriol 25-50ng/kg/day) is preferred for the initial couple of days while the action of cholecalciferol supplementation starts off. In all other situations, cholecalciferol alone, and not active vitamin D, is the recommended form of treatment for hypovitaminosis D.

There is no single widely accepted regimen for treatment of rickets. Investigators have tried different regimens with variable results. Toxicity has been evaluated in only very few studies. The most commonly studied regimes used mega doses of oral/ parenteral vitamin D (Stoss regimen), ranging from 50,000 units once a week for 6 weeks to single doses of 150,000, 200,000, 300,000 or 600,000 units. There is no study which has addressed all of the following issues together: finding the minimum dose (to minimize cost and toxicity) which raises serum 25(OH) D by 15 to 20 ng/ml, produces quick resolution of elevated ALP, and does not cause hypercalcemia. Doses of 400 U/day orally for 6 months in neonates and infants have been shown to be safe and effective as preventive supplementation,[20] as have 2000 U/day for 6 weeks in older infants and toddlers[21] and 14000 U/wk orally for 1 year in[21] adolescents.[22] In 2003, Cesur et al showed that while a single oral dose of 150,000 U could safely heal rickets in infants, hypercalcemia was present in infants given larger doses of 300,000 U and 600,000 U.[23] Similarly, Markestad, et al using 3 doses of 600,000 U, Zeghoud, et al using 2 doses of 300,000 or 600,000 U and Gordon, et al using 50,000 U per week for 6 weeks, orally as prevention in infants, have shown hypercalcemia or elevated serum 25 (OH)D in some of their subjects.[21, 24, 25] In contrast to oral stoss therapy, where a brisk rise of serum 25 (OH)D is observed within 7 days, (which then plateaus for about 2 weeks and then starts falling from 1 month, back to baseline by 2 and a half months), investigators have shown a slow and sustained rise with IM injection of the same dose.[26] Recently, Soliman et al studied single dose injection of 10,000 U/ kg (maximum 150,000 U) cholecalciferol IM in infants and toddlers with rickets.[27] Serum calcium, phosphorus and 25(OH)D concentrations normalized at 1 month after injection and ALP and PTH normalized at 3 months. Complete radiological healing occurred in 95 % of the children by 3 months. There was no documented hypercalcemia in any child. Similar treatment efficacy at 3 months was documented in adolescents with severe vitamin D deficiency with a single dose of 10,000 IU/kg (maximum 600,000 IU) IM cholecalciferol.[28] Urinary calcium excretion, which is an early marker of vitamin D toxicity, was not documented in these studies.

Bearing in mind the available information, compliance issues, the undesirable implications of needle use, and pending more stringent safety and efficacy studies, it might be safe to use smaller oral Stoss doses for treatment. The currently available oral vitamin D formulations in our country include cholecalciferol sachets of 60,000 IU (Calcirol®, Mcirol®, DGain®, Cholical®), tablets of 1000 IU (Ultra D3®) and calcium containing tablets (Vitamin D 125- 400 IU with elemental calcium 250 -500 mg) and syrups (125 IU vitamin D and 250 mg elemental calcium/5ml - Shelcal®, Trical®, Macalvit®, Cipcal®). Hence, for treatment, doses such as 30,000 U (in new borns,

and younger infants) to 60,000 U (in older infants and toddlers) once a month for 3 months, followed by a preventive regimen is a feasible option. For routine prevention, 400 U daily for newborns and infants (or 4000 to 6000 U daily to lactating mother to increase her breast milk vitamin D to a comparable level), and for anyone older, the above mentioned treatment dose of 60,000 U but given once in 2 to 3 months, should be safe.

Who should get routine preventive supplementation in India?

In the light of increasing evidence of vitamin D deficiency in exclusively breast fed infants, and the serious implications there of, it is prudent to provide supplementation throughout infancy. Beyond infancy, the vulnerable groups are those who will not have sufficient exposure of their skin, and whose physiology demands greater vitamin D and calcium. This includes adolescent girls, practically all Indian women, especially those pregnant and lactating, and the elderly. It also includes all children on anticonvulsant medication who require higher doses for treatment and prevention.

Calcium as well as vitamin D deficiency rickets requires provision of generous doses of calcium, generally 1 gm elemental calcium, for 6 months along with ensuring age appropriate daily calcium intake subsequently.[16] All calcium salts have equal bioavailability and is equivalent to milk. Calcium carbonate is the cheapest calcium salt with highest amount of elemental calcium (40%) per gram of salt. Surgical/ orthopedic interventions of rachitic deformities should be undertaken only after complete biochemical and radiological healing of rickets. Mild to moderate deformity normalizes over many years with remodeling. Effective utilization of the freely available natural sunshine can be achieved by encouraging outdoor play and activities, adequate culturally acceptable exposure of skin and discouraging the use of sunscreen.

Vitamin D toxicity

Intoxication due to excess vitamin D intake is not a rarity.[29] The lipophilic nature of vitamin D and its long tissue half life (2 months for cholecalciferol) augments the risk of toxicity. Though serum 25(OH) D> 100 ng/ml (250 nmol/l) is traditionally considered as toxic level, hypercalcemia ensues when the levels are persistently above 150 ng/ml (374 nmol/l) as seen in adults. Intake of doses upto 10,000 U daily in adults has been shown to be safe. Symptoms of acute vitamin D intoxication include nausea, vomiting, constipation, anorexia, polyuria and polydipsia. Severe cases progress to acute fulminant renal failure and cardiac arrhythmias culminating in death. Therapeutic options include induced emesis and activated charcoal (in acute oral intoxication), saline diuresis, loop diuretics (frusemide), glucocorticoids, phosphate binders, bisphosphonates and calcitonin.

Conclusion

Vitamin D and calcium nutrition in children is much more than just rickets. Vitamin D and dietary calcium deficiencies are rampant in India. Routine pharmacological supplementation is needed for vulnerable groups. More studies are needed before formulating recommendations for prevention and treatment of vitamin D and calcium deficiency in India.

Points to Remember

- ***Vitamin D and dietary calcium deficiencies are common.***
- ***Adequate sunlight exposure, diet revision to stress low cost culturally acceptable local seasonal foods rich in vitamin D and calcium and pharmacologic***

supplementation in vulnerable groups such as newborns and infants, adolescent girls and pregnant and lactating mothers are the cornerstones of management.

- ***For prevention of deficiency, currently recommended dose of 400 IU/day appears adequate for infants. Adolescents and adults may require doses of the order of 2000 IU/day.***
- ***Vitamin D toxicity is an important concern while choosing Stoss therapy doses for treatment of rickets.***

References

1. Holick MF. Mc Collum Award Lecture, 1994: Vitamin D-new horizons for the 21st century Am J Clin Nutr 1994; 60: 619-630.
2. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-281.
3. Hoogenboezem T, Degenhart HJ, DeMuinck, Kizer-Schrama SM, Bouillon R, Grose WFA, Hackeng WHL, et al. Vitamin D metabolism in breast-fed infants and their mothers. Pediatr Res 1989; 25: 623-628.
4. Hollis B, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004; 80 (suppl): 1752S–1758S.
5. V. Bhatia. Dietary calcium intake - a critical reappraisal. Indian J Med Res 2008;127: 269-273.
6. Puri S, Marwaha RK, Agarwal N, Tandon N, Agarwal R, Grewal K, et al. Vitamin D status of apparently healthy school girls from two different socioeconomic strata in Delhi: relation to nutrition and lifestyle. Br J Nutr 2008; 99:876-882.
7. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, BhatiaV. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. Am J Clin Nutr 2005; 81: 1060-1064.
8. Harinarayan CV, Ramalakshmi T, Venkataprasad U. High prevalence of low dietary calcium and low vitamin D status in healthy south Indians . Asia Pac J Clin Nutr 2004; 13: 359-365.
9. Mehrotra P, Marwaha RK, Aneja S, Seth A, Singla BM, Ashraf G, Sharma B, Sastry A, Tandon N. Hypovitaminosis D and hypocalcemic seizures in infancy. Indian Pediatr 2010;47:581-586.
10. Balasubramanian S, Shivbalan So, Saravana Kumar P. Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants. Indian Pediatr 2006; 43: 247-251.
11. Balasubramanian K, Rajeswari J, Gulab, Govil YC, Agarwal AK, Kumar A, et al. Varying role of vitamin D deficiency in the etiology of rickets in young children vs. adolescents in northern India. J Trop Pediatr 2003; 49 : 201-206.
12. Sahu M, Bhatia V et al. Vitamin D deficiency in rural girls and pregnant women despite abundant sunshine in northern India. Clin Endocrinol 2009;70:680-684.
13. Holik MF, MacLaughlin JA, Dopplet SH. Regulation of pre vitamin -D3 photosynthesis in man: skin pigment is not an essential regulator. Science, New Series 1981;211: 590-593.
14. Wagner CL, Greer FR. American Academy of Pediatrics Section on Breast-feeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deûciency in infants, children, and adolescents. Pediatrics 2008; 122: 1142-1152.
15. Ross AC, Manson JE, Abrams SA, Aloia JF, Crannon PM, Clinton, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011; 96: 53-58.
16. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Isichei CO, Chan GM. A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children. N Engl J Med 1999; 341: 563-568.

17. Ganpule A, Yajnik CS, Fall HD, et al. Bone mass in Indian children-Relationships to maternal nutritional status and diet during pregnancy: the Pune maternal nutrition study. J Clin Endocrinol Metab 2006; 91: 2994–3001.

18. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: A longitudinal study. Lancet 2006; 67: 36-43.

19. Marya RK, Rathee S, Dua V, Sangwan K. Effect of vitamin D supplementation during pregnancy on foetal growth. Indian J Med Res 1998; 88:488-492.

20. Wagner CL, Howard C, Hollis BW, Hulsey TC, Lawrence RA, Taylor SN, et al. Circulating 25-hydroxyvitamin D levels in fully breastfed infants on oral vitamin D supplementation. Int J Endocrinol. 2010; 235035. Epub 2009 Dec 9.

21. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, et al.Treatment of hypovitaminosis D in infants and toddlers. J Clin Endocrinol Metab 2008: 93:2716-2721.

22. Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfound Z,et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. J Clin Endocrinol Metab 2008; 93: 2693–2701.

23. Cesur Y, Caksen H, Gundem A, Kirimi E, Odabas D. Comparison of low and high dose of vitamin D treatment in nutritional vitamin D deficiency rickets. J Pediatr Endocrinol Metab 2003;16:1105-1109.

24. Markestad T, Hesse V, Siebenhuner M, Jahresis G, Aksnes L, Plenert W, et al. Intermittent high dose vitamin D prophylaxis during infancy: effect on vitamin D metabolites, calcium, and phosphorus. Am J Clin Nutr 1987;46:652-658.

25. Zeghoud F, Ben-Mekhbi H, Djeghri N, Garabedian M. Vitamin D prophylaxis during infancy: comparison of the long-term effects of three intermittent doses (15, 5, or 2.5 mg) on 25 hydroxy vitamin D concentrations. Am J Clin nutr 1994;60:393-396.

26. Romagnoli E, Mascia ML, Cipriani C, Fassino V, Mazzci F, Drasmo E, et al. Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (Vitamin D2) or cholecalciferol (Vitamin D3) in the elderly. J Clin Endocrinol Metab 2008; 93: 3015–3020.

27. Soliman AT, El-Dabbagh M, Adel A, Ali MA, Aziz Bedai EM, Elalally RK, et al. Clinical Responses to a mega-dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets. J Trop Pediatr 2010;56:19-26.

28. Soliman AT, Adel A, Wagdy M, Alali M, Aziz Bedai EM, et al. Manifestations of severe vitamin D deficiency in adolescents: effects of intramuscular injection of a megadose of cholecalciferol. J Trop Pediatr. 2010; 28. [Epub ahead of print].

29. Joshi R. Hypercalcemia due to hypervitaminosis D: report of seven patients. J Trop Pediatr 2009 ;55:396-398.

30. Gopalan C, Rama Shastri BV, Balasubramanian SC. Proximate principles: common foods. In Nutritive value of Indian foods. Revised edn, National Institute of Nutrition, Indian Council of Medical Research 1989;pp74-77.

31. Vitamin and mineral requirements in human nutrition. Joint FAO/WHO Expert Consultation, Bangkok; 1998. Available at whqlibdoc.who.int/publications/2004/9241546123_chap4.pdf.

32. Nutrient requirements and recommended dietary allowances for Indians. A report of the expert group of Indian Council Medical Research 2009. Available at www.icmr.nic.in.

ENDOCRINOLOGY

APPROACH TO GYNECOMASTIA AND CRYPTORCHIDISM

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Abstract: *Gynecomastia is a benign disease, reflection of altered estrogen androgen activity or response. The causes are varied and result from insults occurring in the endocrine system or metabolic milieu. Minimal grade of gynecomastia without fibrosis respond to drug therapy. In resistant cases surgical therapy after puberty is to be considered. Cryptorchidism can result from delay in the maturation signals or defect in molecular mechanism. Most cryptorchid testes are undescended. Retractile testes are considered as a normal variant of normally descended testis. Treatment can be hormonal, surgical or combination of two.*

Keywords: *Cryptorchidism, Gynecomastia, Investigations, Treatment.*

Gynecomastia

Gynecomastia is a benign proliferation of stromal and glandular tissue of the male breast. It is caused by an increase in the ratio of estrogen to androgen activity (Table I). It may be unilateral or bilateral.

Gynecomastia is common in infancy and adolescence. Pseudogynecomastia, which is often seen in obese men, refers to fat deposition without glandular proliferation and does not require evaluation. Gynecomastia must be differentiated from breast carcinoma, which is far less common.

Causes

- Physiological gynecomastia, which resolves spontaneously in most cases, is common in infant and adolescent boys.
- Persistent pubertal gynecomastia occurs in 25 percent
- Drugs contribute 10 to 25 percent
- Idiopathic is 25 percent
- Cirrhosis or malnutrition is a cause in 8 percent
- Hypogonadism is a pertinent cause; primary (8 percent), secondary (2 percent)
- Testicular tumors resulting in gynecomastia in 3 percent
- Hyperthyroidism in 1.5 percent
- Chronic renal insufficiency in 1 percent

Other causes

- Precocious puberty with human chorionic gonadotropin (HCG) secreting hepatoblastoma.
- Klinefelter's syndrome
- Kallmann syndrome
- Androgen insensitivity syndrome
- Seminiferous tubule dysgenesis
- True hermaphrodites
- Isolated luteinizing hormone deficiency

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Puberty

During puberty, the serum estradiol concentrations rises to adult levels before the testosterone concentration. This transient imbalance accounts for much of the estrogen/ androgen imbalance that leads to pubertal gynecomastia. These boys may also have wider fluctuations of estradiol levels, with an absolute increase in 24-hour concentration of estradiol, which may reflect increased conversion of adrenal androgens to estrogens. Adrenal androgen secretion rises during adrenarche, which occurs independently, before the maturation of the hypothalamic-pituitary-gonadal axis (gonadarche).

Endocrine

Regulatory hormones modulate the effects of other factors, which in turn influence breast growth and differentiation. Thyroxine increases the level of Sex hormone binding globulin (SHBG), which preferentially binds to testosterone thereby leaving relatively high free estrogens for action. Cortisol and prolactin lower circulating testosterone levels through hypothalamic and testicular effects.

Drugs

There are many drugs that have been associated with gynecomastia. Spironolactone can increase the aromatization of testosterone to estradiol, decrease the testosterone production rate by the testes and displace testosterone from SHBG, thereby increasing its metabolic clearance rate. Spironolactone also can act as an antiandrogen by binding to androgen receptors and displacing or preventing binding of testosterone and dihydrotestosterone to their receptors.

All drugs within the same class do not cause gynecomastia to the same extent. For example, among the calcium channel blockers, nifedepine has the highest frequency of gynecomastia and diltiazem the lowest.

Another example is the proton pump inhibitors; the incidence of gynecomastia is highest with cimetidine, then ranitidine and lowest with omeprazole.

Tea tree oil and lavender oil, plant-derived oils that are available as over-the-counter skin care products (lotions, soaps, and shampoos), have been associated with gynecomastia.

Cirrhosis or malnutrition

Cirrhosis is accompanied by several changes that probably explain the development of gynecomastia:[1,2] an increased production rate of androstenedione from the adrenals, enhanced aromatization of androstenedione to estrone, and increased conversion of estrone to estradiol. Both gonadotropin and testosterone levels are probably reduced, while estrogen production was normal due to normal estrogen production from adrenal precursors. These changes will promote the development of gynecomastia.

Male hypogonadism

Primary hypogonadism can be due to a congenital abnormality such as Klinefelter's syndrome or an enzymatic defect in the testosterone biosynthetic pathway, or to testicular trauma, infection, infiltrative disorders and vascular insufficiency. The associated reduction in testosterone production leads to a decrease in the serum testosterone concentration and a compensatory rise in Luetinising Hormone (LH) release. The excess LH results in enhanced Leydig cell stimulation with inhibition of the 17, 20-lyase and 17-hydroxylase activities and increased aromatization of testosterone to estradiol; the net effect is an increase in estradiol relative to testosterone secretion.

Testicular neoplasm

Gynecomastia is found in Leydig cell tumors of the testes.[3,4] These tumors are found in 6 to 10 year old boys who present with precocious puberty. Approximately 10 percent of these tumors are malignant. The Leydig cell tumors secrete increased quantities of estradiol and also aromatize more androgen precursors to estrogens.

Chronic renal failure

The primary cause is Leydig cell dysfunction. Serum testosterone levels are low and gonadotropins are elevated.

Other rare cases

Feminizing adrenocortical tumors : The combination of increased secretion of estrogens by the tumour and increased peripheral aromatization of adrenal androgens to estrogens accounts for the gynecomastia.

Ectopic HCG increased serum levels of immunoreactive HCG are found in a wide variety of nontrophoblastic neoplasm.

True hermaphrodites True hermaphrodites harbour both testicular and ovarian tissue and may develop gynecomastia[5] from excessive estrogen secretion by the ovarian component.

Androgen insensitivity syndromes : The androgen insensitivity syndromes are a group of disorders due to defects in or absence of the intracellular androgen receptor in androgen target tissues. In androgen insensitivity, the LH levels tend to increase above normal, which leads to excess stimulation of the Leydig cells and an increased secretion of both androgens and estrogens. The elevated serum testosterone is also aromatized into estradiol. The net effect is an increased serum concentration of estrogens with lack of androgen activity.

Aromatase excess syndrome Familial prepubertal gynecomastia is a rare disorder of increased aromatase activity resulting in severe estrogen excess.[6,7] The disorder appears to be due to heterozygous inversions or polymorphisms of the p450 aromatase gene (CYP19). The mode of inheritance appears to be autosomal dominant.

Evaluation

The combination of a careful history and physical examination and a few diagnostic tests can result in the identification of the cause of gynecomastia in the majority of patients.

In adolescent boys, breast enlargement is almost always due to pubertal gynecomastia, which resolves spontaneously in most cases.

Symptoms and signs of hypogonadism, hyperthyroidism, or liver and kidney disease should be sought.

Laboratory evaluation [serum HCG, LH, testosterone, estradiol, free T4 and Thyroid stimulating hormone (TSH), Liver Function Test (LFT)] is performed. On the other hand, asymptomatic gynecomastia that is discovered during a physical examination in a patient who does not have one of the underlying pathologic conditions noted above and who is not ingesting one of the drugs known to cause gynecomastia may not require further tests, other than a serum testosterone level in the pubertal period to screen for hypogonadism.

Physical examinations

Gynecomastia may be distinguished from pseudogynecomastia by having the patient lie on his back with his hands behind his head. The examiner then places his thumb and forefinger on each side of the breast and slowly brings them together.

- In true gynecomastia, a ridge of glandular tissue will be felt that is reasonably symmetrical to the nipple-areola complex.
- In Pseudogynecomastia, the fingers will not meet any resistance until they reach the nipple.

An abdominal mass might suggest adrenocortical carcinoma and a testicular mass or change in testicular size or consistency might indicate a neoplasm.

Management

The management of gynecomastia depends upon its etiology, duration, severity, and presence or absence of tenderness. In many cases, gynecomastia resolves without therapy.

Potential indications for early therapy include severe breast enlargement, pain, tenderness, and embarrassment that interferes with the patient's normal daily activities. Intervention may also be needed in patients with persistent gynecomastia, including those with pubertal gynecomastia that persists into later adolescence or early adulthood.

Drug therapy

Androgens: Testosterone replacement in hypo gonadal children often improves gynecomastia, but there is no rationale for its use in eugonadal children, in whom it may actually worsen the gynecomastia due to aromatization of the testosterone to estradiol.

The nonaromatizable androgen, percutaneous dihydrotestosterone (DHT), [125 mg in a hydro alcoholic gel twice daily for 4 months] has been reported to be effective for gynecomastia in uncontrolled studies.

Selective estrogen receptor modulators: Although clinical trial data are limited, the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene appear to decrease breast volume in adolescents with gynecomastia. However, complete breast regression is usually not achieved with this approach.

The typical dosages used are tamoxifen 10 to 20 mg/day, raloxifene 60 mg/day for 3 to 9 months. Combination with anti-inflammatory may be helpful in painful gynecomastia

Aromatase inhibitors: Aromatase inhibitors block estrogen biosynthesis, and should theoretically be effective for gynecomastia by decreasing the estrogen to androgen ratio.[8,9] Studies show significant reduction of breast tissue was achieved by anastrozole 1mg daily or testolactone 150 mg three times daily for 6 months. Recently letrazole 2.5 mg/day is being used.

Surgery: Surgical therapy should be considered for patients whose gynecomastia does not regress spontaneously or with medical therapy,[10] is causing considerable discomfort or psychological distress, or is long-standing (greater than 12 months). However, for adolescents, surgery is generally not recommended until adult testicular size is attained, as there may be regrowth of the breast tissue if the surgery is performed before puberty is substantially completed.

The extent of surgery depends upon the severity of the breast enlargement and whether there is also excess adipose tissue present. Many patients are treated with a combination of direct surgical excision of the glandular tissue and liposuction through a periareolar incision of any coexisting adipose tissue. Potential complications of surgical therapy for gynecomastia include sloughing of tissue due to compromise of the blood supply, contour irregularity, hematoma, and numbness of the nipple-areola area.

Cryptorchidism

Cryptorchidism by definition suggests a hidden testicle:[11] a testicle that is not within the scrotum and cannot be manipulated into the scrotum by several months of age. Cryptorchid testes are found in 2.7% of term infants and 21% of preterm infants

Development and descent

At 3 weeks germ cells migrate from yolk sac to genital ridge. By 4 to 8 weeks, in the presence of Y chromosome germ cells coalesce to form primordial testis; Sertoli cells develop and Mullerian Inhibiting Substance (MIS) which causes regression of Mullerian ducts. In the 9th week Leydig cells under influence of HCG secrete testosterone causing development of epididymis, vas deferens and seminal vesicles. During 9 to 28 weeks transabdominal migration occurs. From 28 weeks to term transinguinal migration of testis occurs.

Pathogenesis, varieties and causes

The mechanisms responsible for normal testicular descent are not well understood. The intraabdominal descent is thought to be androgen-independent and mediated by descendin. Passage through the inguinal canal, which begins in the 28th week of gestation, is believed to result from interaction between mechanical and hormonal effects. Changes in abdominal pressure, patency of the processus vaginalis, gubernacular regression, androgens, gonadotropins, and Mullerian inhibiting substance (MIS) are all thought to play a role.

Molecular factors are beginning to be elucidated.[12,13,14] Insulin-like factor 3 [(INSL3), also called relaxin-like factor (RLF) and Leydig insulin-like peptide)] is produced by the Leydig cells and acts upon the gubernaculum to retain the testis in the inguinal area. INSL3 binds to a G-protein coupled receptor, [(G-protein coupled receptor affecting testis descent), also called leucine-rich repeat containing G-protein coupled receptor 8 (LGR8)]. Mutations in this receptor-ligand complex may play a role in the development of cryptorchidism. Immune cause has also been suggested by the demonstration of antigonadotropic cell antibodies.

Most cryptorchid testicles are undescended. True undescended testicles have stopped short along their normal path of descent into the scrotum. They may remain in the abdominal cavity or they may be palpable in the inguinal canal or just outside the external ring (canalicular and suprascrotal, respectively).

Ectopic testes descend normally through the external ring but then are diverted to an aberrant position. They may be palpable in the superficial inguinal pouch (most common), suprapubic region, femoral canal, perineum, or contra lateral scrotal compartment (least common).

Testes occasionally are noted to be in a scrotal position in early childhood and then to "ascend" and become undescended.[15] Ascending testicles probably represent ectopic testes that have enough laxity to reach the scrotum in early childhood, but become tethered in place and pulled out of the scrotum as the child grows.

Retractile testes are suprascrotal testes that can be brought into a dependent scrotal position and will remain there if the cremasteric reflex is overcome.

Cryptorchidism can affect one or both testes; approximately 10 percent of cases are bilateral; among the unilateral cases, a left-sided predominance exists.

It occurs more commonly among patients with congenital disorders of testosterone secretion or action (eg, Kallmann syndrome),

abdominal wall defects, neural tube defects, cerebral palsy and various genetic syndromes (eg: trisomy 18, trisomy 13, Noonan syndrome, Prader-Willi syndrome, Laurence-Moon-Biedl, Aarskog and Cornelia de Lange syndrome). Patients who have cryptorchidism and hypospadias have an increased risk of having disorders of sexual differentiation (mixed gonadal dysgenesis and true hermaphroditsm).

Natural history

Undescended testes : Testicles that are undescended at birth complete their descent within the first few months of life. Those that do not will require surgical manipulation into and attachment to the scrotum (Orchidopexy).

Retractile testes : Retractile testes have classically been considered to be a normal variant of normally descended testes.

Evaluation

History : Important aspects of the history in a patient with cryptorchidism include evidence of endocrine disturbance during pregnancy, family history of unexplained neonatal deaths or genital anomalies, abnormal pubertal development, or infertility; and whether or not the testes were in a scrotal location in the neonatal period (i.e., before the cremasteric reflex becomes active).

Physical examination

Boy with cryptorchidism should be examined for any features of a malformation syndrome. Such features may reveal an underlying cause for the cryptorchidism, although most cases are idiopathic.

Genital examination

Genitalia should be examined for any abnormality, particularly hypospadias, because the combination of hypospadias and cryptorchidism is associated with disorders of sexual differentiation, especially if the testes are nonpalpable and the meatus is posteriorly located. Additional signs of testicular abnormalities include a hypoplastic or defectively rugated scrotum and inguinal fullness.

The testicular examination in the infant and young child requires two hands. The hands may be lubricated with surgical lubricant or warm, soapy water. One hand is placed near the anterior superior iliac spine and the other on the scrotum. The first hand is swept from the anterior iliac spine along the inguinal canal to gently express any retained testicular tissue into the scrotum. A true undescended or ectopic inguinal testis may slide or "pop" under the examiner's fingers during this manoeuvre. A low ectopic or retractile testis will be felt by the second hand as the testis is milked into the scrotum by the first hand.

Several manoeuvres can be used in an attempt to bring a retractile testis into the scrotum or to differentiate an ectopic from a retractile testis. In the OPD frog leg squatting posture is easy to differentiate.

Investigation

Ultrasound may be advisable in some circumstances:

- To look for gonads and exclude the presence of a uterus in the phenotypically male infant with bilateral nonpalpable testes
- In obese boys, in whom intracanalicular testes may be difficult to feel

The initial laboratory evaluation depends upon the age, associated clinical picture and signs: which includes karyotype, ultrasound of the pelvic structures; measurement of electrolytes, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone,

Mullerian inhibiting substance (MIS) and adrenal hormones and metabolites (eg, 17-hydroxy-progesterone).

The diagnosis of testicular absence requires negative Human Chorionic Gonadotropin (HCG) stimulation test and elevated gonadotropins. The HCG stimulation test is performed to elicit evidence of testosterone production in response to the administration of intramuscular HCG (1000 to 1500 international units per day for three to four days). Boys with anorchidism do not respond, whereas boys with bilateral cryptorchidism respond with increased testosterone production.

Complications of cryptorchidism

The complications of undescended testes include testicular neoplasm, sub fertility, testicular torsion, inguinal hernia and trauma.

Treatment

The treatment for cryptorchidism can be hormonal, surgical, or a combination of the two.

Testicular descent sometimes can be induced with administration of hormone because normal testicular descent is at least in part a hormonally mediated process.

HCG [16] and Luetinising hormone releasing hormone (LHRH) are approved for use in the treatment of cryptorchidism. Most common schedule is (as per International health foundation)

HCG dose:

Infants – 250 IU/dose

Up to 6 years – 500 IU/dose

More than 6 years 1000 IU/dose

Given twice a week for 5 weeks

Route of administration is intra muscular

Success rates for descent into scrotum are 25-55% in uncontrolled studies.[17]

Testis located more distally in inguinal canal and high scrotum responds well to this therapy.

GnRH/LHRH

Stimulate the release of pituitary gonadotropins, LH and FSH resulting in temporary increase in gonadal steriodogenesis.

Administration

Given as nasal spray. Dose: 200-400mcg, 3-6 times a day, 4 weeks. Low-dose GnRH given by nasal spray every other day for 6 months after Orchidopexy appear to improve spermatograms in adult life.

Surgical

Orchidopexy is a well-established operation for the palpable undescended testis. Orchidopexy is a surgical procedure in which the testicle is manipulated into the scrotum and sutured in place. It has been demonstrated to be a safe procedure in infants younger than one year of age (i.e., the age group that has the greatest likelihood of surgical success).

Postoperative management is fairly straightforward. To prevent dislodgement of the testis from the scrotum, straddle toys such as bicycles are avoided for several weeks. Examination in the early postoperative period allows assessment of wound healing and testicular location. Repeat examination is performed at least three months postoperatively to assess testicular position and size.

Although rare, the most significant complication of orchidopexy is testicular atrophy. Ischemia leads to testicular atrophy. Other complications include ascent of the testis (requiring reparative orchidopexy), infection and bleeding.

Surgery for the nonpalpable testis is both diagnostic and potentially therapeutic. The first surgical objective is to determine whether or not the testis is present; viable testes are positioned and fixed within the scrotum, viability of testes is assessed by testosterone response to HCG; nonviable testicular remnants are removed.

References

1. Gordon GG, Olivo J, Fereidoon R, Southren AL. Conversion of androgens to estrogen in cirrhosis of the liver. J Clin Endocrinol Metab 1975; 40:1018-1026.
2. Smith SR, Chhetri MD, Johanson AJ, Radfar N, Migeon CJ. The pituitary-gonadal axis in men with protein-calorie malnutrition. J Clin Endocrinol Metab 1975; 41:60-69.
3. Tseng A Jr, Horning SJ, Freiha FS, Resser KJ, Hannigan JF, Tortic PM, et al. Gynecomastia in testicular cancer patients. Prognostic and therapeutic implications. Cancer 1985; 56:2534-2538.
4. Bercovici JP, Nahoul K, Ducasse M, Tater D, Kerlan V, scholler R. Leydig cell tumor with gynecomastia: Further studies - the recovery after unilateral orchidectomy. J Clin Endocrinol Metab 1985; 61:957-962.
5. Van Niekerk WA. True hermaphroditism. In: The Intersex Child, Josso, N (Ed), Karger, Basel 1981, p. 80.
6. Quigley CA, De Bellis A, Marschke KB, Cl-pwady MK, Wilson EM, Fresnch FS. Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev 1995; 16:271-321.
7. Braunstein GD. Aromatase and gynecomastia. Endocr Relat Cancer 1999; 6:315-324.
8. Gruntmanis U, Braunstein GD. Treatment of gynecomastia. Curr Opin Investig Drugs 2001; 2:643-649.
9. Gikas P, Mokbel K. Management of gynaecomastia: an update. Int J Clin Pract 2007; 61:1209-1215.
10. Cordova A, Moschella F. Algorithm for clinical evaluation and surgical treatment of gynaecomastia. J Plast Reconstr Aesthet Surg 2008; 61:41-49.
11. Pillai SB, Besner GE. Pediatric testicular problems. Pediatr Clin North Am 1998; 45:813-830.
12. Ivell R, Hartung S. The molecular basis of cryptorchidism. Mol Hum Reprod 2003; 9:175-181.
13. Ferlin A, Simonato M, Bartoloni L, Rizzo G, Bettella A, Dofforini, et al. The INSL3-LGR8/GREAT ligand-receptor pair in human cryptorchidism. J Clin Endocrinol Metab 2003; 88:4273-4279.
14. Zimmermann S, Steding G, Emmen JMA, Brinkmann AO, Nayernia K, Holstein AF, et al. Targeted disruption of the Insl3 gene causes bilateral cryptorchidism. Mol Endocrinol 1999; 13:681.
15. Docimo SG. Testicular descent and ascent in the first year of life. Urology 1996; 48:458-460.
16. Kaleva M, Arsalo A, Louhimo I, Rapola J, Perheenbupa J, Henriksen K, et al. Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. Int J Androl 1996; 19:293-298.
17. Pyorala S, Huttunen NP, Uhari M. A review and meta-analysis of hormonal treatment of cryptorchidism. J Clin Endocrinol Metab 1995; 80:2795.

ENDOCRINOLOGY

PRECOCIOUS PUBERTY - WHEN AND HOW FAR TO INVESTIGATE?

*** *Anna Simon***

Abstract: *Precocious puberty is defined as the onset of puberty at an age earlier than expected for the normal population (i.e.) 2 SD earlier than the mean for the population. Premature activation of HPG (hypothalamo-pituitary-gonadal) axis results in true or central precocious puberty (CPP) and exposure to sex steroids independent of this axis results in pseudo or peripheral precocious puberty. Variations of normal pubertal development like premature thelarche and premature adrenarche can occur in otherwise healthy children and may mimic precocious puberty. These conditions do not require any treatment other than reassurance and follow-up every 3-6 months. Advancement of skeletal age occurs with pathological forms of precocious puberty. GnRH stimulation test may help to distinguish central precocious puberty from peripheral precocious puberty when basal levels of LH and FSH are not diagnostic. All causes of peripheral precocious puberty have to be investigated and managed appropriately depending on the underlying cause. CNS imaging should be considered in all boys less than 9 years and in girls less than 6 years with central precocious puberty. Suppression of central precocious puberty with GnRH analogues should be considered only when there is significant compromise of adult stature and/or with psychological and behavioural concerns.*

Keywords: *Precocious puberty, Skeletal age, Thelarche, Adrenarche.*

Puberty is characterized by the appearance of secondary sexual features and transition from the sexually immature form to the sexually mature form. Precocious puberty is defined as the onset of puberty at an age earlier than expected for the normal population - 2 SD earlier than the mean for the population. Puberty sets in with activation of the hypothalamo-pituitary-gonadal (HPG axis). The hypothalamo-pituitary-gonadal (HPG) axis is relatively quiescent during childhood under higher inhibitory influences that still remain incompletely understood. Any disruption to this normal inhibition of the HPG axis during childhood results in true or central precocious puberty (CPP). Abnormal secretion or exposure to sex steroids independent of the HPG axis results in pseudo or peripheral precocious puberty (PPP).

The main challenges when dealing with precocious puberty are

1) Identifying children with pathological forms of precocious puberty and differentiating normal variants of pubertal development from the pathological forms.

2) Determining whether the etiology is central (GnRH dependent) or peripheral (GnRH independent). This is crucial for planning appropriate investigations and therapy.

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A clear concept of normal puberty and the variations of normal pubertal development is required to understand the pathology of precocious puberty.

Normal puberty

Pubertal development coincides with the activation and maturation of the HPG axis and also with the maturation of the adrenal cortex. The maturation of the HPG axis is responsible for testicular enlargement and increase in penile size in boys and breast development and menarche in girls. The increased androgen production from the adrenal cortex is responsible for development of pubic hair, body odor and acne.

Pulsatile release of GnRH from the hypothalamus marks the onset of puberty. GnRH release is regulated by the hypothalamic peptide hormone kisspeptin and GPR54 (aG protein coupled receptor).[1] GnRH stimulates the anterior pituitary to secrete luteinising hormone (LH) and follicle stimulating hormone (FSH). LH and FSH enter the systemic circulation and stimulate the ovaries and testes to produce estrogen and testosterone respectively. These sex steroids exert a complex feedback on GnRH and gonadotropin release.

Maturation of the adrenal cortex (adrenarche) leads to production of increased adrenal androgens which are responsible for many of the secondary sexual characteristics like pubic hair (pubarche), body odor and acne. Adrenarche is a gradual process and may precede central puberty.

Physical changes occurring during puberty (secondary sexual characteristics) are a result of GnRH-driven sex steroids (estrogen and testosterone) and the adrenal androgens. The first sign of central puberty in boys is testicular enlargement (4ml) and in girls is breast development. Pubic hair may precede breast development in many girls. The sequence of progression of sexual development in both boys and girls has been well described (Refer Tanner staging or SMR staging).[2] The growth spurt occurring during puberty is the result of increased sex hormones and also growth hormone secretion. In boys the peak growth velocity occurs in midpuberty, whereas in girls it occurs with the onset of puberty. Maturation of the epiphyseal plates and accrual of bone mineral density also occurs during puberty and is dependent on estrogen.

Timing of puberty is dependent on genetic, psychosocial and environmental factors. Many studies have demonstrated that black girls enter puberty earlier than white girls.[3] Environmental factors like nutrition also play a role in the timing of puberty, with obese girls entering puberty much earlier.[4]

The standards for pubertal timing as demonstrated by observational studies by Tanner and Marshall[5,6] were between 9.5 years and 13 years with mean of 11.6 years in males as evidenced by enlargement of testes. In females the age of pubertal onset was between 8.5-13 years with mean age of 11.2 years as evidenced by breast enlargement.

Variations of normal pubertal development

Variations of normal pubertal development like premature thelarche and premature adrenarche can occur in otherwise healthy children and may mimic precocious puberty. These conditions do not require any treatment other than reassurance and follow-up every 3-6 months. However, it is important to distinguish these conditions from pathological precocious puberty.

Premature thelarche

Premature thelarche is characterized by isolated breast enlargement in girls younger than 8 years of age. This condition is self-limited and

is not associated with height acceleration or advancement of bone age. Premature thelarche may be unilateral or bilateral and regression may happen when it occurs in girls less than 2 years of age. There may be mild rise in estradiol levels. GnRH stimulation test demonstrates an increased FSH response with prepubertal LH response. This condition requires no treatment, but mandates close follow-up to ensure that there is no rapid progression to CPP.[7]

Premature adrenarche

Girls are more frequently affected than boys[2] and the benign form of premature adrenarche should be differentiated from pathological forms. With benign premature adrenarche the bone age advancement is < 2 years from the chronological age or equivalent to the height age. Serum DHEAS and testosterone levels may be elevated for age, but are appropriate for the Tanner stage of pubic hair development. There will be no signs of gonadal maturation in boys or girls. The presence of clitoral hypertrophy or hirsuitism in girls suggests pathological adrenarche. No treatment is necessary for the benign form of premature adrenarche, but close follow-up for abnormal pubertal progression is important. Girls with premature adrenarche have an increased risk for hyperinsulinism and ovarian hyperandrogenism later in life.

Precocious puberty

Precocious puberty is defined as the onset of puberty at a younger age than expected for normal population. Based on Tanner's and Marshal's observational studies[5,6], pubertal signs occurring prior to 8 years in girls and prior to 9 years in boys are considered precocious. Recent data however have shown a secular trend in the timing of puberty with many girls attaining puberty earlier[8] and thereby opening a debate as to whether the age of onset of normal puberty should be reduced to 7 years in girls.

Central precocious puberty

Children with central precocious puberty exhibit isosexual pubertal development at an early age due to premature activation of the HPG axis. The pubertal stages in CPP are similar to normal puberty but may progress more rapidly. Idiopathic CPP is more common in girls.[9] Boys with CPP are more likely to have an underlying CNS lesion like CNS mass lesions or malformations.[10] Risk factors for a CNS lesion include a younger age and male gender. The causes of CPP are listed in Table 1.

In girls, breast development and estrogenisation of vaginal mucosa are the first signs of puberty. Pubarche happens next and if untreated is followed by menarche. Boys have testicular enlargement followed by increased penile size, pubarche, increased muscle mass and deepening of voice. Along with pubertal progression, growth acceleration with significant advancement of bone age occurs. Neurological symptoms like headache, visual disturbances and seizures raise the suspicion of a CNS lesion. Gelastic seizures, which manifest as laughing spells are characteristic of hypothalamic hamartomas.

Peripheral precocious puberty

Peripheral precocious puberty is less common than CPP. It occurs independent of the HPG axis maturation. The HPG axis in peripheral precocious puberty is suppressed by abnormally elevated androgens or estrogens. These sex steroids may originate from the adrenal glands, gonads, other organs or an exogenous source. Estrogen excess induces isosexual precocious puberty in girls and heterosexual puberty in boys; similarly increased androgens induce isosexual precocious puberty in boys and heterosexual puberty in girls.

Peripheral precocious puberty has many different causes (Table II). It can be due to

Table. I. Etiology of precocious puberty

GnRH dependent (central or true)

Idiopathic

- Central nervous system abnormalities
  - Acquired
    - Trauma, post-surgical, radiation, inflammation, granulomas.
  - Congenital anomalies
    - Hypothalamic hamartoma, arachnoid cysts, suprasellar cysts, septo-optic dysplasia.
  - Tumors
    - Craniopharyngiomas, pinealomas, gliomas, LH secreting adenoma.
- Chronic exposure to sex steroids: uncontrolled CAH, testotoxicosis
- Untreated primary hypothyroidism

GnRH independent (peripheral or pseudo)

- CAH males
- McCune Albright syndrome
- LH receptor activating mutation
- Tumors
  - Adrenal : adenoma, carcinoma
  - Ovarian : granulosa cell tumor, gonadoblastoma, carcinoma
  - Testicular : Leydig cell tumor
  - Gonadotropin producing : dysgerminoma, hepatoblastoma, hepatoma, teratoma, choriocarcinoma.
- Exogenous sex steroids
- Ovarian cyst

external factors like therapeutic or accidental excess of androgens or estrogens. Other causes include sex hormone secreting tumors of the gonads, CNS, adrenals, liver or other organs, defects in steroid biosynthesis or activating mutations of the LH receptors.

Diagnostic evaluation

Approach to evaluation in case of Precocious puberty among 1) Girls with breast enlargement and pubic hair development, 2) Girls with isolated breast enlargement and 3) Boys with pubic hair/and or penile enlargement are shown in Figs. 1 to 3).

The diagnostic evaluation of all patients with precocious puberty should begin with a proper and thorough history. The history of age of onset of puberty in other family members is important. History of accidental or iatrogenic exposure to sex steroids should be enquired. Also a history of CNS trauma, infection, presence of neurological symptoms or hypothyroid symptoms will provide important clues to the diagnosis.

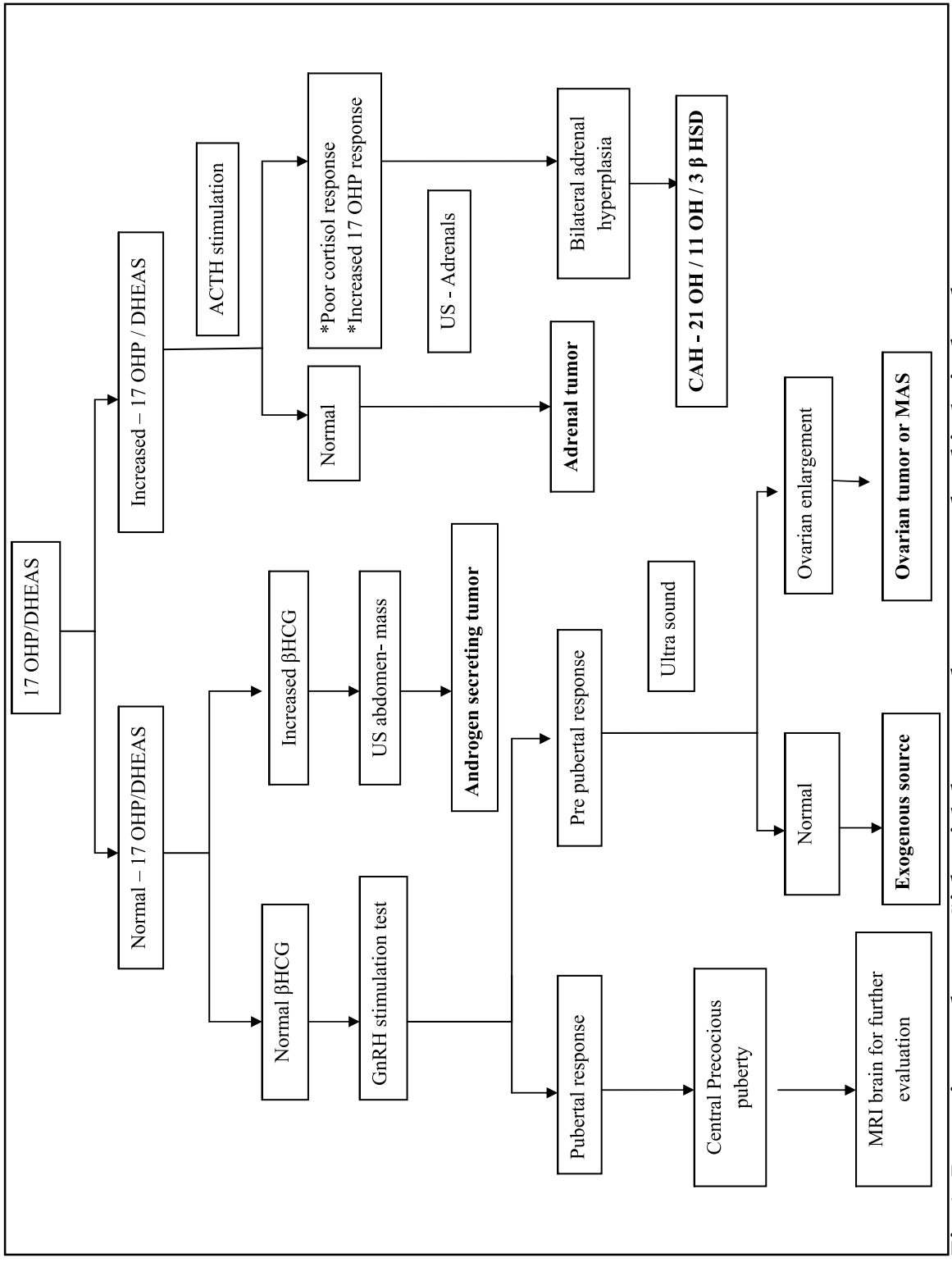

Fig.1. Precocious puberty: Girls with breast enlargement and pubic hair development

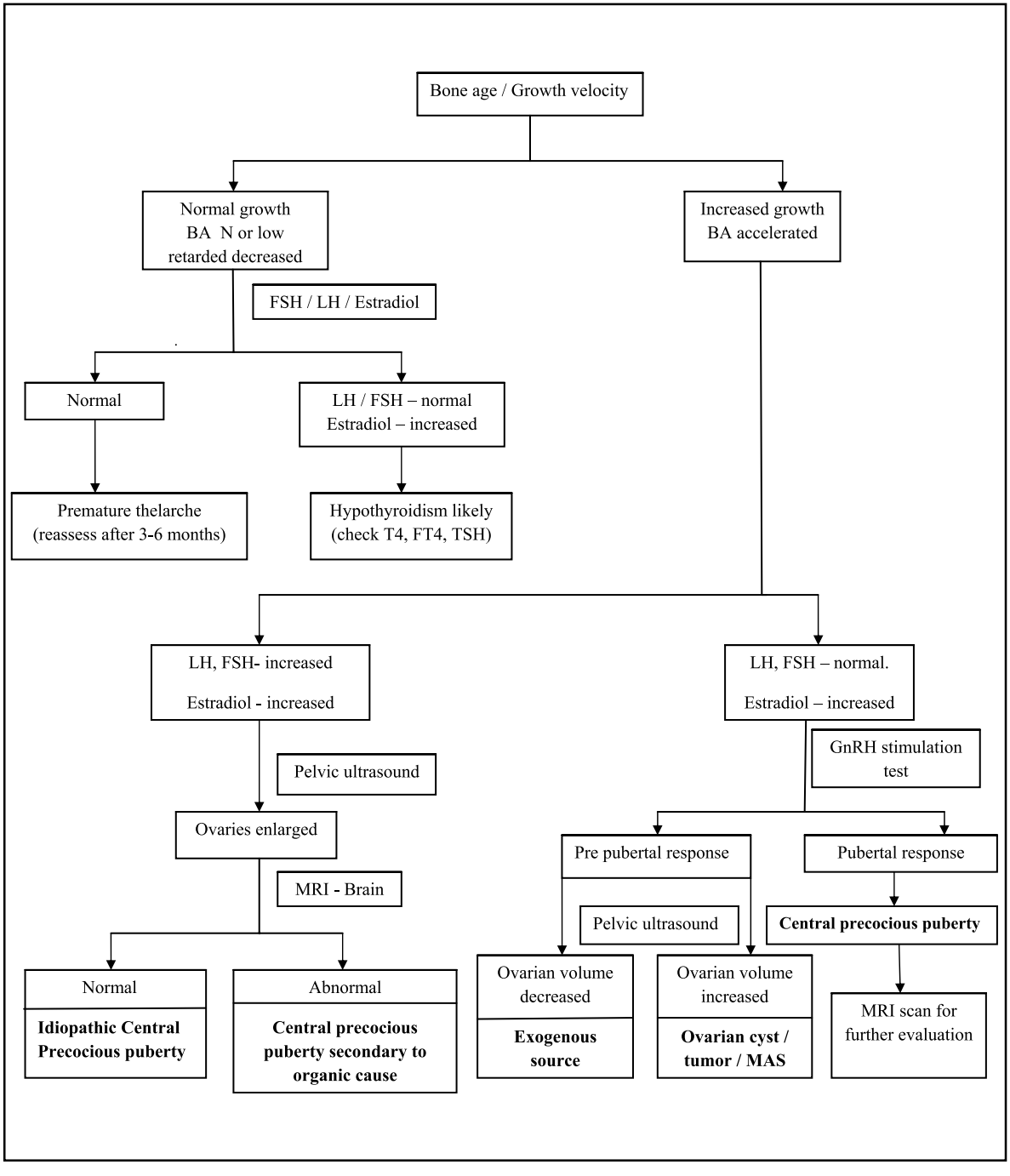

Fig.2. Precocious puberty evaluation: Girls with isolated breast enlargement

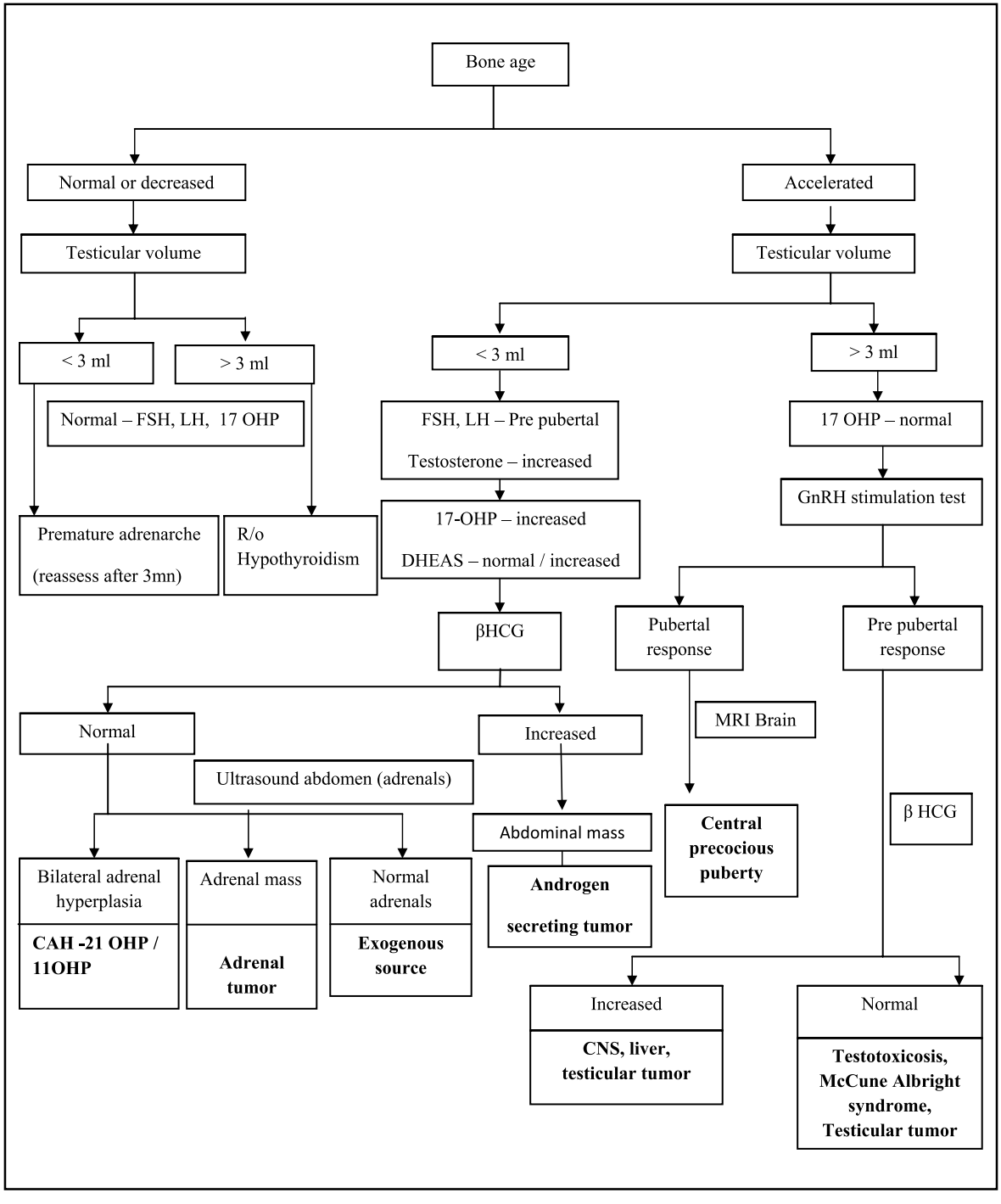

Fig.3. Precocious puberty evaluation in boys with pubic hair + / or penile enlargement

A thorough physical examination should include careful measurement of height, weight, assessment of body proportions and pubertal staging by Tanner or SMR staging. Any evidence of accelerated growth or growth spurt should be recorded. Other secondary sexual features like acne, breaking of voice and body proportions have to be noted. A complete neurological examination including fundoscopy and visual field defects should be done. The physical examination should include signs for specific causes of precocious puberty such as café-au-lait patches or bony lesions of fibrous dysplasia which are commonly seen in McCune Albright syndrome and neurofibromatosis. Any clinical finding suggestive of hypothyroidism or a palpable thyroid may give a clue to the etiology.

Investigations should be planned based on the probable diagnosis after the history and physical examination.Unnecessary investigations should be avoided if features of precocious puberty are inconsistent or are not clearly evident and the patient must be reviewed after a few months for reassessment. A skeletal age assessment is mandatory. The skeletal age in patients with precocious puberty is significantly advanced (more than 2 years) than their chronological age. The skeletal age can also be used to predict adult height; predicted adult height is an important factor to be considered when planning treatment for precocious puberty.

Initial blood tests should include LH, FSH, estradiol in girls and testosterone in males. Levels of sex steroid measurements must be done in the morning. DHEAS should be done whenever the patient presents with premature adrenarche. Elevated serum levels of sex steroids (testosterone and estradiol) confirm the diagnosis of precocious puberty but do not differentiate the cause. In girls, estradiol levels are highly variable and have a low sensitivity for diagnosing precocious puberty. Basal elevated LH and FSH levels point towards CPP. A GnRH stimulation test is very valuable in differentiating CPP from PPP, when baseline gonadotrophins are inconclusive. This involves baseline LH and FSH estimation followed by 30 minutes and 60 minutes stimulated values of LH and FSH with intravenious GnRH 100 μg. Peak LH values are used to differentiate pubertal activity of the HPG axis from prepubertal stage. Pre pubertal patients or those with peripheral precocious puberty have little or no response to GnRH stimulation.[11].

Pelvic sonography is a very useful tool in girls to determine the uterine size, uterine corpus: cervix ratio and ovarian size. The uterus and ovaries are appropriately enlarged in CPP. Unilateral enlargement of ovaries may indicate a cyst or tumour as in PPP. MRI of the pituitary - hypothalamic region is indicated in all boys and in girls less than 6 years of age with CPP to exclude a CNS lesion. MRI may be avoided in girls with CPP between 6-8 years as the etiology is most often idiopathic CPP. If there are clinical features to suggest an underlying CNS lesion, a MRI scan of the brain should be considered in this age group also.

All cases of PPP should be investigated and treated appropriately; the main causes of PPP, the investigation modalities and treatment options are listed in Table.2. Suppression of puberty with GnRH analogues should be considered for CPP when there is significant advancement of skeletal age and at younger age group as they are at risk of adult short stature due to premature epiphyseal fusion. Girls in the age group 6-8 years with slowly progressive CPP or unsustained CPP may not require treatment as the adult heights are not compromised.

Behavioural problems and psychological stress are also indications for suppression of puberty.

No treatment is required for normal puberty variants like premature thelarche or premature

Table. II. Differential diagnosis and management of precocious puberty

Diagnosis	Presentation	Investigations	Management
Central precocious puberty			
Idiopathic CPP	Breast development and advanced pubic hair in girl, testicular and penile enlargement, pubic hair in boys. Increased growth velocity. Normal sequence of puberty, but may progress rapidly.	High estradiol or testosterone. Elevated basal LH Elevated peak LH with GnRH stimulation	GnRH agonist
CPP due to CNS lesions	Similar to the idiopathic form. Also symptoms and signs of neurological involvement	Similar to above. CT or MRI demonstrating the underlying lesion.	Treatment for underlying CNS lesion+/- GnRH agonist
Peripheral precocious puberty			
Adrenocortical tumors	Virilization in boys and girls. No testicular enlargement in boys.	Elevated DHEAS, androstenedione. Low basal LH. CT or US demonstrating tumor Prepubertal response to GnRH stimulation.	Resection. +/- chemotherapy
Gonadal tumors (Leydig cell or granulosa cell)	Asymmetric testes, rapid increase in penile size and pubic hair in boys. Rapid onset breast enlargement and menstruation in girls.	Elevated testosterone or estradiol levels. US or CT demonstrating lesion. Low basal LH & prepubertal response to GnRH stimulation.	Resection
HCG secreting tumors	Breast enlargement and pubic hair in girls. Testicular enlargement, increase penile size and pubic hair in boys.	Elevated â-HCG. Elevated testosterone or estradiol. Imaging for tumor. Low basal LH & pre-pubertal response to GnRH stimulation.	Resection
CAH	Premature pubarche/ virilisation Ambiguous genitalia, +/- salt wasting, Gonads remain pre-pubertal	Elevated 17 OHP, DHEAS, 11deoxycortisol. Hyperplastic adrenals on imaging.	Glucocorticoid replacement. +/- mineralocorticoid
McCune-Albright syndrome	Irregular café-au-lait spots, polyostotic fibrous dsysplasia, other endocrine dysfunction.	Elevated estradiol. Multicystic ovaries on US. Low basal LH & pre-pubertal response to GnRH stimulation.	Tamoxifen Testolactone/ aromatase inhibitor
Male-limited precocious puberty.	Virilisation in early childhood. Large testes.	Elevated testosterone. Pre-pubertal response to GnRH stimulation.	Spironolactone and aromatase inhibitor +/_ ketoconazole.

adrenarche. Reassurance and close follow-up to exclude rapid progression to CPP is all that is required for these patients.

Conclusion

All children presenting with precocious puberty require a detailed history and clinical evaluation before commencing investigations and treatment. Normal pubertal variants like premature thelarche and premature adrenarche require only reassurance and periodic follow-up. The pediatrician therefore should be adept in differentiating normal pubertal variants from pathological precocious puberty. Unnecessary investigations should be avoided if features of precocious puberty are inconsistent or not clearly evident and the patient must be reviewed after a few months for reassessment. All forms of PPP should be managed according to the etiology, predicted adult height and psychological concerns. Suppression of CPP with GnRH analogues should be considered when there is significant compromise to adult stature and behavioural issues.

Points to Remember

- ***It is important to distinguish precocious puberty from normal variants of pubertal development.***
- ***Unnecessary investigations should be avoided if features of precocious puberty are inconsistent or not clearly evident and the patient must be reviewed after a few months for reassessment.***
- ***Suppression of CPP with GnRH analogues should be considered only when there is significant compromise to adult stature and behavioural issues.***

References

1. Rosenfield RL, Cooke DW, Radovick S. Puberty and its disorders. In: Pediatric Endocrinology, 3rd Edn, Sperling M, Ed, Saunders Elsevier, Philadelphia 2008;pp530 - 609.
2. Lee PA, Houk CP. Puberty and its disorders. In: Pediatric Endocrinology, 5th Edn, Vol.2, Lifshitz, Informa Healthcare, New York 2007;pp273 - 290.
3. Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: Third national Health and Nutrition Examination Survey. Pediatrics 2002; 110: 752 - 757.
4. Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SR, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics 2001; 108: 347 - 353.
5. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970; 45: 13 - 23.
6. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child. 1969; 44: 291 - 303.
7. Carel JC, Leger J. Precocious Puberty. N Engl J Med 2008; 358(22): 2366 - 2377.
8. Kaplowitz PB, Oberfield SE. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Pediatrics 1999;104:936 – 941.
9. Cisternino M, Arrigo T, Pasquino AM, Tinelli C, Antoniazzi F, Beduschi L, et al. Etiology and age incidence of precocious puberty: A multicentric study. J Pediatr Endocrinol Metab 2000;13 Suppl 1: 695-701.
10. Cassio A, Cacciari E, Zucchini S, Balsamo A, Diegoli M, Orsini F. Central precocious puberty: clinical and imaging aspects. J Pediatr Endocrinol Metab 2000;13 Suppl 1:703 - 708.
11. Iughetti L, Predieri B, Ferrari M, Gallo C, Livio L, Milioli S, et al. Diagnosis of central precocious puberty: endocrine assessment. J Pediatr Endocrinol Metab 2000;13 Suppl 1:709 - 715.

ENDOCRINOLOGY

PRACTICAL APPROACH TO SHORT STATURE

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Abstract: *Short stature is a common childhood problem for which an endocrine opinion is sought. It is important to use updated growths charts, follow growth velocity and consider midparental height when diagnosing short stature. Common causes of short stature seen in India are chronic malnutrition, systemic diseases, familial short stature, chromosomal abnormalities including syndromic short stature, endocrine diseases and disorders of bones. Children who are well below the third percentile for height are likely to have an endocrine disorder or skeletal dysplasia. A systematic and analytical approach is the key to the etiological diagnosis and successful management of short children.*

Keywords: *Short stature, Growth charts.*

Short stature is a common childhood problem for which an endocrine opinion is sought. Short stature is not a diagnosis by itself but a presenting symptom of a variety of systemic, nutritional, infectious, genetic and hormonal disorders. Short stature can sometimes be the only symptom of systemic or endocrine disease and a high index of suspicion, good diagnostic acumen and a systematic approach are needed to reach the etiological diagnosis and to reduce the number of tests, which are often expensive and unnecessary.

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Definition

A child is considered to be short when his/her height is below the third percentile on a height chart for the specific population. It is important to use country specific updated growth charts so that appropriate population standards are applied and over-diagnosis of short stature is avoided. While using growth charts, parents' heights should be considered and adjusted mid parental height (sex specific target height) should be plotted.

Growth Charts: Commonly used growth charts are the height, weight and body mass index (BMI) charts where age in years is on the X-axis and height, weight or BMI are on the Y-axis. Similarly, height velocity and proportion charts are essential tools in the diagnosis of short stature. A height velocity chart consists of age on the X-axis and height velocity per annum on the Y-axis. When growth velocity observed over a period of 6 months or more falls below 25th percentile on the velocity chart, it is considered abnormal and has more significance than a single height reading below the 3rd percentile on a distance chart. Growth velocity is a very sensitive and reliable way to decide whom to investigate. Proportion charts consist of sitting height and sub-ischial leg (SIL) length. These are expressed as standard deviation scores and not as percentiles. When the disproportion between SIL and sitting height is

more than 2 standard deviations, the child is considered to be disproportionate.

Height charts are useful as a primary screening tool when evaluating a child with short stature. When a child is detected to have short stature, velocity charts are used to follow his/her progress over a period of time. In 2007 the Indian Academy of Pediatrics published guidelines for growth monitoring incorporating data by Agarwal, et al for use by pediatricians in India.[1,2] It is recommended that every country should have growth charts updated once in 10 years to incorporate the influence of secular trends, this is particularly true of countries in nutritional transition.[3] In a recent study updated national growth charts on affluent Indian children are published and can now be used as contemporary descriptive charts for Indian children.[4] This study has shown mild secular trend in height and major worrying trend of childhood obesity in urban India. In 2006, World Health Organization published a multination study that provides prescriptive growth charts for children under the age of 5 years.[5] WHO recommends use of these growth standards for all children under the age of 5 years around the world and government of India has given a directive to use these charts for under 5 children in India in all areas and across all socio-economic classes.[6]

Mid parental height and familial short stature

Parents' height should be taken into consideration so that child's height can be properly interpreted for the family's genetic potential. The formula used for calculation of target height (TH) is (Mother's height + Father's height) divided by 2 + 6.5 cms for a boy and - 6.5 cms for a girl. This value is then plotted as adult height at 18 years and the spread for target range is 6 cms on either side of the TH. This then becomes target range and if the child's height is within these percentiles, it is considered as normal. Auxological data mainly TH, child's current height, height velocity and body proportions are some of the most important tools for proper evaluation and management of short stature. Judicious use of these techniques will reduce the cost of subsequent investigations.

Etiology of short stature

Common causes of short stature seen in India are as follows:

1. Chronic malnutrition
2. Chronic systemic disease
   - Chronic infections such as tuberculosis
   - Chronic renal failure
   - Cardiac disease
   - Respiratory disease such as asthma
   - Collagen vascular disease e.g. JRA
   - Inflammatory bowel disease
   - Celiac disease (Gluten sensitive enteropathy)
3. Familial short stature
4. Chromosomal abnormalities and syndromes
   - Down
   - Turner
   - Russell-Silver Syndrome
5. Endocrine disease
   - Hypothyroidism
   - Growth hormone (GH) deficiency and GH resistance syndromes
   - Cushing syndrome
   - Delayed puberty
6. Disorders of bones
   - Rickets
   - Skeletal dysplasias

The proportion of etiologies for short stature in Indian referral centers is familial short stature

(20%), systemic disease (10-20%), syndromes and skeletal dysplasia (10-19%), Turner syndrome (7-10%), growth hormone deficiency (15%) hypothyroidism (5-10%) and constitutional delay of growth and puberty in 10-15%.[7]

Clinical clues

ICP Model of growth: The infancy-childhood-puberty (ICP) model of growth suggests that during infancy the main determinant of growth is nutrition, during childhood years it is thyroxine and growth hormone and during puberty it is sex steroids. Based on this model if the growth failure starts for the first time in infancy nutritional deficiency is the likely cause, where as if it starts in childhood, hypothyroidism or GH deficiency are more likely. Growth failure first time during adolescent years is usually due to disorders of puberty and commonest cause being constitutional delay of growth and puberty particularly in boys.[8]

In general, children who are severely short and well below the third percentile for height for the population are likely to have an endocrine disorder or skeletal dysplasia whereas children who are just under the third percentile are less likely to have a serious condition.

Certain clinical clues are useful to reach the diagnosis and are summarized in the table below:

Besides the features mentioned in the table, characteristic clinical signs can be seen in syndromes such as Russell Silver, Down or Turner.

In a disproportionately short child, short limbs usually suggest skeletal dysplasia such as achondroplasia or hypochondroplasia, where as short spine suggests a metabolic defect such as mucopolysaccharidosis.

Height age and weight age: In a short child who is also thin, height age higher than weight age suggests chronic malnutrition or chronic systemic disease where as weight age higher than height age (short and fat) suggests a hormonal disease such as GHD or hypothyroidism.

Tanner sexual maturity rating (SMR): Growth disorders that manifest around puberty are often caused by delayed puberty or disorders of puberty. One of the most important clinical clues to reach the diagnosis of puberty disorders is sexual maturity rating. As a routine, Tanner SMR staging should be done in all children who manifest with short stature.

Table I. Clinical clues towards diagnosis

Clue	Etiology
Disproportion	Dysplasia, rickets, metabolic disorders
Dysmorphology	Syndromes, hypopituitarism
Frontal bossing, micropenis	GHD, Multiple pituitary hormone deficiency
Goiter, coarse skin	Hypothyroidism
Obesity, buffalo hump	Cushing syndrome
Short metacarpals	Turner, short stature homeohox gene defect (SHOX), parathyroid disorders
Ophthalmic problems	Pituitary tumor, Craniopharyngioma, Septo-optic-dysplasia

Investigations

Fig 1 and 2 give algorithms that help in deciding which investigations are necessary for the diagnosis of a short child with and without distinguishing features.

1. Hemogram, ESR, 2. S. creatinine, urea, 3. Liver function tests, 4. Bone health parameters viz. Ca, Phosphorus, Alkaline phosphatase, 5. Bone age, skull x ray, 6. Antigliadin antibodies, 7. Thyroid function tests, 8. GH stimulation tests, 9. IGF-1, IGF – BP3, 10. Neuroimaging – MRI, 11. Karyotype and DNA studies.

Following is a brief interpretation of some of the important tests.

Bone age: The method used for calculation of bone age are Tanner Whitehouse and Grulich and Pyle. With Tanner Whitehouse method it is possible to assess bone age to an accuracy of 0.1 year. Bone age is a very useful, inexpensive and reliable tool for the assessment of short stature. When the bone age is retarded by 2 years or more it is abnormal and usually suggests an endocrine disease such as hypothyroidism, growth hormone deficiency or Cushing disease. In children who have chronic systemic disease or delayed puberty, bone age is delayed but not as much as in endocrine deficiency. It is also possible to predict final height based on bone age and this helps in deciding the length of treatment in disease such as growth hormone deficiency, Turner syndrome and precocious puberty.

Karyotype and genetic studies: Turner syndrome does not always manifest with characteristic features but may only present as short stature. It is therefore important to check Karyotype in a girl with unexplained short stature. Recently a new genetic condition, the Short Stature Homeobox (SHOX) gene defect has been described that leads to a heritable form of short stature, short 4,5 metacarpals, bowing of forearm bones and exostosis. This condition has been shown to respond to GH therapy. Similarly, conditions such as Down syndrome, Prader -Willi syndrome can be detected by chromosomal/ DNA analysis.

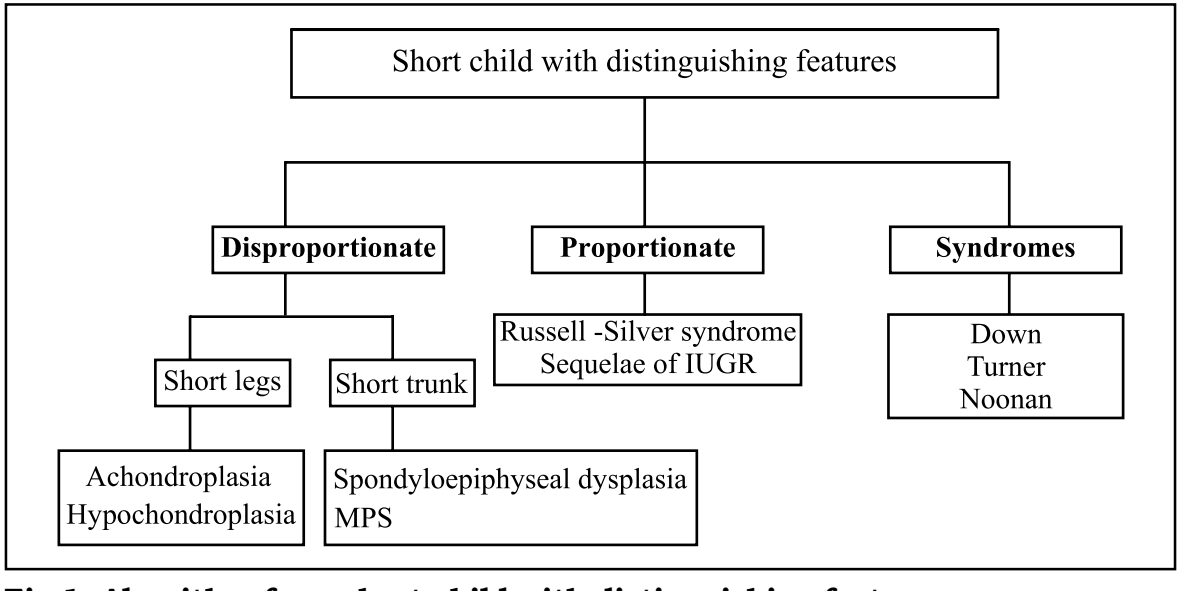

Fig.1. Algorithm for a short child with distinguishing features

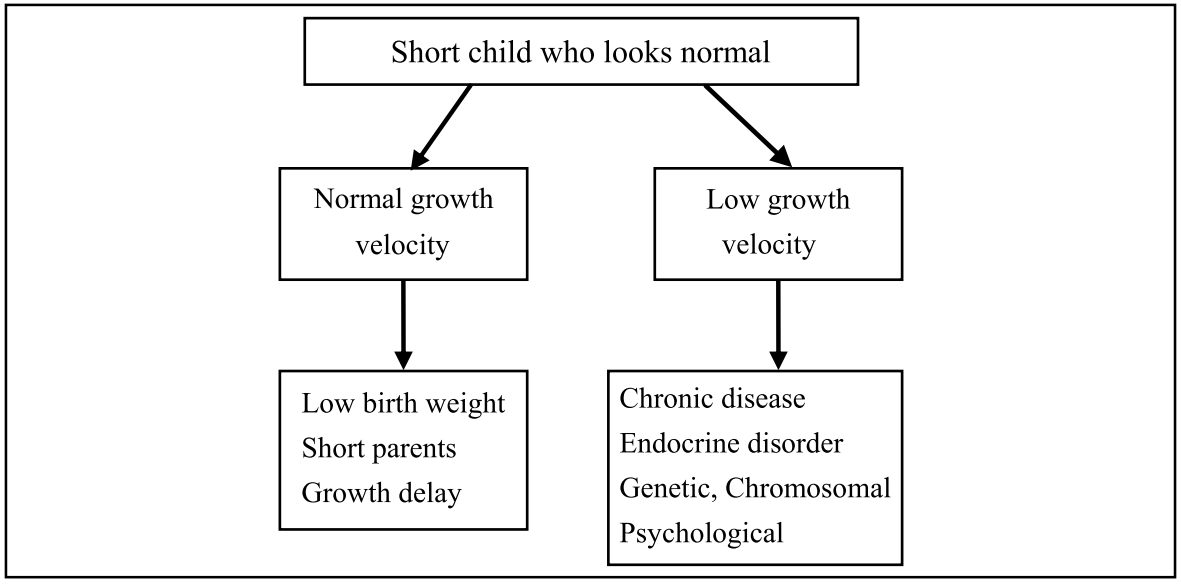

Fig.2. Algorithm for a short normal looking child

Test for growth hormone secretion: Growth hormone stimulation test is one of the most difficult tests in terms of reproducibility and reliability. A non-stimulated fasting GH does not give much information and should be avoided. GH should be checked after stimulation with either Clonidine, l-dopa, Glucagon, Arginine or insulin induced hypoglycemia. Insulin induced hypoglycemia is a risky test and may be avoided in young children. Stimulated GH is not always reliable and hence use of newer tests is being explored. Some experts recommend priming the patient with sex steroids before GH stimulation test especially in peri-pubertal children. Growth hormone values below 7 ng/dl on a stimulated sample are considered to be low suggesting GH deficiency.

Other tests which may help in the diagnosis of GH deficiency are Insulin like growth factor 1(IGF-I) and Insulin like growth factor binding protein 3 (IGF BP3). IGF - I is influenced significantly by nutritional status but BP3 is not and the two together are a better guide for the diagnosis of GH deficiency.[9]

In a recent review of the available methods for diagnosis of GH deficiency, it was suggested that a combination of auxology, GH stimulation test, IGF-I, BP3 and neuroimaging is more reliable and reproducible way to diagnose GHD particularly when combined with genetic studies.[10]

Neuroimaging: Contrast enhanced MRI is the best neuroimaging modality to diagnose pathology of the pituitary gland and the hypothalamic area.

Growth formulae

A combination of chronological age (CA), height age (HA), weight age (WA) and bone age (BA) can help in reaching a diagnosis in many children as shown below:

CA>HA>WA = Malnutrition or chronic disease (Mild BA retardation)

CA<HA<WA = Exogenous obesity (BA Mildly advanced)

CA<WA<HA = Precocious puberty (BA significantly advanced)

WA>CA>HA = Endocrine obesity (BA significantly retarded)

In conclusion, the diagnostic ability and treatment avenues for short children are ever expanding. A systematic and analytical approach is the key to the etiological diagnosis and successful management of short children.

Points to Remember

- ***It is important to use appropriate growth charts and monitor growth velocity in a child with short stature***
- ***It is necessary to consider parental height in a child with short stature***
- ***Children who are well below the third percentile for height are likely to have an endocrine disorder or skeletal dysplasia***
- ***A systematic and analytical approach is the key to the etiological diagnosis and successful management of short children.***

References

1. Agarwal DK, Agarwal KN, Upadhyay SK, Mittal R, Prakash R, Rai S. Physical and sexual growth pattern of affluent Indian children from 5-18 years of age. Indian Pediatr 1992; 29: 1203-1282.
2. Khadilkar VV, Khadilkar VV, Choudhury P, Agarwal KN, Ugra D, Shah NK. IAP Growth monitoring guidelines for children from birth to 18 years. Indian Pediatr 2007; 44: 187-197.
3. Buckler JMH. Cross-sectional Growth Curves for Height, Weight and Body Mass Index for Affluent Indian Children, 2007. In:Growth disorders in Children. 1st Edn, London: BMJ Publishing Group 1994.
4. Khadilkar VV, Khadilkar AV, Cole TJ, Sayyad MJ. Cross-sectional Growth Curves for Height, Weight and Body Mass Index for Affluent Indian Children, 2007. Indian Pediatr 2009; 46: 477-489.
5. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr 2006; 450:76-85.
6. Prinja S, Thakur JS, Bhatia SS. Pilot testing of WHO child growth standards in Chandigarh: implications for India's child health programmes. Bull World Health Organ 2009; 87: 116-122.
7. Desai MP, Bhatia V, Menon PSN, V Bhatia. Growth retardation. In*:* Pediatric Endocrine Disorders. Desai MP, Bhatia V, Menon PS, editors. 1st ed. Hyderabad: Orient Longman; 200; pp 41-83.
8. Hindmarsh PC, Brook CGD. Normal growth and its endocrine control. *In:* Clinical Pediatric Endocrinology, Ed. Brook CGD, 3rd Edn, Blackwell science, Oxford 1995;pp 85-106.
9. Dattani M, Preece M, Growth hormone deficiency and related disorders: Insights into causation, diagnosis and treatment. Lancet 2004; 363: 1977-1987.
10. Badaru A, Wilson DM. Alternatives to growth hormone stimulation testing in children. Trends in Endocrinol Metab 2004; 15: 252-258.

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ENDOCRINOLOGY

GROWTH HORMONE - EXPANDED USE

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Abstract: *The advancement of genetic engineering led to increased production of previously sparsely available growth hormone (GH). In the last few decades, extensive experience has been gained in the use of growth hormone in various disorders associated with short stature other than growth hormone deficiency (GHD). GH use in chronic kidney disease (CKD), Turner syndrome, small for gestational age (SGA), Prader Willi syndrome (PWS) and idiopathic short stature (ISS) have been approved by the FDA. The usual dose of GH in many of these conditions is higher than that used in GHD (except in PWS) and requires earlier initiation and longer duration of therapy for reasonable benefits. Further, monitoring for adverse events of chronic GH therapy including insulin resistance is recommended.*

Keywords: *Growth hormone, Uses.*

The role of pituitary in somatic growth is known from late nineteenth century from studies on hypophysectomized animals. Prior to isolation of growth hormone (GH), intraperitoneal instillation of pituitary (anterior lobe) extracts showed significant increase in length and weight of hypophysectomized puppies and rats. Later, the growth hormone molecule was isolated and the chemistry was known, however, clinical use was highly restricted as the only source of GH was from cadaveric pituitaries and hence availability and cost were the major limiting factors. Only the most severely affected GH deficiency (GHD) patients benefited from the therapy. The advancement in genetic engineering and recombinant DNA technology paved way for large scale production of GH. Gradually, its clinical use in various disorders associated with short stature other than GHD was studied. In the last couple of decades the spectrum of indications for GH has widened considerably. In this article, we intend to focus on the expanded non – GHD uses of GH. Initially, the FDA approved indications are discussed and later the off label potential uses are also mentioned. Acknowledging the varying etiology of the growth problem among non-GHD conditions, the primary goal of treatment of children who have non-GHD growth disorders is to increase height velocity and normalize height relative to peers, not to treat the underlying condition. Therefore, for these non-GHD conditions, GH is used in a pharmacologic manner rather than as physiologic replacement.

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Chronic kidney disease (CKD) in children

Children suffering from CKD are prone to develop severe growth failure. In a recent analysis of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), 37%, 47%

and 43% of children on conservative treatment, dialysis and transplantation, respectively, presented with severe short stature (standardized height less than -2 SDs).[1] The causes of growth retardation in renal insufficiency are manifold including energy malnutrition, water and electrolyte disturbances, metabolic acidosis, anemia and hormonal disturbances affecting the somatotropic and gonadotropic axes. In addition, the underlying renal condition and the different modes of treatment they receive including transplantation influence the growth. Further, in few studies the short stature was associated with increased morbidity and mortality in children with CKD. From somatotropic axis point of view CKD is in general considered as a state of GH resistance. Pathophysiologically, various alterations have been elucidated in the GH-IGF-1 (Insulin like growth factor) pathway including: elevated GH levels, altered binding protein levels, reduced IGF generation at hepatic level and reduced expression and sub cellular signaling of GH receptors. Hence, GH dose used in CKD is slightly higher than the replacement dose (0.35mg/kg/wk) to start with and titrated to keep IGF-1 levels in the normal/high normal range. Usually the indication to start treatment is growth failure (subnormal growth velocity) rather than short stature (height below a particular centile). The height response to GH is usually good in the first year of starting the therapy and treatment is continued till transplantation. There are reports, however, where in a small group of children, therapy was continued even after transplantation. In general, outcome is better in children in whom therapy is started earlier, at a younger age and with milder renal insufficiency. Though side effects are rare, it is prudent to monitor children with CKD on GH for intracranial hypertension and insulin resistance (diabetes) especially those who are on prolonged therapy.[2] In animal studies there were few reports of GH therapy being associated with glomerulosclerosis and also of rejection after transplantation. However, no clear association is observed in the large NAPRTC study.

Turner syndrome (TS)

This is one of the most common chromosomal disorders characterized by partial or complete loss of one X chromosome. Various phenotypic features are described with some correlation to the genotypic pattern, but, one common feature of all genetic varieties of TS is short stature. Majority of untreated TS girls are less than fifth centile by 4 yrs of age and coupled with lack of pubertal growth spurt they reach a mean adult height of 140cm or less which is at least 20cm below the average adult female height in Caucasians. With other social and nutritional factors the untreated TS girls in India may fair worse. From the etiological point of view the short stature in TS is at least in part due to the haploinsuficiency of the short stature homeobox-containing (SHOX) gene located in the pseudoautosomal region on the X chromosome. Except in rare instances of a pituitary dysfunction coexisting with TS almost all children with this disorder are GH sufficient.[3] As discussed above, growth hormone is used in pharmacological doses to augment growth with a goal to reach near normal height commensurate with the ethnic, familial and genetic potential. The initial dose recommended is usually 0.35mg/kg/wk and titrated later to keep the IGF-1 level in normal/high normal range. For girls less than 9 years age, usually GH therapy alone would suffice. In older girls, or those who have extreme short stature, addition of a nonaromatizable anabolic steroid such as oxandrolone (0.05mg/kg/day) may be considered with close monitoring of liver functions.[4] Therapy is usually continued until a satisfactory height has been achieved or until growth potential remains (bone age greater than or equal to 14yrs and growth velocity less than 2cm/yr). Review of various controlled studies

reveal that height response to GH is variable and occurs slowly up to an average gain of 6-8 cms depending on the age of initiation of therapy and induction of puberty. The salient factors which help in predicting better adult stature include: younger age of initiation of therapy, a long duration of therapy, relatively taller height at initiation of treatment, tall parental heights and a higher dose of GH than traditionally used in GHD. As discussed above, monitoring for metabolic effects (insulin resistance) and other rare adverse events like raised intracranial pressure and slipped capital femoral epiphyses etc. is advisable when girls with Turner syndrome are on long term treatment with GH.[5]

Small for gestational age (SGA) children

SGA has been conventionally defined as birth weight below the 3rd or 10th percentile for gestational age. Recently a more rigid criterion (<-2SDS) has been advocated due to better predictive value of postnatal growth failure. Using these criteria an infant could be SGA for weight (SGA-W), length (SGA-L) or both (SGA-WL). Most SGA children show catch-up growth in the early postnatal period. Maximum catch-up occurs by 6 months of age and 85-90% catch-up by 2 years of age. Around 10% of SGA children fail to show "catch up" by 2 years which may be associated with adult short stature.[6] In India, due to a higher prevalence of SGA, adult short stature rate is more common. This prevalence is probably significantly higher than the prevalence of GHD and Turner syndrome and second only to Idiopathic Short Stature in the etiology of short stature. GH treatment is indicated in SGA infants who fail to show catch-up growth. The consensus statement of the Lawson Wilkins Pediatric Society and European Society of Pediatric Endocrinology suggest initiation of GH in SGA infants with reduced growth velocity and height (below -2.5SDS) at two to four years of age. GH is used as a pharmacological agent in short SGA children as against physiological replacement in growth hormone deficiency. The recommended dose (0.23-0.35 mg/kg/wk) is therefore significantly higher than that in GHD. Higher dose is associated with increased initial catch-up growth and is recommended in children with severe growth retardation. GH treatment is associated with significant short and long term growth benefits in short SGA children.[7] The expected gain is to the tune of 1-1.4 SDS after 7-10years of treatment. This translates into a benefit in final height of 1cm per year of GH treatment. The OPTIMA study showed that the growth response did not significantly differ among the two doses of GH treatment (individually adjusted GH dose starting from 0.30mg/kg/wk versus fixed high dose regimen 0.60 mg/kg/wk). Children on GH therapy should be followed up once in three months to assess the compliance, response to treatment and complications.[8] Fasting blood glucose and insulin levels should be measured before initiating treatment and then annually as SGA children are at increased risk of insulin resistance and metabolic syndrome. IGF-1 level should be measured annually and the aim is to keep it in the high normal range. Features of potential complications of GH therapy in the form of headache (benign intracranial hypertension), hip pain (slipped capital femoral epiphyses) swelling (fluid retention) and osmotic symptoms (glucose intolerance) should be enquired. The treatment should ideally be continued till complete epiphyseal fusion as suggested by bone age above 14 years in girls and 16 years in boys along with growth velocity lower than 0.5cm per year. Given the likelihood of catch-up growth in majority of SGA children, careful selection of patients for GH therapy is essential.

Idiopathic short stature (ISS)

Idiopathic Short Stature (ISS) is a diagnosis that is not based on positive findings in the diagnostic workup, but on exclusion of other recognizable conditions. The ability to find underlying pathology depends totally on the completeness of the medical history, the thoroughness of the physical examination and the choices made with respect to additional investigations. Therefore, the cornerstones for the definition of ISS are the definition of short stature, the description of the disorders that must be excluded and the investigations necessary to confirm the same. The criteria for the diagnosis of ISS include:

1. Height more than 2SD below the mean for age, sex and reference population.
2. Absence of an underlying identifiable systemic or endocrine abnormality.
3. Normal weight for gestation at birth.
4. Normal body proportions.
5. Presence of adequate food/calorie intake.
6. No psychiatric or severe emotional disturbance.
7. Peak GH response on standard stimulation test of more than 10ng/mL.

These criteria include children with Constitutional Delay in Growth and Puberty (CDGP) and Familial Short Stature (FSS). ISS could be sub-categorized as children whose heights are within the parental target height and those who are short for their parents and also by the presence or absence of bone age delay, indicating better predicted adult height. The natural history of ISS is important for management decisions. Typically these children are normal at birth and start falling off the growth centiles by preschool age so that the average height is < 2 SD by early childhood. Subsequently they continue to grow parallel to their centile in the growth chart with normal or subnormal growth velocity. Although there is some degree of growth catch-up at puberty, the adult height of the untreated remains below normal for age, sex and genetic target.[9,10]

The height criteria for consideration of GH therapy for ISS vary based on geographical and clinical parameters. There are no accepted biochemical criteria for initiating GH treatment in ISS. In the United States and seven other countries, the regulatory authorities have approved GH treatment for children shorter than - 2.25 SDs. Among the working consensus group, opinions regarding the appropriate height below which GH therapy could be considered ranged from -2 to -3 SDs. Age should be taken into account when decided to initiate treatment. It is felt that an optimal range for initiating treatment is 5 years to early puberty. Lesser the height of the child, greater is the consideration to be given for GH treatment. The current FDA approved doses for GH in ISS are up to 0.3-0.37mg/kg/wk. It is recommended to adjust the GH dose to maintain the IGF-1 levels in the upper normal range. As with any other condition treated with GH, 3 to 6 monthly regular follow up with monitoring of height, weight, pubertal development and any signs of adverse effects is essential. Features of scoliosis, papilloedema and slipped capital femoral epiphysis must be looked for. Assessment of response to therapy is by calculation of height velocity, height velocity SDS and height SDS at the end of 1 year. Duration of therapy is guided by the target growth achieved, patient- parent satisfaction and cost-benefit effects. One recommended strategy is to stop GH therapy when near adult height is achieved (height velocity < 2cm/year and/or bone age >16 years in boys and >14 years in girls). Suggested criteria for poor first year response include height velocity SDS less than-1 or change in height SDs less than 0.3-0.5, depending on age.

If the growth response is poor and compliance is assured, one of the options is to consider increasing the dose of GH.[11] IGF-I values can be used to assess compliance and sensitivity to GH. If after 1-2 year of therapy with higher doses of GH, the growth rate is still inadequate, GH treatment should be stopped and alternative therapies could be entertained. If height prediction is below-2.0 SDs at the time of pubertal onset in either sex, the addition of GnRH analogues may be considered. Alternatively, in boys, aromatase inhibitors may be an option. However, long-term efficacy and safety data are not available for either of these interventions.

Prader-Willi syndrome (PWS)

Prader-Willi syndrome (PWS) is a genetic disorder caused by an abnormality of chromosome 15. The efficacy of rhGH, particularly in children with PWS, has provided a new outlook on life that goes beyond obvious improvements in height and somatic appearance. Multiple studies have documented the benefits of GH therapy in individuals with PWS, including, improvements in lean body mass, decreased body fat, increased bone mineral density, and normalization of adult height. Further, GH treatment in infants and children with PWS has been shown to improve strength, agility, and motor development. Treatment with GH has also been shown to positively affect nitrogen balance and increase energy expenditure in individuals with PWS. Moreover, there is evidence that beginning GH therapy prior to two years of age is beneficial because of the positive effects of this treatment on mental and motor development. But, it has to be remembered that growth hormone is contraindicated in patients with PWS who are severely obese or have severe respiratory impairment. The risks and benefits of GH treatment should be thoroughly discussed with the child's parents or guardians before making a decision to treat. Treatment should commence using standard dose guidelines (0.16-0.23 mg/kg/week) given as a daily subcutaneous injection.[3,12]

Skeletal dysplasia

Skeletal dysplasias comprise a diverse group of conditions that usually have compromised linear growth and body proportions. Reported experience of GH treatment in short children with skeletal dysplasias is sparse and often limited to short treatment periods and knowledge of its effects on final height and body proportion is generally lacking. Most of the formal studies are confined to achondroplasia as it is the commonest entity in the group. First-year response is typically a 2–3 cm increase in growth velocity in pre pubertal children, or a gain of about 0.5 SDs or less in relative height from a baseline level of – 4 to – 5 SDs. GH treatment for up to 5 years in achondroplasia can produce a total height gain of about 1 SD compared to untreated children with the same condition. Though, GH therapy is moderately effective for height gain, it is ineffective in cases with severe spinal deformities, because, although bone growth is promoted, the ligaments and matrix are too weak to support muscle tone and the effects of gravity, resulting in worsened kyphosis and lordosis. Of theoretical interest is that in many syndromic or non-syndromic short-statured children, body proportion i.e. trunk to leg length ratio, is not dependent on the degree of GH sufficiency and is usually remains unchanged by GH treatment.[3]

Cystic fibrosis

In 1950s, children with cystic fibrosis generally died before the age of 8. But with antibiotics and other medical advances, the median age of survival has increased to 37yrs by 2008, and a lot of ancillary problems have become more apparent. In the cases studied, the researchers found that human growth hormone added 1.25 inches in height and three pounds of

weight to the patients. Internal organs may also show some growth, particularly the lungs, making breathing easier. GH also appears to improve the mineral content in bones, making them stronger. There is not enough evidence that it prevents osteoporosis, a common longterm problem in cystic fibrosis. For those who received human growth hormone, annual hospitalization rate also decreased by half, from about three per year to 1.5, thus decreasing the economic burden.[3]

Wasting syndrome

Wasting syndrome (WS) is the most frequent and late clinical presentation in people suffering with HIV/AIDS. It is less common in the pediatric age group. The causes are serious: very advanced HIV disease, diarrhea and opportunistic infections and is frequently associated with poor response to HAART. GH has an anabolic effect and increases the weight gain, body cell mass and CD 4 count. Human growth hormone is well known for its anabolic effects on protein synthesis and cell growth. In patients with other catabolic conditions such as sepsis, burns and trauma, studies have demonstrated decreased urinary nitrogen excretion, increased protein synthesis and resultant increases in lean-body mass.[3]

Miscellaneous conditions

GH treatment results in normal growth velocity in Down syndrome but does not affect head circumference or mental or gross motor development. Growth velocity declines once treatment is stopped. GH treatment results in sustained catch-up growth and final height almost nearing the target height range for the majority of children with systemic or polyarticular juvenile idiopathic arthritis.[13] The importance of GH in overall health extends beyond its impact on height. GH contributes to optimal bone mineralization, normal accrual of lean mass, and the regulation of adipose tissue accumulation.

Table I. Growth hormone dose for various conditions

Indication	mg/kg/week
Growth Hormone Deficiency	0.23 - 0.30
Turner syndrome	0.35 - 0.50
Chronic Kidney Disease	0.30 - 0.35
Small for Gestational Age	0.23 - 0.35
Prader Willi Syndrome	0.16 - 0.23
Idiopathic Short Stature	0.24 - 0.37

Osteopenia is a common finding in children with cerebral palsy and is associated with an increase in the risk of fractures, including spontaneous fractures. There is also abundant evidence that GH therapy leads to an increase in BMD.[14] GH has been abused by sportsperson even in the juvenile age group. Although GH has not been shown to unequivocally increase muscle strength or to improve performance, it is considered one of the drugs of choice in doping, because it is extremely difficult to prove that one is receiving it as the structure of recombinant human GH is identical to the main isoform of naturally secreted GH.

In summary, GH use in non-GHD conditions discussed above are by and large safe as demonstrated by various controlled trials and post marketing surveillance. The doses of GH in various conditions have been listed in Table.1. At an individual level, since higher doses are used, long term clinical observation and monitoring of IGF-1 and IGF BP 3 seems appropriate as recommended by professional societies such as the GH Research Society and the Lawson Wilkins Pediatric Endocrine Society.

Points to Remember

- ***Growth hormone is approved for use in many conditions associated with short stature other than growth hormone***

deficiency viz. Turner syndrome, small for gestational age, chronic kidney disease, idiopathic short stature, Prader Willi syndrome, etc.

- ***Except in Prader Willi syndrome, the dosage of growth hormone in these conditions is in general higher than that used for growth hormone deficiency.***
- ***Children on growth hormone therapy should not only be monitored for height increment but also for metabolic parameters including sugars and lipids.***
- ***Height outcome is reasonable if therapy is started early and continued for adequate duration.***

References

1. Seikaly MG, Waber P, Warady BA, Stablein D. The effect of rhGH on height velocity and BMI in children with CKD: a report of the NAPRTCS registry. Pediatr Nephrol 2009; 24:1711–1717
2. Greenbaum LA, Warady BA, Furth SL. Current Advances in Chronic Kidney Disease in Children: Growth, Cardiovascular, and Neurocognitive Risk Factors. Semin Nephrol 2009; 29: 425–434
3. Quigley AC. Growth Hormone Treatment of Non–Growth Hormone-Deficient Growth Disorders. Endocrinol Metab Clin N Am 2007; 36 : 131–186.
4. Bolar K, Hoffman AR, Maneatis T, Lippe B. Long-Term Safety of Recombinant Human Growth Hormone in Turner Syndrome J Clin Endocrinol Metab 2008;93: 344–351.
5. Franklin SL, Geffner ME. Growth Hormone: The expansion of available products and indications. Endocrinol Metab Clin N Am 2009; 38: 587-611.
6. Bajpai A. Growth hormone therapy in small for gestational age children. Indian J Pediatr 2009; 76: S7-10.
7. Maiorana A, Cianfarani S. Impact of Growth hormone therapy on adult height of children born small for gestational age. Pediatrics 2009; 12: e519-26.
8. Jung H, Land C, Nicolay C, Jean De Schepper, et al. Growth response to an individualized versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study. European J Endocrinology 2009; 160: 149-156.
9. Chandrashekar SC. Growth hormone therapy in Idiopathic Short Stature. Indian J Pediatr 2009; 76: S11-14.
10. Wit JM, Clayton PE, Rogol AD, Savage MO, et al. Idiopathic Short Stature: Definition, epidemiology, and diagnostic evaluation. Growth Hormone and IGF Research 2008; 18: 89-110.
11. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, et al. Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature: A Summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab 2008; 93:4210–4217.
12. Paterson W, Donaldson M. Growth hormone therapy in the Prader-Willi syndrome. Arch Dis Child. 2003; 88: 283–285.
13. Bechtold S, Ripperger P, Pozza RD, Bonfig W, Häfner R, Michels H, Schwarz HP. Growth Hormone Increases Final Height in Patients with Juvenile Idiopathic Arthritis: Data from a Randomized Controlled Study. J Clin Endocrinol Metab 2006; 92: 3013-3018.
14. Ali O, Shim M, Fowler E, Greenberg M, Perkins D, Oppenheim W, Cohen P. Growth Hormone Therapy Improves Bone Mineral Density in Children with Cerebral Palsy: A Preliminary Pilot Study. J Clin Endocrinol Metab 2007; 92: 932-937.

ENDOCRINOLOGY

TYPE 2 DIABETES IN CHILDREN– AN EMERGING PROBLEM IN INDIA

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Abstract:*The prevalence of type 2 diabetes in children and adolescents is increasing rapidly both globally as well as in India. This is probably driven by the obesity epidemic which is also rising in parallel in India. Due to the younger age at onset, the risk of developing micro and macrovascular complications of diabetes by the time these children reach young adulthood is very high. In high-risk children and adolescents, eg., those with positive first degree family history or obesity/overweight, screening for diabetes/ glucose intolerance seems to be justified in Indians. Early detection and treatment of diabetes are the cornerstones to reduce morbidity and mortality due to this disorder.*

Keywords: *Type 2 diabetes, Children, Obesity, Family history, Asian Indians, South Asians.*

The prevalence of type 2 diabetes in developing countries in Asia is amongst the highest worldwide[1] and is increasing rapidly particularly in urban India.[2] Another disturbing observation is the increasing trend of type 2 diabetes occurring in Asians, including Indian children and adolescents, which is associated with increasing prevalence of obesity and increased insulin resistance in association with low birth weight and sedentary lifestyle on a background of a strong family history of type 2 diabetes.[3-7]

Type 2 diabetes in children and adolescents is a rising global public health concern which is rapidly spreading to South Asia also. As the prevalence of diabetes in youth increases there is a risk of development of micro and macrovascular complications of diabetes by early adulthood i.e., during the height of their productivity which potentially could affect the economy of the nation apart from posing a large burden to an individual and his/her family.[8]

Although population based prevalence data on type 2 diabetes in children are not generally available, existing information from clinic based studies/reports indicate that the prevalence of type 2 diabetes in children and adolescents is increasing disproportionately among Asian ethnic groups worldwide. Unfortunately, information on the natural history and etiology of type 2 diabetes in children is sparse. Other deficiencies include a lack of uniformity in case definition, data collection and follow-up, with the diagnosis often made retrospectively.[9]

Till recently, type 2 diabetes mellitus was considered rare in children. A study from Chennai published in 1995 reports a zero prevalence rate for diabetes in children after screening 3515 school children.[10] However other studies

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Table I. Percentage of type 2 diabetes among children, adolescents and young adults reported in India

S.No	Place, Name of the author and institution	Year	n (%)	Sample	AOD size	Ref. no
1	**Chennai**					
	S.Venkatraman (Madras Medical college)	1979-89	2(1.2%)	160	<20yrs	13
	V.Mohan (Diabetes Research centre)	1981-83	2l9(4.8%)	4560	<25yrs	11
	A.Ramachandran (Diabetes Research centre)	2002		18 cases	<15yrs	6
	V.Mohan (Dr.Mohan's Diabetes Specialities Centre)	2006	l l6(26.7%)	434	<l 6yrs	7
	V.Mohan (Dr.Mohan's Diabetes Specialities Centre)	1992-2009	1262(48.0%)	2630	<25yrs	20
2	**Hyderabad**					
	BK Sahay(Sahay Diabetes Centre)	1999-2002	19(26.8)%	71	<20yrs	18
3	**Calcutta**					
	S.Banerjee (NRS Medical College)	2004	13(19.4%)	67	6 to 25 yrs	15
4	**Indian multicenter study (MEDI)**	2006-2008	36(6%)	603	<20yrs	14
	AG.Unni krishnan					
5	**Lucknow**	2004	12(7.5%)	160	<18yrs	19
	V.Bhatia (SGPlMS)					

AOD : Age at onset of diabetes

from Chennai have reported on type 1 as well as type 2 diabetes based on clinic data.[6,7,10-13,20] Young-onset type 2 diabetes has also been reported from other parts of India[14, 15] from China, Korea, Malaysia and Singapore[16] and the highest prevalence of type 2 in children has been reported from Japan.[17] Table 1 summarizes the major studies from India. [6, 7, 11, 13-15, 18-20]

There are increasing reports of type 2 diabetes in children worldwide. The SEARCH study which is one of the largest studies on diabetes in children reports an incidence per 100,000 of 0.8 in the 5-9 year olds, 8.1 in 10-14 years and 11.8 in 15-19 years.[21] Another large transnational study from Canada, reports an incidence of 0.27 in children less than 10 years and 3.1 in the 10 -18 year olds per 100,000 per year.[22] One study has reported children as young as 8 years being affected.[23] An excellent review on type 2 diabetes in children highlights the increasing trends and high prevalence of diabetes in the young especially in the minority groups and indigenous populations that are undergoing economic and social transitions.[24]

Type 2 diabetes in children has now become a reality even though there is difficulty in diagnosis in earlier days, particularly in

differentiating type 1 DM from type 2 DM in youth. The reason for this difficulty in differentiation is that obesity and Insulin Resistance (IR) increasingly co-exist with type 1 DM while ketosis or antibody positive can be present in type 2 DM.[25]

Risk factors

The rising occurrence of type 2 diabetes has been attributed to the increasing rate of obesity in children.[26] Obesity is the most important modifiable risk factor for the development of insulin resistance independent of sex, age and ethnic background.[27] The presence of both obesity and insulin resistance (IR) confer greater risk for CVD in young type 2 diabetic patients compared with that expected with either obesity or IR alone.[28] In India, a recent study reported that 18% of 13-18yr olds are overweight with the prevalence correlating positively with age and socio economic status and negatively with physical activity.[29]

IR in youth typically occurs during puberty and is thought to coincide with occurrence of type 2 diabetes. Pancreatic beta cells of some adolescents cannot overcome the physiologic rise in IR and therefore a relative insulin deficiency develops, eventually leading to type 2 diabetes. In addition to diabetes, IR is also associated with the metabolic syndrome, cardiovascular disease, poly cystic ovarian syndrome, non alcoholic fatty liver disease, hypertension and hyperlipidemia all of which are not uncommon in children with type 2 diabetes.

Many studies show a strong family history among affected youth with 45-80% having at least one parent with diabetes and 74-100% having a first or second degree relative with type 2 diabetes.[30,31] The increasing frequency of exposure to diabetes in utero has been hypothesized to account for some of the increase in diabetes prevalence in Pima Indian children.[32]

Clinical features

As in adults, the type 2 diabetes is largely asymptomatic in children, and often is diagnosed during routine clinical examination or when complications develop. Often the child complains of frequent acute infections, excessive tiredness and irritability, or their injuries may take a long time to recover. A family history of diabetes is a strong pointer. Acanthosis nigricans and skin tags are also other suggestive findings. An adolescent girl with polycystic ovarian syndrome is highly likely to be having glucose intolerance or even overt type 2 diabetes.

Diagnosis and management

According to International Society for Pediatric and Adolescent Diabetes, the targets for diagnosis are (1) whose BMI are in the 85-95th percentile (2) Ethnicity-Asian children, (3) family history of diabetes and (4) signs of insulin resistance-acanthosis, hypertension, and dyslipidemia or poly cystic ovarian syndrome.[33] An oral GTT should be done in these patients, and those who satisfy the IDF or WHO criteria with a fasting glucose of above >126mg/dl and a 2 hour glucose level of >200mg/dl should be started on treatment.

Lifestyle change is the cornerstone of type 2 diabetes management. This includes: attainment and maintenance of a healthy bodyweight, improved exercise capacity, normalization of blood glucose levels, minimization of hypoglycemia and the management and the prevention of complications, including hypertension, hyperlipidemia, nephropathy and non alcoholic fatty liver disease. Education should be age-appropriate and culturally sensitive, and must focus on lifestyle and health behaviors of the entire family in order to be effective.[34]

If the life style interventions are unsuccessful in controlling blood glucose levels,

in addition to it, metformin should be initiated. The dosage of metformin for children can be started with 250mg once a day initially and can be increased to twice a day. If the glycemic control is not achieved, we can increase the dosage to 500mg or 850mg accordingly. After a period of 3 to 6 months, if control is not improving with metformin and life style interventions, then additional therapy like sulphonylureas like glibenclamide and glimepride can be started with a minimum dosage of 2.5mg and 1mg respectively.

Metformin is more commonly associated with side effects like diarrhea and abdominal pain whereas sulphonylureas are associated with hypoglycemia and weight gain. Metformin should not be given to patients with renal impairment, hepatic disease, cardiac or respiratory insufficiency or when receiving radiographic contrast materials, whereas sulphonylureas should not be given to those who have impairment of liver and kidney function. Very often, insulin may be required at least in the early stages to control symptoms and later if secondary failure to OHA develops. Patients should be monitored frequently and doses of drugs adjusted until normoglycemia is achieved. Glycated hemoglobin (HbA1C) should be done at 3 monthly intervals.

Complications

As with adults youth with type 2 diabetes are also prone to develop both micro and macro-vascular complications. Studies on type 2 diabetes in youth have important implications as they will be able to quantify the risk of developing complications occurring at a relatively young age. Such studies at present are rare. Diabetes complications such as micro - and macroalbuminuria and clustering of cardio vascular risk factors such as dyslipidaemia and hypertension have been observed among teenage Pima Indians[35] and in other pediatric populations in the United States.[36,37]

Diabetes and its complications will place a significant burden on health budgets as well as society as a whole, as many of these people would be entering their peak working life and earning capacity. Early detection and intervention is therefore essential to reduce the risk of future complications of diabetes.

Prevention of type 2 diabetes in children

In high-risk cases, e.g., those with strong family history, obesity, acanthosis nigricans, or polycystic ovarian disease, screening for diabetes seems to be justified in youth. Early detection and treatment are the cornerstones to reduce morbidity and mortality due to youth-onset type 2 diabetes.[7]

The increasing prevalence of type 2 diabetes in the young may be arrested by encouraging increasing physical activity, and changing dietary habits. Interventional programmes should be considered to address the underlying cause, with an emphasis on diet, weight, exercise and lifestyle issues. It is far better to try to put our public health efforts on primordial and primary prevention of diabetes, rather than dealing with diabetes and its late stage complications. Life style modification should be encouraged and implemented for all children and adolescents at the school level.

Physical activity plays a critical role in the treatment of pediatric type 2 diabetes. Increased physical activity results in improved insulin sensitivity, increased glucose uptake at the level of the muscle and a decreased need for insulin therapy.[38]

What are the current gaps in knowledge?

Compared to adults there is a paucity of information on both the epidemiology and natural history of type 2 diabetes in the young. This needs to be urgently addressed given the potential threat of an explosion in childhood type 2 diabetes. Notably, there is also a lack of standardization in study methods, with many surveys only examining small numbers of people, as well as using different diagnostic methods and criteria. There is an urgent need to standardize and validate the diagnostic criteria.

What can be done to prevent an epidemic of type 2 diabetes in children?

• Screening methods should target the high-risk youth population who can be identified by simple clinical clues: presence of overweight or obesity along with any two of the following risk factors like positive family history of diabetes, insulin resistance markers like acanthosis nigricans and/or polycystic ovarian disease, ethnic groups like Asians, Americans and Latinos and finally maternal diabetes history (Gestational diabetes mellitus). An Oral GTT should be done in those who have the above risk factors. Testing for type 2 diabetes in asymptomatic children should be initiated at the age of 10 years or at onset of puberty, if puberty occurs at an younger age in these children.[39]

• To find ways to help people to be more physically active and improve their diets which require an integrated approach, and involve other sectors outside of health, for example those that influence urban design and food legislation.

• Policy-makers need to integrate plans for the prevention of diabetes into national health systems. Countries have to find ways to make economic progress in a way that is not harmful to health. This requires intersectoral creative thinking and legislation that encourages people to be physically active and eat appropriately.

• Education imparted to diabetic patients, their families and the community at large will go a long way in achieving this goal. When more families are tested not only once but periodically, the search for hidden diabetes becomes successful.

• Regular follow up and constant motivation is required to ensure that these preventive measures are put into practice over a number of years

All of the above factors can be integrated into the Government of India's National Program for the Prevention and Control of Diabetes Cardiovascular disease and Stroke which can be rolled out across the country.

In summary, type 2 diabetes in children has the potential to grow into an epidemic in our country. Several factors contribute to this and luckily the majority of them are preventable. Lifestyle interventions, particularly increasing physical activity and promoting healthy eating by themselves, without any additional interventions can help substantially reduce the incidence of diabetes in children. The time for action is now!

Points to Remember

- ***Type 2 diabetes in children is no longer a rare entity and is slowly emerging as a potential epidemic in parallel with the epidemic of childhood obesity.***
- ***Even though screening of at-risk youth for type 2 diabetes remains controversial, we should target and screen the young with risk factors like overweight/obesity, family history of diabetes and presence of signs of insulin resistance like acanthosis nigricans.***

- ***When both parents are diabetic, and the child is overweight or obese, screening for diabetes should be definitely considered.***
- ***Treatment and management of type 2 diabetes in childhood requires lifestyle changes (more physical activity, appropriate food intake) plus addition of oral hypoglycemic agents whenever indicated. If these measures fail, insulin should be instituted.***
- ***Awareness, education and repeated counseling among the community and families will go a long way in prevention of type 2 diabetes in children.***

References

1. International Diabetes Federation Diabetes Atlas. Unwin N, Whiting D, Gan D, Jacqmain O, Ghyoot G (eds). IDF Diabetes Atlas. Fourth Edition. International Diabetes Federation, Belgium, 2009: 12-27.
2. Mohan V, Deepa M, Deepa R, Shanthirani CS, Farooq S, Ganesan A, Datta M. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India: the Chennai Urban Rural Epidemiology Study (CURES-17). Diabetologia. 2006; 49:1175–1178.
3. Kitagawa.T, Owada.M, Urakami T, Yamauchi. K, Increased incidence of non-insulin dependent diabetes mellitus in Japanese school children correlates with an increased intake of animal protein and fat, Clin. Pediatr. 1998;37: 111–115.
4. Likitmaskul. S, Kiattisathavee.P, Chaichanwatanakul K, Punnakanta L, Angsusingha K, Tuchinda C, Increasing prevalence of type 2 diabetes mellitus in Thai children and adolescents associated with increasing prevalence of obesity, J. Pediatr. Endocrinol. Metab. 2003;16:71–77.
5. Urakami T, Kubota S, Nitadori Y, Harada K, Owada M, Kitagawa T, Annual incidence and clinical characteristics of type 2 diabetes in children as detected by urine glucose screening in the Tokyo metropolitan area, Diabetes Care. 2005;28:1876–1881.
6. Ramachandran A, C. Snehalatha, Satyavani K, Sivasankari S, Vijay V, Type 2 diabetes in Asian-Indian urban children, Diabetes Care. 2003;26: 1022–1025.
7. Mohan V, Jaydip R, Deepa R. Type 2 diabetes in Asian Indian youth. Pediatric Diabetes. 2007: 8 (Suppl. 9): 28–34.
8. Amed S, Daneman D, Mahmud FH, Hamilton J. Type 2 diabetes in children and adolescents. Expert Rev Cardiovasc Ther. 2010;8:393-406.
9. Dabelea D. Pettitt DJ, Jones KL, Arslanian SA. Type 2 diabetes mellitus in minority children and adolescents. An emerging problem. Endocrinol Metab Clin North Am.1999;28:709-729.
10. Bai PV, Krishnaswami CV, Chellamarippan M, Kumar,GV, Subramaniam JR, Srivatwa A, Subramanyam B, Rao MB. Prevalence of diabetes in the young in south India. Indian Pediatr.1995;32:1173-1176.
11. Mohan V, Ramachandran A, Snehalatha C, Rema M, Bharani G, Viswanathan M High prevalence of maturity onset diabetes of the young (MODY) among Indians. Diabetes Care. 1985;8:372-374.
12. Ramachandran A, Mohan V, Snehalatha C, Bharani G, Chinnikrishnudu M, Rema M, Viswanathan M. Clinical features of diabetes in the young as seen at a diabetes centre in South India. Diabetes Res Clin Pract. 1988; 4:117-125.
13. Venkatraman S, Suresh K, Sundaram A, Hariharan RS, Madhavan R, Manjula N, Seshiah V. Diabetes in the young – A profile. International journal of diabetes in developing countries. 1991;10:21 – 23.
14. Unnikrishnan AG, Bhatia E, Bhatia V, Bhadada SK, Sahay RK, Kannan A, Kumaravel V, Sarma D, Ganapathy B, Thomas N, John M, Jayakumar RV, Kumar H, Nair V, Sanjeevi CB. Type 1 Diabetes Type 2 Diabetes with Onset in Persons younger than 20 Years of Age Results from an Indian Multicenter study. Ann NY Acad Sci 2008; 1150:239-244.

15. Banerjee S, Uday S Ghosh, Dibakar B. Profile of young diabetes mellitus and its clinical implications. Int J Diab Dev Countries. 2007;27:50-55.
16. Cockram C S, Diabetes mellitus: perspective from the Asia- Pacific region, Diabetes Res Clin Pract 2000; 50 (Suppl. 2): S3–S7.
17. Kida K: Obesity and type II diabetes in childhood. In Proceedings of Diabetes in Asia, 2002. Colombo, Sri Lanka, Diabetes Association of Sri Lanka, 2002, p. 44.
18. Sahay BK, Sahay RK. Type 2 Diabetes in the Young. International Journal of Diabetes in Developing Countries. 2003;23:51-54.
19. Bhatia V, Arya V, Dabadghao P, Balasubramanian K, Sharma K, Verghese N, Bhatia E. Etiology and outcome of childhood and adolescent diabetes mellitus in North India. J Pediatr Endocrinol Metab. 2004;17:993-999.
20. Amutha A, Datta M, Unnikrishnan IR, Anjana RM, Rema M, Venkat Narayan KM, Mohan V. Clinical profile of diabetes in the young seen between 1992 and 2009 at a specialist diabetes centre in south India. Prim Care Diabetes. 2011 May 19. [Epub ahead of print]
21. Dabelea D, Bell RA, D'Agostino RB Jr et al. Incidence of diabetes in youth in the United States. JAMA. 2007; 297: 2716–2724.
22. Amed S, Dean HJ, Panagiotopoulos D et al. Type 2 diabetes, medication-induced diabetes, and monogenic diabetes in Canadian children: a prospective national surveillance study. Diabetes Care. 2010 Apr;33(4):786-91.
23. Pihoker,C. Scott,C.R. Lensing,S.Y. Cradock,M.M. Smith,J. Non-insulin dependent diabetes mellitus in African-American youths of Arkansas. Clin Pediatr (Phila).1998; 37: 97-102
24. Nadeau K, Dabelea D..Epidemiology of type 2 diabetes in children and adolescents. Endocrine Research. 2008; 33;35-58.
25. Shaw J. Editorial: Pediatric Diabetes 2007: 8 (Suppl. 9): 4-6
26. Bloomgarden ZT. New insights in obesity. Diabetes Care. 2002;25:789–795.
27. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. Diabetes Care. 2006; 29: 2427–2432.
28. Sinaiko AR, Steinberger J, Moran A etal. Relation of body mass index and insulin resistance to cardiovascular risk factors, inflammatory factors, and oxidative stress during adolescence. Circulation. 2005;111:1985–1991.
29. Ramachandran A, Snehalatha C, Vinitha R, Thayyil M, Kumar CK, Sheeba L, Joseph S, Vijay V. Prevalence of overweight in urban Indian Adolescents school children. Diabetes Res Clin Pract 2002;57:185-190.
30. Kahn R. Type 2 diabetes in children and adolescents. American Diabetes Association. Diabetes Care.2000; 23: 381-389.
31. Sinha AK, Rourke O, Leonard SO, Yarker S. Early onset Type 2 diabetes (T2DM) in the indigenous communities of Far North Queensland (FNQ). In Australian Diabetes Society Annual Scientific Meeting. Cairns, Australia. 2000;p90
32. Dabelea D, Pettitt DJ. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. J Pediatr Endocrinol Metab. 2001;14:1085-1091.
33. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. ISPAD Clinical Practice Consensus Guideline 2006–2007. Type 2 diabetes mellitus in the child and adolescent. Pediatr. Diabetes. 2008; 9: 512–526.
34. Libman IM, Arslanian SA. Prevention and treatment of Type 2 diabetes in youth. Horm. Res. 2007;67: 22–34.
35. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr. 2000;136:664–672.

36. Deckelbaum RJ, Williams CL. Childhood obesity: the health issue. Obes Res 2001; 9(suppl 4): 239S–243S

37. Crawford PB, Story M, Wang MC, Ritchie LD, Sabry ZI. Ethnic issues in the epidemiology of childhood obesity. Pediatr Clin North Am. 2001;48: 855–878.

38. Giannini C, de Giorgis T, Mohn A, Chiarelli F. Role of physical exercise in children and adolescents with diabetes mellitus. J. Pediatr. Endocrinol. Metab. 2007;20:173–184.

39. American Diabetes Association. Standards of Medical Care in Diabetes—2011. Diabetes Care. 2011 Jan;34 Suppl 1:S11-61.

Karemaker R et al. Effects of Neonatal Dexamethasone Treatment on the Cardiovascular Stress Response of Children at School Age. Pediatrics. November 2008, VOLUME 122 / ISSUE 5.

The goal was to investigate cardiovascular responses to a psychosocial stressor in school-aged, formerly premature boys and girls who had been treated in neonatal period with dexamethasone or hydrocortisone because of chronic lung disease. The data demonstrated that neonatal treatment with dexamethasone has long-term consequences for the cardiovascular and noradrenergic stress responses; at school age, the cardiovascular stress response was blunted in dexamethasone-treated children. Hydrocortisone-treated children did not differ from the reference group, which suggests that hydrocortisone might be a safe alternative to dexamethasone for treating chronic lung disease of prematurity.

GENERAL ARTICLES

MALOCCLUSION OF TEETH: ROLE OF PEDIATRICIAN IN EARLY DIAGNOSIS

*** Sankalp Sood**
**** Mangla Sood**

Abstract: *Oral health care is recommended in young children to promote positive outcomes during childhood and later adulthood. Pediatricians see children during their first few years of life and are in an ideal and unique position to advise families about the prevention of malocclusion. By educating themselves about orofacial growth, pediatricians may enhance the implementation and eventual success of oral health preventive programmes. This article describes the most common and distinctive symptoms appearing frequently in the early stages of a child's development that are easily detectable by clinicians. Though malocclusion of teeth is of multifactorial origin, some recognized behaviors should be discouraged to allow for ideal craniofacial development and require early referral to the pediatric dentist or orthodontist. Some easily diagnosed disorders by the pediatrician include different sucking habits persisting beyond 3 years of age, mouth breathing and significant deviations from established teeth eruption norms.*

Keywords: *Malocclusion, Pediatrician, Orthodontist*

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Oral diseases are highly prevalent in our society, and lead to physical, economic, social and psychological consequences. They seriously impair quality of life in a large number of individuals including function, appearance and interpersonal relationships.[1] Pediatricians have frequent contact with families during routine preventive visits in the child's first few years of life and thus have the opportunity and should have the knowledge to provide parents with good advice regarding issues on oral health in infants and children. In modern society, where there is a great emphasis on personal appearance, prevention of malocclusion and giving the child the best chance of proper and healthy oral development should be important to both parents and health professionals.

What is malocclusion?

Ideal occlusion is defined as a relationship of maxillary and mandibular teeth with all the teeth fitting easily without crowding, spacing or rotation and the teeth should not be twisted or leaning forward/ backward. Maxillary teeth should be slightly overlapping the mandibular teeth and the cusp tip of the molars should fit into the grooves of the opposite molars combining minimum stress on the temporomandibular joint, optimal function of the orofacial complex, stability, aesthetics of the dentition, protection and health of the periodontium.[2,3] Malocclusion may be defined as a significant deviation from what is defined as a normal or ideal occlusion. Normal occlusion is representative of around 30% to 40% of the population.[4,5] Slight generalized spacing is

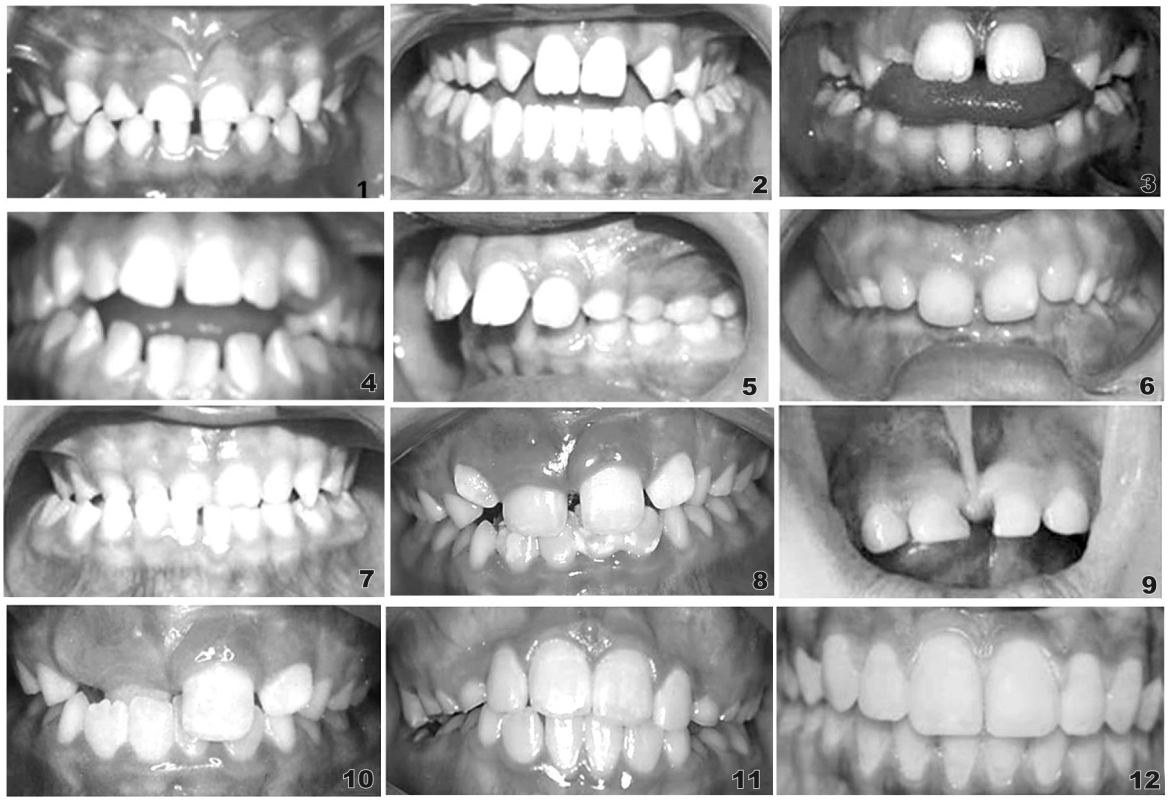

Fig. 1. Normal occlusion in primary dentition.

Fig. 2. Diastema (abnormal spacing between teeth owing to absence of lateral incisors) (also note the posterior crossbite).

Fig. 3. Open bite with an anterior position of the tongue at rest (malocclusions such as this are frequently associated with a dysfunctional tonguethrust swallow and articulation disorders, prolonged digit-sucking habit, prolonged pacifier use).

Fig. 4. Open bite malocclusion: pretreatment.

Fig. 5. Increased overbite.

Fig. 6. Deep bite

Fig. 7. Anterior crossbite and right posterior crossbite representing a relatively narrow maxilla (the upper teeth are positioned behind the lower teeth at rest).

Fig. 8. Ugly duckling stage.

Fig. 9. High frenum attachment in primary dentition.

Fig. 10. Maxillary incisor crossbite: pretreatment.

Fig. 11. Maxillary incisor crossbite corrected after treatment.

Fig. 12. Normal occlusion established after treatment.

considered to be normal in primary dentition (Fig.1). There is some evidence that malocclusion increases within well-defined populations after a transition from rural villages to the city.[6] Facial phenotype is the result of both genetic and environmental factors.[7] Causes of malocclusions are multifactorial but deleterious habits and local factors play an important role in facial and occlusal features. Hence the intervention should be directed at early detection and addressing the environmental factors that cause malocclusion during growth and development.[7]

Signs and symptoms of malocclusion

Symptoms which should be considered during occlusal assessment may include the following:

- Crowded or misaligned teeth
- Abnormal spacing between teeth, most often occurring because teeth are small or missing (Fig.2) or the dental arch is very wide.
- An open bite, occurring when the upper and lower incisors do not touch each other during biting, thereby putting all of the chewing pressure on the back teeth and resulting in inefficient chewing and excessive tooth wear (Figs.2,3,4).
- An excessive overbite in which the upper incisors protrude, often caused by a lip sucking, digit sucking, tongue thrusting habit or lower jaw that is significantly shorter than the upper jaw (Fig.5).
- A deep bite (vertical overlap more than 2mm between upper and lower teeth), in which the lower incisors bite closely to or into the gingival tissue or palate behind the upper teeth (Fig.6)
- A crossbite, in which a protruding lower jaw (prognathism) that is bigger than the upper jaw causes the upper front or back teeth to bite inside the lower teeth (Figs.7,2)

These disorders can be easily diagnosed by the pediatrician and represent conditions in which early intervention might be appropriate to prevent future possible orofacial dysfunction.

Bottle feeding and sucking habit as a risk of future malocclusion

The importance of breastfeeding in a child's life is well documented. The World Health Organization recommends that exclusive breastfeeding should be carried out until at least 6 months of age.[8] As the newborn's mouth is brought into contact with an object, the sucking reflex is elicited. The infant's oral cavity with its physiological mandibular retrusion, the contact of gingival rims, the highly positioned larynx and long soft palate is perfectly formed for effective sucking to receive adequate nourishment.

It has been observed that children who had been breast-fed for fewer than 6 months had significantly more non-nutritive sucking habits[7] which fulfilled physiological needs during infancy but persistence of these habits beyond 3 years of age significantly increased the probability of developing malocclusion at the end of the primary dentition stage.[9] Early weaning, i.e. short breastfeeding duration, seems to be associated with an increased risk of development of a posterior crossbite. Children with prolonged non-nutritive sucking habits, mostly digit or pacifier sucking should be monitored for the primary dentition in order to prevent the development of crossbites, anterior open bite and functional shifts.[10] Other habits such as lip or cheek sucking may also cause local dentoalveolar disturbances. They may cause abnormalities in tooth position, articulation disorder and unusual patterns of swallowing.[11] On the basis of various studies[9-13] the authors suggest that doctors should draw parents' attention to the fact that if their children do have a finger- or pacifier-sucking habit, it should be stopped by 3 years of age.

No one should, however, force the child to stop his/her harmful habit if the child is not yet really convinced to do so. It should be the child's own decision; if it is not, it could have adverse effects on the child's psyche. The pediatrician with the parents should instead search for psychological reasons of harmful habits and try to change undesirable behaviors. Sometimes it happens that a child wants to stop the habit but is unable to break it. Under these circumstances, it can be helpful to fabricate a habit breaking appliance, as a 'reminder' not to put the finger into the mouth.

In summary, it should be noted that breastfeeding and short pacifier use do not cause disturbance to a child's occlusion but prolonged pacifier or finger sucking can cause characteristic occlusion defects that may remain even after cessation of the habit.

Mouth breathing as a risk factor of malocclusion

Infants are obligate nose breathers. Any obstruction of the upper airways due to structural and morphological defects or upper respiratory tract infection may promote mouth breathing. Mouth breathing can be a risk factor for malocclusion, the severity of which depends on the duration and the inherent direction of growth of the child's face.[13] Mouth breathing causes the lower jaw and tongue to be lowered and withdrawn. It also leads to tension in the cheeks, hypotonia of orbicularis oris muscle and hyper tonicity of buccinators muscle. This situation leads to the 'adenoidal facies' or 'long-face syndrome'. Removing upper respiratory tract obstruction does not automatically restore the correct breathing pattern as some children are mouth breathers even without any upper airways obstruction and these children should be referred to an orthodontist.

Tooth eruption patterns

The monitoring of the primary and permanent dentition plays an important role in the prevention of malocclusions.[14] The first tooth to erupt is usually the lower central incisor. By the age of 3 years, all 20 primary teeth should be present in the arches. Continued jaw growth provides space for the larger permanent anterior teeth. At about the age of 6 years, the primary incisors should be spaced, occlude edge to edge and may well show signs of attrition (Fig.1). The mixed dentition (i.e. the transition stage when both primary and permanent teeth are present) begins at approximately 6 years of age with the shedding of the lower primary incisors and the eruption of the first permanent molars. The arrival of larger permanent incisor teeth in child-sized jaws results in some irregularity of the teeth. After the age of 9 years, any incisor crowding is unlikely to resolve spontaneously. All 28 permanent teeth should be present by 13 years of age (excepting the third molars or 'wisdom teeth'). In the upper arch, the canine is the last tooth to erupt and consequently the one most frequently impacted. Although the incidence of ectopic eruption of the maxillary canine is relatively low, the potential sequelae are significant enough to warrant great care in the screening of patients.

Variation in the normal eruption and exfoliation of teeth is a common finding, but significant deviations from established norms (Table I) should alert the clinician to investigate further. Failure of a tooth eruption is usually because of insufficient space or the presence of a supernumerary tooth blocking its eruption path. Delayed tooth eruption (Table II) might be a harbinger of a systemic condition or an indication of altered physiology of the craniofacial complex.

Other common problems

The maxillary midline diastema (space between teeth) is a common aesthetic

problem. It can be seen in primary, mixed and early permanent dentitions and can be physiological or pathological. In physiological diastema, also known as 'ugly duckling' stage (Fig.8), permanent maxillary incisors erupt with flared and spaced crowns in children aged 7–9 years and treatment is not indicated until after the eruption of permanent maxillary canines (11 to 12 years), as the diastema is usually transitory and will close spontaneously. There are multiple causes for pathological spacing, including high frenal attachment[15] (Fig.9), microdontia, macrognathia, presence of unerupted supernumerary teeth, peg or missing lateral incisors (Fig.2), midline cysts and habits such as thumb sucking, mouth breathing and tongue thrusting[16] and early referral to an orthodontist is indicated when any of these conditions are observed.

Cleft lip and/or palate being a serious developmental problem needs multidisciplinary treatment and follow-up from birth to adulthood. The pediatric dentist and orthodontist will have to take care of the patient until the final oral cavity rehabilitation, when all permanent teeth erupt.

Different dental injuries in primary dentition can lead to abnormal permanent dentition development and be the reason for some later orthodontic complications. It is essential for the parents to know that each dental trauma and any sequel should be monitored by a dentist.

Pre treatment (Figs.10 and 4) and post treatment (Figs.11 and 12) photographs of children with anterior crossbite and anterior open bite are presented. With timely referral these patients can be treated with a simple removable appliance instead of fixed orthodontics. So the benefits of early diagnosis and intervention are:

- Correct obvious problems.
- Intercept developing problems.
- Prevent obvious problems from becoming worse.
- Prevent unnecessarily extended treatment cost and duration.

Table.I. Primary teeth development chart

Upper Teeth	When tooth erupts	When tooth exfoliates
Central incisor	8 to 12 months	6 to 7 years
Lateral incisor	9 to 13 months	7 to 8 years
Canine	16 to 22 months	10 to 12 years
First molar	13 to 19 months	9 to 11 years
Second molar	25 to 33 months	10 to 12 years
Lower Teeth		
Central incisor	6 to 10 months	6 to 7 years
Lateral incisor	10 to 16 months	7 to 8 years
Canine	17 to 23 months	9 to 12 years
First molar	14 to 18 months	9 to 11 years
Second molar	23 to 31 months	10 to 12 years

Table.II. Causes of delays in tooth eruption

- Impedance of tooth eruption by adjacent or overlying tooth or bone.
- Impacted teeth
- Congenital hypothyroidism
- Rickets
- Down syndrome
- Cleidocranial dysplasia
- Gaucher disease
- Osteopetrosis

Table.III. Factors to be assessed in a child

Abnormal habits and functional aberrations	
Pacifier habit	Encourage parents to stop this habit at the earlierst and latest by age 3, later refer to pediatric dentist or orthodontist.
Thumb and/or digit sucking Tongue thrusting Abnormal Lip sucking	Refer to paediatric dentist or orthodontist if the habit persists beyond 4 years of age.
Mouth breathing	Check for upper airway obstruction, if none diagnosed, refer to pediatric dentist or Orthodontist.
Local factors	
Abnormalities in tooth number such as: Supernumerary and missing teeth Abnormal tooth size and shape	Refer to pediatric dentist or orthodontist as soon as the problem has been detected
High labial frenum causing spacing between the upper anterior teeth	Tell the parents not to worry and wait until permanent maxillary canines erupt
Premature tooth loss with drifting of the adjoining and opposite teeth	Refer to pediatric dentist or orthodontist as soon as the problem has appeared
Prolonged retention of the primary teeth Delayed eruption of the permanent teeth	Compare with the same tooth on the other side of the jaw; observe 6 months after the estimated time of eruption and if the primary tooth is still there and/or the permanent tooth is not erupting refer to pediatric dentist or orthodontist
Abnormal eruptive paths	Refer to pediatric dentist or orthodontist as soon as diagnosed
Dental trauma and accidents	Refer to pediatric dentist or orthodontist as soon as possible

Conclusion

It is difficult to device preventive strategies to prevent malocclusion owing to its multifactorial origin. There are some recognized behaviors, however, that should be discouraged to allow for ideal craniofacial development and some that require early referral to the pediatric dentist or orthodontist. These disorders are easily diagnosed and represent conditions in which early intervention might be appropriate to prevent future possible orofacial dysfunction. In general, measures to prevent malocclusion should be based on providing good incentives to promote normal growth and development of the face and the elimination of potential interferences that may harm these processes.

Early referral to a pediatric dentist or orthodontist is indicated when any of these conditions are observed (Table III).

Points to Remember

- ***Though malocclusion is multifactorial in origin early diagnosis helps prevent its severity.***
- ***Early intervention is required in sucking habits persisting beyond 3 years of age, mouth breathing and significant deviations from established teeth eruption norms.***

References

1. Gift HC, Redford M. Oral health and quality of life. Clin Geriatr Med 1992; 8:673–683.
2. Daskalogiannakis J. Glossary of orthodontic terms. Quintessence 2000.
3. Andrews LF. The six keys to normal occlusion. Am J of Orthod 1972; 62:296–309.
4. Das UM, Reddy DVS. Prevelance of malocclusion among school children in Bangalore, India. Int J Clin Ped Dent 2008;1: 10-12.
5. Trehan M, Chugh VK, Sharma S. Prevalence of Malocclusion in Jaipur, India. Int J Clin Ped Dent 2009; 2: 23-25.
6. Evensen J, Ogaard B. Are malocclusions more prevalent and severe now? A comparative study of medieval skulls from Norway. Am J Orthod Dentofacial Orthop 2007; 131:710–716.
7. Mossey PA. The heritability of malocclusion: part 2. The influence of genetics in malocclusion. Br J Orthod 1999; 26:195–203.
8. Global strategy for infant and young child feeding. Geneva: WHO; 2003. Available from: http://www.who.int/child_adolescent_health/documents/9241562218/en/
9. Karjalainen S, Rönning O, Lapinleimu H, Simell O. Association between early weaning, non-nutritive sucking habits and occlusal anomalies in 3-year-old Finnish children. Int J Paediatr Dent 1999; 9:169–173.
10. Warren JJ, Bishara SE. Duration of nutritive and nonnutritive sucking behaviors and their effects on the dental arches in the primary dentition. Am J Orthod Dentofacial Orthop 2002; 121:347–356.
11. Josell SD. Habits affecting dental and maxillofacial growth and development. Dent Clin North Am 1995; 39:851–860.
12. Poyak J. Effects of pacifiers on oral development. Int J Orthod Milwaukee 2006; 17:13–16.
13. Josell SD. Habits affecting dental and maxillofacial growth and development. Dent Clin North Am 1995; 39:851–860.
14. Kurol J. Impacted and ankylosed teeth: why, when, and how to intervene. Am J Orthod Dentofacial Orthop 2006; 129: S86–S90.
15. Edwards JG. The diastema, the frenum, the frenectomy. Am J Orthod 1977; 7l: 489-508.
16. Angle EH. Treatment of malocclusion of the teeth. 7th Edn, S.S. White Dental Manufacturing Co: Philadelphia, 1907; pp103-104.

GENERAL ARTICLE

FUNGAL SEPSIS IN NEONATES

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Abstract: *Fungal sepsis in neonates is not uncommon. Over last two decades with advancements in preterm care, increased incidence of neonatal candidal infections are seen (10-20%). Invasive fungal infection is an important cause of mortality and morbidity in very low birth weight infants. Mortality rises to more than 30% in extreme low birth weight babies. Clinical features, risk factors and treatment modalities are discussed.*

Keywords: *Fungal sepsis, Neonates*

Fungemia in neonates is not uncommon. Over last two decades with advancements in preterm care, increased incidence of neonatal candidal infections are seen. Invasive fungal infection is an important cause of mortality and morbidity in very low birth weight infants.

Incidence

Fungal infection accounts for 10% of all nosocomial sepsis in very low birth weight(VLBW)babies. The incidence increases upto 20% in babies less than 26 weeks and 750 gms.[1]

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What are the risk factors for invasive fungal infection

1. Extreme low birth weight and gestational age
2. Multiple courses of broad spectrum antibiotics (especially third-generation cephalosporins and carbepenems)
3. Fungal colonisation of multiple sites
4. Presence of a central venous catheter
5. Parenteral nutrition and central venous lines.
6. Prolonged use of percutaneous central venous lines (PCVC) and delay in starting enteral feeds
7. Gastrointestinal disease or surgery/ Severe illness
8. Use of H_2 receptor blocking agents and proton pump inhibitors
9. Prolonged intubation and ventilation.

   Presence of an endotracheal tube, mechanical ventilation and suctioning predisposes intubated VLBW infants to respiratory tract fungal colonization and infection
10. Postnatal corticosteroid exposure: Association of steroids and invasive fungal infection has been inconsistent. Large multivariate analyses, have not identified steroid use as an independent risk factor.

Mycology

Most commonly isolated fungus is Candida albicans. It has got increased adherence to and penetration of vascular endothelium. Over the last 10 years, another important nosocomial pathogen is Candida parapsilosis accounting for 25% of invasive fungal infection in VLBW. However it causes fewer deep-seated infections than C albicans, because of its poorer ability to adhere to and penetrate endothelium. Candida tropicalis also has been an increasing pathogen in India. Candida glabrata and Candida krusei are azole resistant. Infections with other fungi like Aspergillus species and Malassezia species are extremely rare in neonates.[1]

Clinical presentation is similar to bacterial infection. It is one important cause of late-onset infection in preterm babies in most NICUs, with the mean onset of infection between 15 to 33 days of age. Clinical features include lethargy, hypotonia, apnea, bradycardia, hypotension, abdominal distension, gastric aspirates, bloody stools, hypo or hyperglycemia, increasing oxygen requirements and need for assisted ventilation

Marked thrombocytopenia, increased WBC count with shift to left and markedly increased C-reactive protein are suggestive of fungal infection.

Fungal infection causes significant morbidity and mortality in VLBW babies with a crude mortality rate of 30%.

Congenital Candidiasis

Presents within 24 hours with isolated skin infection or systemic fungal disease. Clinical spectrum include pustules, vesicles, skin abscesses and erythematous maculopapular rash over the trunk and extremities. Placenta may show hyphae, micro-abscesses and granulomas.

In invasive candidiasis, end-organ dissemination may present as endocarditis, endophthalmitis, dermatitis, peritonitis, osteomyelitis, septic arthritis and fungal abscesses in CNS, kidneys, liver, spleen, skin, bowel and peritoneum.

Invasive fungal infection

Systemic infection is strongly associated with preceding colonisation.

C albicans is the leading cause (>50%), followed by C parapsilosis.[2]

Early diagnosis is difficult and treatment often delayed due to inability to consistently recover organism from blood, CSF or urine. A high index of suspicion is needed for early diagnosis

Screening high risk babies

Urine KOH smear – for budding yeast cells / hyphae

Culture of fungus from blood, urine, CSF

Additional laboratory and clinical tests, including retinal examination, echocardiography and kidney

If fungemia persists for > 5 days, screening for dissemination includes the following: echocardiography, diagnostic imaging of liver, spleen and kidney, cranial ultrasonography, indirect ophthalmoscopy and peritoneal cultures if laparotomy is performed for necrotizing enterocolitis or biliary peritonitis.

Newer diagnostic tests include fungal PCR -to detect the gene for 18S ribosomal RNA, beta-glucan of the cell wall, anti-Candida antibodies, D-arabinitol (candidal metabolite) and fungal chitin synthase.[2]

Treatment of candidemia[2,3]

1. Removal of any potentially contaminated medical hardware-Central venous catheter (CVC) / bladder catheter
2. Systemic antifungal agents

Removal of central venous catheter/ fungal mass as soon as fungemia is detected results in increased clearance of infection and reduced mortality.

Failure to remove CVC has been associated with increased mortality rate (0 versus 39 %). Early removal of catheter versus late removal is associated with less duration of candidemia (3 versus 6 days). Prompt removal of central catheter within 24 hours of positive culture showed lowered mortality rates, reduced end-organ dissemination, improved neuro-developmental outcomes and increased scores on the Bayley scale.

Surgical resection of infected tissue is also indicated if failure of antifungal therapy or functional impairment is noted.

Systemic antifungal therapy: 4 different classes of antifungal agents.

1. Polyenes Amphotericin B : most commonly used antifungal.

Mechanism of action

Binds to ergosterol in the fungal cell membrane leading to cell wall leakage/pore and cell death.

Most Candida species are sensitive. CSF penetration of amphotericin B is variable. Hence for CNS infections add Fluconazole or Flucytosine. Both penetrate CSF well and are synergistic to Amphotericin B

Dose 1 mg/kg/d IV once daily.

Side effects Less common and less severe in neonates

1. Potential for nephrotoxicity and hypokalemia
2. Hypomagnesemia
3. Bone marrow suppression - anemia and thrombocytopenia
4. Increase in hepatic enzymes.

These are however dose dependent and resolve with stopping of the drug.

Serial monitoring of serum potassium, magnesium, creatinine, liver function tests and complete blood count should be done while baby is receiving Amphotericin B.

Duration of therapy

Minimum of 14 days after sterilization of the infected body fluid, with longer courses for meningitis and deep-seated infections.

Amphotericin B lipid formulations

Lipid-based Amphotericin B formulations deliver higher dose with lower levels of toxicity

Three lipid formulations are available now:

1. Amphotericin B lipid complex (ABLC : Ampholip, Bharat Serums)
2. Amphotericin B colloidial dispersion (ABCD or Amphotec)
3. Liposomal amphotericin B (AmBisome)

Liposomal amphotericin B is the only true liposomal formulation of the drug and is less nephrotoxic but more expensive.

Fungisome is an Indian research product, economical and less nephrotoxic but needs sonicator for use. We have found it quite useful.

2. Azoles

2 classes . Imidazoles (eg. Ketoconazole) and Triazoles (eg. Fluconazole, Itraconazole, Voriconazole etc).[3]

Most commonly used triazole in neonates is Fluconazole, a first generation triazole.

Fluconazole has excellent tissue penetration**,** excellent bioavailability when taken orally, reducing need for IV administration,

excellent therapeutic levels including CSF and excellent for Candida UTI (excreted unchanged in high concentrations into urine)

Mechanism of action

Inhibits fungal enzyme 14-alpha-sterol demethylase, which is necessary for the production of ergosterol, a major component of the fungal cell membrane.

Major disadvantage : Emergence of resistance (C. krusei, C. glabrata, and C. parapsilosis). Widespread use of fluconazole for prophylaxis may be a contributing factor for resistance. It should not be concomitantly administered with cisapride, cotrimoxazole, cyclosporine, phenytoin, rifampin, or macrolides.

Dose : 12mg/kg stat and 6 mg/kg/day IV or Oral. Dosing interval 48 hourly in ELBW with impaired renal clearance.

Prophylaxis: intermittent 3-mg/kg dosing

Lower doses of 3 mg/kg twice weekly is adequate to prevent candidal infections in pre-terms less than 30 wks.

Monitor liver functions, renal function and CBC

Voriconazole: Second generation triazole

Broader spectrum of activity and increased potency. Effective in fluconazole-resistance and in aspergillosis. 4-6 mg/kg/dose every 12 h but no data in neonates

Ravuconazole; Posaconazole

Structurally similar to fluconazole and voriconazole. No neonatal data

Itraconazole : orally active but inferior

3.Nucleoside analogue Flucytosine, a fluorine analogue of cytosine.

Used in combination with amphotericin B in CNS candidal infections. Excellent penetration into CSF and synergistic with amphotericin B. Monotherapy is limited due to rapid development of resistance

Mechanism of action

Inhibits thymidylate synthetase, which disrupts DNA synthesis. (not specific to fungus-significant side effects).

4. Echinocandins: Promising new antifungals

Prevent formation of glucan polymers (a major component of the fungal cell wall) by inhibiting 1,3-beta-D-glucan synthase enzyme complex.Well-tolerated and resistance is uncommon

Include Caspofungin, Anidulafungin and Micafungin.

Micafungin is well-tolerated in neonates. Caspofungin is approved to treat aspergillosis and infection with refractory Candida species but data in newborns is limited.

Muco-cutaneous candidiasis

Topical antifungal agents alone are effective in oropharyngeal candidiasis (thrush), diaper dermatitis and uncomplicated congenital candidiasis.

Systemic antifungal fluconazole is given when infection is refractory to topical therapy

Prophylactic oral nystatin for preterm babies

Introduction of prophylactic nystatin for babies <33 weeks showed significant reduction in fungal colonisation and invasive fungal infection.[4]

1 ml Nystatin (100 000 units/ml) every 6 hrly is given. Nystatin is a polyene antifungal

with good safety profile. Unlike azole group of antifungal agents, nystatin prophylaxis does not require monitoring of LFT, as it is not absorbed from the GIT.

Topical/oral non-absorbed antifungal prophylaxis with nystatin and miconazole decrease fungal colonisation on skin and mucosal surfaces, including GIT in VLBW infants. Available trial data in Cochrane review indicates that prophylaxis lowers incidence of invasive fungal infection (Inexpensive, simple and safe).[4,5]

Systemic prophylaxis

Meta analysis of Fluconazole prophylaxis in VLBW and ELBW babies showed reduced incidence and mortality in invasive fungal infection.[5,6]

But the main danger of systemic prophylaxis is the emergence of azole resistance. Antifungal resistance may take many years after the introduction of fluconazole prophylaxis to become established in NICUs. Also no statistically significant effect on mortality was seen after systemic prophylaxis.

Outcome

Prognosis of invasive candidal infections is poor. All-cause mortality in VLBW is to the tune of 28 to 32% and mortality is higher in ELBW (37 to 40%).Survivors show significant risk of neurodevelopmental impairment, especially in CNS invasive disease . Neuro-developmental impairment is seen more in ELBW infants

Points to Remember

a) High index of suspicion and early diagnosis is needed

b) Appropriate antifungal therapy - Amphotericin B or Fluconazole monotherapy or in combination especially in CNS involvement

References

1. Smith H, Congdon P. Neonatal systemic candidiasis. Arch Dis Child 1985;60;365-369.
2. Brecht M, Clerihew L, McGuire W. Prevention and treatment of invasive fungal infection in very low birthweight infants Arch Dis Child Fetal Neonatal Edn. 2009;94;F65-F69.
3. Saini S, Kumar P. Anti-fungal Drugs in Neonatology. J Neonatol 2007;21:24-29.
4. Healy M, Judith R. Campbell, Zaccaria E, Baker CJ. Fluconazole Prophylaxis in Extremely Low Birth Weight Neonates Reduces Invasive Candidiasis Mortality Rates Without Emergence of Fluconazole-Resistant Candida Species. Pediatrics 2008;121:703-710.
5. Clerihew L, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants Cochrane review The Cochrane Library2009, Issue 2 http://www.thecochranelibrary.com
6. Ganesan K, Harigopal S, Neal T, Yoxall CW. Prophylactic oral nystatin for preterm babies under 33 weeks' gestation decreases fungal colonisation and invasive fungaemia Arch Dis Child Fetal Neonatal Edn. 2009;94; F275-F278.

DRUG PROFILE

BETA LACTAMASE INHIBITOR COMBINATIONS IN PEDIATRIC PRACTICE

**** Jeeson C Unni***

Abstract: *β-lactam antibiotics have been extremely useful in the treatment of pediatric infections. However, increase in β-lactam resistance among community and hospital-acquired pathogens, mainly due to β-lactamase production, has emerged as a obstacle to the use of these antibiotics. The development of β-lactamase inhibitors for co-administration with a number of established β-lactam agents has restored their usefulness in pediatrics. This article will review the literature on the use of these combinations in childhood infectious disease.*

Keywords:*β-lactamase inhibitor, Combinations.*

WHO's World Health Day (7/4/11) theme for this year - Antimicrobial Resistance "No Action Today, No Cure Tomorrow" - amply highlights the growing global concern regarding the emergence of this 'silent epidemic' of bacterial resistance to first line antimicrobials.[1] β-lactam antibiotics have long played a central role in the management of pediatric infections. The emergence of resistance to β-lactams has been reported worldwide and poses a serious challenge to the management of pediatric infections. The most common mechanism of resistance involves the production of an enzyme the β-lactamase - that inactivates the antibiotic before it can be effective.[2]

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β-lactamases

The β-lactamases produced by Gram-negative bacteria are its main defense against β-lactam antibiotics. They are either enzymes with a serine residue at the active site, similar to bacterial penicillin-binding proteins, from which they probably evolved,[3] or metalloenzymes with zinc ion as a cofactor and with a separate heritage.[4] It has been estimated that the serine group has been around for a couple of billion years and after introduction of β-lactam antibiotics, the β-lactamases have co-evolved with them.[5] The β-lactamases may be classified on the basis of their primary structure into four molecular classes-A through D,[6] or on the basis of their substrate spectrum and responses to inhibitors into a larger number of functional groups.[7] Initially detected only occasionally in Staphylococcus aureus, they soon spread to H influenzae and N gonorrhoeae. As new antibiotics that had the property to resist the then common β-lactamases were introduced, microorganisms responded producing a variety of new β-lactamases including extended spectrum β-lactamases (ESBLs) first detected in 1983,[8] plasmid-mediated AmpC enzymes,[9] and carbapenem-hydrolyzing β-lactamases (carba penemases)[10] and the latest the New Delhi metallo-β-lactamase (NDM-1), also a carba penemase.[11]

β-lactamase inhibitiors

A β-lactamase inhibitor is a drug given in conjunction with a β-lactam antibiotic to inhibit the activity of the bacterial β-lactamases and thus combat bacterial resistance. Clavulanate, sulbactam, and tazobactam are β-lactamase inhibitors of clinical use.[12] All three are identical in their mode of activity but differ modestly in their potency and spectrum of enzyme inhibition.[13] The combination of β-lactam antibiotics with these molecules help to (a) bind and inactivate β-lactamases thereby protecting the antibiotic from hydrolysis and (b) potentiate the activity of the antibiotic perhaps by binding directly to bacterial penicillin binding proteins. As a result, synergistic activity is observed against a variety of bacteria.

Clavulanic acid is a naturally occurring, low molecular weight substance isolated as a metabolite of Streptomyces clavuligerus,[14] clavulanic acid inhibits β-lactamases through a time-dependent irreversible reaction. Because the compound binds initially at the enzyme active site and is converted into an inactivator by action of the β-lactamase, it is known as a "suicide inhibitor". Clavulanic acid by itself is a β-lactam antibiotic which possesses weak intrinsic antibacterial activity against some Entero bacteriaceae, gram-positive bacteria and anaerobes. It has moderate activity against H influenzae, good activity against N gonorrhoeae[15] and Helicobacter pylori.[16] Because of its overall weak antibacterial activity and limited spectrum, clavulanic acid has no role as monotherapy in treating infections. In combination with many penicillins and cephalosporins, however, clavulanic acid acts synergistically to improve their activity.[17] Improvement is marked against bacteria that owe their resistance to β-lactamases that can be inhibited by clavulanic acid. For strains of bacteria that produce β-lactamases not inhibited by clavulanic acid, synergy is rarely observed. Clavulanic acid has been shown not to possess activity against the inducible chromosomally mediated cephalosporinases produced by strains of Enterobacter, Citrobacter, Serratia, and Pseudomonas.[12] In some studies clavulanic acid has shown a potential for induction of these enzymes.

Sulbactam, a semisynthetic penicillanic acid sulfone, is a potent irreversible β-lactamase inhibitor possessing weak, intrinsic, therapeutically insignificant antibacterial activity against strains of Neisseria, B.fragilis, and Acinetobacter calcoaceticus. The profile is similar to that of clavulanic acid with significant inhibition of β-lactamases produced by Staphylococcus aureus, many gram-negative bacteria and Bacteroides species; slightly more against cephalosporinases[18] and slightly less against beta-lactamase produced by enterobacteriaceae. Sulbactam, unlike clavulanic acid, has not been shown to induce chromosomal β-lactamases in susceptible bacteria.[19]

Tazobactam sodium is a penicillinic acid sulfone β-lactamase inhibitor with a structure similar to that of sulbactam. It possesses relatively little antibacterial activity of its own. Compared to clavulanic acid and sulbactam, it exhibits the least intrinsic activity against Enterobacteriaceae and nonfermentative gram-negative bacilli.[20] A potent β lactamase inhibitor, it accounts for many chromosomally mediated enzymes of gram-negative bacilli – as effective as clavulanic acid and better than sulbactam;[21] as well as the β-lactamases of Staphylococcus aureus and anaerobes such as Bacteroides fragilis.[12] Tazobactam is a weak inducer of the chromosomal type I β-lactamases. This characteristic may help to minimize therapeutic failure attributable to antibiotic resistance as a result of induction.

Antibiotic-clavulanic acid and antibiotic-tazobactum combinations

Amoxicillin-clavulanic acid

Amoxicillin-clavulanic acid was the first of the combined betalactam/β–lactamase inhibitor antibiotics to be released commercially.

Antibacterial spectrum – Adding clavulanic acid to amoxicillin expands the antibacterial spectrum of the latter to include β-lactamase-producing strains of S. aureus, H. influenzae, H. ducreyi, M. catarrhalis, Bacteroides species, N. gonorrhoeae, E. coli, P. mirabilis, Klebsiella and selected other Enterobacteriaceae.[22] S pneumoniae demonstrating intermediate and high level resistance to penicillin have been shown to be susceptible to this combination.[23] Amoxicillin-clavulanic acid may have a role in the therapy of disease caused by multi-drug resistant (MDR) strains of M. tuberculosis.[24] The combination has little or no activity against Pseudomonas, Enterobacter, Serratia, Citrobacter, and strains of methicillin-resistant staphylococci.

Pharmacokinetics: The pharmacokinetics of the two components of coamoxiclav is closely matched. Absorption is not affected by food and peak serum levels of both occur about one hour after oral administration.[25] Absorption is optimized at the start of a meal. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum. Doubling the dose of co-amoxiclav approximately doubles the serum levels achieved. Amoxicillin and clavulanic acid are distributed into many tissues and body fluids including the liver, gallbladder, prostate, lungs, urine, middle ear effusions, bronchial secretions, maxillary sinus secretions, and synovial, pleural and peritoneal fluids. Minimal levels are attained within the CSF when meninges are not inflamed; these levels are increased with inflammation. The drugs cross the placenta. Approximately 10% of an amoxicillin dose is metabolised to inactive derivatives; most (60 to 80%) of the drug is eliminated unchanged. Amoxicillin and its metabolites are primarily excreted into the urine primarily via tubular secretion and glomerular filtration. Clearance of clavulanic acid has both a renal (30% to 50%) and a non-renal component. Clavulanic acid appears to be extensively metabolised, although the exact mechanism is not fully established. A small percentage of amoxicillin and clavulanic acid is excreted in breast milk. In patients with normal renal function, the elimination half-lives of amoxicillin and clavulanic acid are roughly 1-1.5 hours. The elimination half-lives of both amoxicillin and clavulanic acid increase as renal function declines-up to 7.5 hours for amoxicillin and 4.5 hours for clavulanic acid in patients with end-stage renal disease. Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed.

Indications: The combination, because it covers gram positive, gram negative and anaerobic organisms, is the drug of choice in mixed infections seen in human and animal bites,[26,27] rhinosinusitis[28] and mixed soft tissue infections and the second line drug for recurrent otitis media[36] respiratory tract infection[30] and UTI.[31]

Dosage: Dosed on amoxycillin content. Neonates - 30mg/ kg/day in 2 divided doses. Children 20-45 mg/kg in 2-3 divided doses. Higher doses of 80mg/kg/day may be required in otitis media.

Administration: Oral: give at the start of a meal. Dispersible tablets should be stirred into a little water before taking. IV: reconstitute a 300 or 600mg vial with 10ml water for Injections (final volume 10.5ml) and a 1.2g vial with 20ml (final volume 20.9ml). Give by slow IV injection (over 3-4 minutes, within 20 minutes of reconstitution) or infuse over 30-40 minutes and

complete infusion within 4 hours of reconstitution. For infusion the reconstituted injection can be diluted to 5 times its volume in NaCl 0.9%. Do not infuse in glucose solutions, as co-amoxiclav is less stable in infusions containing glucose.

Ticarcillin-clavulanic acid and piperacillin + tazobactam

Piperacillin with tazobactam and ticarcillin with clavulanic acid are combinations of anti - psuedomonal penicillin with β-lactamase inhibitor. They are very broad spectrum antibiotics[32] but a study showed that Piperacillin + tazobactam was inferior to cefipime against ceftazidime-resistant Enterobacteriaceae and P. aeruginosa[33] and another demonstrated that carbapenems were superior to Ticarcillin-clavulanic acid and cefipime in treating mulyi-drug resistant P. aeruginosa.[34] Being broad spectrum and with reports of resistance debveloping to these high end antibiotics, their use must be restricted to certain very specific indications. Some centres use them for empiric treatment of fever in a neutropenic child as monotherapy[35] and evidence shows that there is no clinical advantage of combination therapy over monotherapy, even in subgroups of patients with bacteraemia (including patients with Pseudomonas aeruginosa) or severe neutropenia <0.1 x 10^9/L (level I evidence).[36] Some centres use these drugs in combination with aminoglycosides for the same indication.[37,38] Others reserve these antibiotic combinations for serious infections resistant to other antibiotics.

Pharmacokinetics: Both are given IV and peak serum concentrations of both components of each combination are achieved within ½ hour with mean serum half-lives of approximately 1hour. Because both combinations are primarily excreted by the kidneys, dose adjustments are required if the creatinine clearance is less than 60mL/min. For patients undergoing hemodialysis, an additional half-dose of ticarcillin with clavulanic acid is required at the end of dialysis. Piperacillin and tazobactam are widely distributed into many tissues and body fluids, including lung, skin, reproductive tissues, intestinal mucosa and fluid, gallbladder, and bile. Synergestic activity of ticarcillin-clavulinic acid are found in blister fluid, bone, bile, and joint fluid. Although ticarcillin and clavulanic acid may enter cerebrospinal fluid in the presence of inflamed meninges, the combination is not recommended for treatment of meningitis.

Dosage: Piperacillin and tazobactam:[39] LRTI, UTI, Intraabdominal and skin infection and bacterial septicemia: IV over 3-5min or as IV infusion: Neonate 90mg/kg 8th hourly; 1 month – 1 year 90mg/kg 6th-8th hourly (max 4.5gm every 6 hours), 12-18 years 2.25 gm - 4.5 gm 6th - 8th hourly (usually 4.5gm 8th hourly). Febrile neutropenia: (along with aminoglycoside) 1-18years 90mg/kg (max 4.5gm) 6th hourly. Complicated appendicitis: 2-12years 112.5mg/kg (max 4.5gm) 8th hourly for 5-14 days. In renal impairment (dose expressed as a combination of piperacillin and tazobactam - both as sodium salts). Child under 12 years 90 mg/kg (max. 4.5 g) every 8 hours if estimated glomerular filtration rate 20-40 mL/minute/1.73 m^2; 90 mg/kg (max. 4.5 g) every 12 hours if estimated glomerular filtration rate less than 20 mL/minute/ 1.73 m^2. Child 12-18 years max. 4.5 g every 8 hours if estimated glomerular filtration rate 20-80 mL/minute/1.73 m^2; max. 4.5 g every 12 hours if estimated glomerular filtration rate less than 20 mL/minute/1.73 m^2.

Ticarcillin and clavulinic acid:[40] Expressed as a combination of ticarcillin (as sodium salt) and clavulanic acid (as potassium salt) in a ratio of 15:1 Infections due to Pseudomonas and Proteus spp.–IV infusion; Preterm

<2kg 80mg/kg 12thhourly; Preterm >2kg and neonates 80mg/kg and 1 month-18 years < 40 kg - 8th hourly (6th hourly in severe infections); <18 years > 40 kg - 3.2 g 6th–8th hourly (4 hourly in severe infections).

Antibiotic- sulbactam combination

Ampicillin-sulbactam

Ampicillin/sulbactam was developed over two decade ago.

Ampicillin alone has activity against most strains of streptococci, enterococci, Listeria and β-lactamase negative strains of S. aureus, H. influenzae, E. coli, P. mirabilis, Salmonella, and Shigella. In combination with sulbactam, activity is enhanced against many β-lactamase-producing bacteria, including S. aureus, H. influenzae, M. catarrhalis, E. coli, Proteus, Providencia, Klebsiella, and anaerobes.[41,42,43] Using the ampicillin/sulbactam combination the MICs for ampicillin is significantly reduced such that drug levels achieved in body fluids and tissues is more than sufficient for activity against the majority of pathogens. For example, the MIC_{90} (the concentration inhibiting 90% of strains) for ampicillin in β-lactamase-positive *S.*aureus is reduced from 64 μg/ml to 2 μg/ml when it is combined with sulbactam. The main cautionary note is that ampicillin/sulbactam is not effective against P aeruginosa and Enterobacteriaceae that produce high levels of Class I chromosomal β-lactamases against which sulbactam is not highly active. Many clinical laboratories have noted resistance or intermediate susceptibility to ampicillin-sulbactam in 20% to 30% of E. coli isolates.

Pharmacokinetics: Ampicillin and sulbactam are readily absorbed from the gastrointestinal tract and rapidly hydrolyzed to release equimolar concentrations of ampicillin and sulbactam into the peripheral circulation. The pharmacokinetic profiles of ampicillin and sulbactam, administered together both orally and parenterally, in pediatric patients are comparable to those reported in adults.[44,45] Serum half-lives are approximately 1 hour for both ampicillin and sulbactam. More than 75% of both drugs are excreted via the kidneyand therefore dose modification is required in the presence of renal failure. Both agents penetrate into extravascular fluids and tissues rapidly. Peritoneal fluid levels are >90% of serum levels.[46] In the presence of inflamed meninges, good cerebrospinal fluid levels are also achieved.[45]

Dosage: >1year age – IV[47] - mild to moderate infections - 100-150mg/kg of ampicillin in 4 divided doses; severe infections/meningitis - 200-400mg/kg of ampicillin in 4 divided doses (max adult dose 6-12gm/day).

Clinical efficacy of ampicillin/ sulbactam in pediatric infections

This is not an often used antibiotic in pediatric practice and therefore does not find a mention in BNF for children and the IAP Pediatric Drug Formulary. However, studies have shown its effectiveness in treating children with a range of mild to moderate pediatric infections such as otitis media and urinary tract infections;[48] intra-abdominal infection – along with an aminoglycoside to cover P aeroginosa and E coli which are not susceptible to ampicillin sulbactam[49] and as an alternative therapy in acute appendicitis;[50] orbital cellulitis, chronic sinusitis or parasinus infection, human and animal bites, pelvic inflammatory disease, cellulitis, osteomyelitis and pyogenic arthritis;[51] and community acquired pneumonia.[52]

Unorthodox β-lactam – β-lactamase combinations

Many new combinations have entered the market in India. But only the above mentioned combinations are listed in the pediatric drug

formularies – BNF for children and IAP Drug Formulary. The Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency, Centre for Infections, London in an article states that 'Clinical development of clavulanate with cefepime, cefpirome or cefpodoxime does not seem likely in the West, considering ownership and patent issues. Cefpisome-tazobactum is, however being launched in India, where the licensing regime is more liberal'.[53] The article also suggested that cefpodoxime-clavulanate is not ideal combination, in terms of 'pharmacological matching'.

However, there have been isolated reports of efficacy of ceftriaxone-tazobactam/sulbactam combinations,[54,55,56] cefpodoxime-clavulanate,[57] cefixime-clavulanate,[58] cefepime-clavulanate[59] and cefoperazone-sulbactam.[60] These studies need to be substantiated with many more RCTs before their use could be recommended for routine use.

Points to Remember

- ***The combinations that are licensed for use in pediatrics are Co-amoxiclav, Piperacillin + tazobactam, Ticarcillin + clavulanic acid and, to some extent, ampicillin sulbactam.***
- ***Clavulanic acid / tazobactam bind with β-lactamases of staph aureus, Gm –ves : H fluenzae, M catarrhalis, many E. coli, Klebsiella, bacteroides. But they are inactive against β-lactamases of Pseudomonas, Enterobacter, Serratia, Citrobacter sp.***
- ***Co-amoxiclav is the drug of choice (because it covers Gm+ve, Gm-ve and anaerobes) for treatment of human / animal bites, bacterial rhinosinusitis, mixed soft tissue infections and second line drug for acute otitis media (only if resistance to amoxicillin is β-lactamase related), respiratory infection and UTI.***
- ***Piperacillin + tazobactam and ticarcillin + clavulanic acid are combinations of anti-pseudomonal penicillin + β-lactam inhibitor - (broad spectrum) but they are not effective against Enterobacter; Some centres use it for empiric treatment of fever in a neutropenic child in combination with aminoglycoside; Others reserve it for serious infections resistant to other antibiotics.***

References

1. World Health Day – 7 April 2011. Antimicrobial resistance: no action today, no cure tomorrow. http://www.who.int/world-health-day/2011/en/index.html. Accessed on 26/4/11.
2. Dajani AS. Beta-lactam resistance: clinical implications for pediatric patients. J Int Med Res 2002; 30 Suppl 1: 2A-9A.
3. Joris B, Ghuysen JM, Dive G, Renard A, Dideberg O, Charlier P, et al. The active-site-serine penicillin-recognizing enzymes as members of the Streptomyces R61 DD-peptidase family. Biochem J 1988; 250:313-324.
4. Garau G, Garcia-Saez I, Bebrone C, Anne C, Mercuri P, Galleni M, et al. Update of the standard numbering scheme for class B β-lactamases. Antimicrob Agents Chemother 2004; 48: 2347-2349.
5. Medeiros AA. Evolution and dissemination of β-lactamases accelerated by generations of β-lactam antibiotics. Clin Infect Dis 1997; 24 Suppl 1: S19-S45.
6. Ambler RP. The structure of β-lactamases. Philos Trans R Soc Lond B Biol Sci 1980; 289: 321-331
7. Bonnet R, Sampaio JL, Chanal C, Sirot D, De Champs C, Viallard JL, et al. A novel class A extended-spectrum â-lactamase (BES-1) in Serratia marcescens isolated in Brazil. Antimicrob Agents Chemother 2000; 44: 3061-3068.

8. Knothe H, Shah P, Kremery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of Klebsiella pneumoniae and Serratia marcescens. Infection 1983; 11: 315-317.
9. Philippon A, Arlet G, Jacoby GA. Plasmid-determined AmpC-type beta-lactamases. Antimicrob Agents Chemother 2002; 46: 1-11.
10. Rasmussen BA, Bush K. Carbapenem-hydrolyzing beta-lactamases. Antimicrob Agents Chemother 1997; 41: 223-232.
11. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske CG, Irfan S, Krishnan P, Kumar AV, Maharjan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike R, Rao B, Ray U, Sarma JB, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livermore DM, Woodford N. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis 2010; 10: 597-602.
12. Bush LM, Johnson CC. Ureidopenicillins and beta-lactam/beta-lactamase inhibitor combinations. Infect Dis Clin North Am 2000; 14: 409-433.
13. Payne D, Cramp R, Winstanley D, Knowles DJ. Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important beta-lactamase. Antimicrob Agents Chemother 1994; 38: 767-772.
14. Reading C, Cole M. Clavulanic acid: A beta-lactamase-inhibiting beta-lactam from Streptomyces clavuligerus. Antimicrob Agents Chemother 1977; 11: 852-857.
15. Neu HC, Fu KP. Clavulanic acid, a novel inhibitor of beta-lactamases. Antimicrob Agents Chemother 1978; 14: 650-655.
16. Horii T, Mase K, Suzuki Y, Kimura T, Ohta M, Maekawa M, et al. Antibacterial activities of beta-lactamase inhibitors associated with morphological changes of cell wall in Helicobacter pylori. Helicobacter 2002; 7: 39-45.
17. Hunter PA, Coleman K, Fisher J, Taylor D. In vitro synergistic properties of clavulanic acid, with ampicillin, amoxicillin, and ticarcillin. J Antimicrob Chemother 1980; 6: 455-470.
18. Bush K. Beta-lactamase inhibitors from laboratory to clinic. Clin Microbiol Rev 1988; 1: 109-123.
19. Moosden F, Keeble J, Williams JD. Induction/inhibition of chromosomal beta-lactamases by beta-lactamase inhibitors. Rev Infect Dis 1986; 8(Suppl 5): S562-568.
20. Moosdeen F, Williams JD, Yamase S. Antibacterial characteristics of YTR 830, a sulfone beta-lactamase inhibitor, compared with those of clavulanic acid and sulbactam. Antimicrob Agents Chemother 1988;32:925-927.
21. Chaïbi EB, Sirot D, Paul G, Labia R. Inhibitor-resistant TEM beta-lactamases: phenotypic, genetic and biochemical characteristics. J Antimicrob Chemother 1999; 43: 447-458.
22. Weber DJ, Tolkoff-Rubin NE, Rubin RH. Amoxicillin and potassium clavulanate: an antibiotic combination. Mechanism of action, pharmacokinetics, antimicrobial spectrum, clinical efficacy and adverse effects. Pharmacotherapy 1984; 4: 122-136.
23. Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC. Susceptibilities of Streptococcus pneumoniae and Haemophilus influenzae to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. Surveillance study. Antimicrob Agents Chemother 1999; 43: 1901-1908.
24. Dinçer I, Ergin A, Kocagöz T. The vitro efficacy of beta-lactam and beta-lactamase inhibitors against multidrug resistant clinical strains of Mycobacterium tuberculosis. Int J Antimicrob Agents 2004; 23: 408-411.
25. Co-amoxiclav. In: IAP Drug Formulary 2009. Unni JC, Nair MKC, Menon PSN, Bansal CP. Eds. Publication of Indian Academy of Pediatrics. Pixel Studio Cochin. 2009: 282-283.
26. Gilbert DN, Moellering RC Jr, Sande MA, Eds. The Sanford guide to antimicrobial therapy. 29th ed. Hyde Park, Vt.: Antimicrobial Therapy, 1999; 33: 52-53, 64.

27. Brakenbury PH, Muwanga C. A comparative double blind study of amoxycillin/clavulanate vs placebo in the prevention of infection after animal bites. Arch Emerg Med 1989; 6: 251-256.
28. Passàli D, Passàli GC, Damiani V, Passàli FM, Bellussi L. Aetiological Considerations on Chronic Sinusitis and Therapeutic Consequences. Oto-Rhino-Laryngologia Nova 2002/2003; 12: 71-76 (DOI: 10.1159/000070914).
29. Brook I, Gober AE. Effect of amoxicillin and co-amoxiclav on the aerobic and anaerobic nasopharyngeal flora. J Antimicrob Chemother 2002; 49: 689-692.
30. Blackburn RM, Henderson KL, Lillie M, Sheridan E, George RC, Deas AH, Johnson AP. Empirical treatment of influenza-associated pneumonia in primary care: a descriptive study of the antimicrobial susceptibility of lower respiratory tract bacteria (England, Wales and Northern Ireland, January 2007-March 2010). Thorax 2011; 66: 389-395.
31. Kennedy KM, Glynn LG, Dineen B. A survey of the management of urinary tract infection in children in primary care and comparison with the NICE guidelines. BMC Fam Pract 2010; 11: 6.
32. Bush LM, Calmon J, Johnson CC. Newer penicillins and beta-lactamase inhibitors. Infect Dis Clin North Am 1995, 9: 653-686.
33. Pfaller MA, Sader HS, Fritsche TR, Jones RN. Antimicrobial activity of cefepime tested against ceftazidime-resistant Gram-negative clinical strains from North American Hospitals: report from the SENTRY Antimicrobial Surveillance Program (1998-2004). Diagn Microbiol Infect Dis 2006; 56(1): 63-68.
34. Japoni A, Alborzi A, Kalani M, Nasiri J, Hayati M, Farshad S. Susceptibility patterns and cross-resistance of antibiotics against Pseudomonas aeruginosa isolated from burn patients in the South of Iran. Burns 2006; 32: 343-347.
35. Corapcioglu F, Sarper N, Zengin F. Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. Pediatr Hematol Oncol 2006; 23: 177-186.
36. Tam CS, O'Reilly M, Andresen D, Lingaratnam S, Kelly A, Burbury K, et al. Australian Consensus Guidelines 2011 Steering Committee. Use of empiric antimicrobial therapy in neutropenic fever. Australian Consensus Guidelines 2011 Steering Committee. Intern Med J 2011; 41(1b): 90-101.
37. Schaison G, Reinert P, Leverger G, Leaute JB. Timentin (ticarcillin and clavulanic acid) in combination with aminoglycosides in the treatment of febrile episodes in neutropenic children. J Antimicrob Chemother Suppl C 1986; 17: 177-181.
38. Fleischhack G, Schmidt-Niemann M, Wulff B, Havers W, Marklein G, Hasan C, et al. Piperacillin, beta-lactam inhibitor plus gentamicin as empirical therapy of a sequential regimen in febrile neutropenia of pediatric cancer patients. Support Care Cancer 2001; 9: 372-379.
39. Piperacillin. In: BNF for Children 2005. Eds Rylance G, et al. BMJ publications Group Ltd.; Royal Pharmaceutical Society of Great Britain; RCPCH Publications Ltd. 2005: 286.
40. Ticarcillin. In: BNF for Children 2005. Eds, Rylance G, et al. BMJ publications Group Ltd.; Royal Pharmaceutical Society of Great Britain; RCPCH Publications Ltd. 2005: 287.
41. Retsema JA, English AR, Girard A, Lynch JE, Anderson M, Brennan L, et al. Sulbactam/Ampicillin: In Vitro Spectrum, Potency, and Activity in Models of Acute Infection. Clin Infect Dis 1986; 8(Suppl 5): S528-S534. doi:10.1093/clinids/8.Supplement_5.S52.
42. Sessarego FV, Botta GA, Pesce A, Schito GC. Antibacterial activity of the sulbactam-ampicillin combination. J Chemother 1989; 1: 384-387.
43. Campoli-Richards DM, Brogden RN. Sulbactam/ampicillin: a review of its antibacterial activity, pharmacokinetic properties, and therapeutic use. Drugs 1987; 33: 577-609.

44. Foulds G: Pharmacokinetics of sulbactam/ ampicillin in humans: a review. Rev Infect Dis 1986; 8: S503 – S511.

45. Foulds G, McBride TJ, Knirsch AK, Rodriguez WJ, Khan WN. Penetration of sulbactam and ampicillin into cerebrospinal fluid of infants and young children with meningitis. Antimicrob Agents Chemother 1987; 31: 1703 – 1705.

46. Wise R, Donovan IA, Andrews JM, Drumm J, Bennett S. Penetration of sulbactam and ampicillin into peritoneal fluid. Antimicrob Agents Chemother 1983;24:290-292.

47. Red Book - 2009 Report of Committee of Infectious Diseases, American Academy of Pediatrics. Eds: Committee of Infectious Diseases, American Academy of Pediatrics, Pickering LK, Baker CJ, Kimberlin DW, Long SS. 28TH Ed. Jaypee Brothers Medical Publishers Pvt Ltd. New Delhi. Pg753t.

48. Eduardo LL, Noemi RA. Clinical use of sultamicillin (ampicillin/sulbactam) in children. Pediatric Infectious Disease Journal, 1998; 17: S12-S14.

49. Michelle CD, Adnan DS, Kwang KS, Denis KR, Sheldon KL, Parvin AH, et al. The multicenter group. Comparison of ampicillin/sulbactam plus aminoglycoside vs. ampicillin plus clindamycin plus aminoglycoside in the treatment of intraabdominal infections in children. Pediatric Infectious Disease Journal 1998; 17: S15-S18.

50. Foster MC, Kapila L, Morris DL, Slack RC. A randomized comparative study of sulbactam plus ampicillin vs. metronidazole plus cefotaxime in the management of acute appendicitis in children. Rev Infect Dis 1986; 8: S634-638.

51. Dajani AS. Use of Ampicillin/Sulbactam and Sultamicillin in Pediatric Infections: a Re-evaluation. The Journal of International Medical Research 2001; 29: 257-269.

52. Tapýsýz A, Ozdemir H, Ciftçi E, Belet N, Ince E, Doðru U. Ampicillin/sulbactam for children hospitalized with community-acquired pneumonia. J Infect Chemother. 2011;22. [Epub ahead of print]

53. Livermore DM, Hope R, Mushtaq S, Warner M. Orthodox and unorthodox clavulanate combinations against extended-spectrum beta-lactamase producers. Clin Microbiol Infect 2008;14 Suppl 1:1 89-93.

54. Georgopoulos A, Buxbaum A, Graninger W. Efficacy of beta-lactam and inhibitor combinations in a diffusion chamber model in rabbits. J Antimicrob Chemother 1999; 43: 497-501.

55. Aldridge KE, Morice N, Schiro DD. Increased in vitro activity of ceftriaxone by addition of tazobactam against clinical isolates of anaerobes. Diagn Microbiol Infect Dis 1994; 19: 227-234.

56. Fantin B, Pangon B, Potel G, Caron F, Vallée E, Vallois JM, Mohle J, Buré A, Philippon A, Carbon C. Activity of sulbactam in combination with ceftriaxone in vitro and in experimental endocarditis caused by Escherichia coli producing SHV-2-like beta-lactamase. Antimicrob Agents Chemother 1990 ; 34: 581-586.

57. Pal RB, Pal P, Jain S, Kulkarni KP. In vitro study to compare sensitivity of amoxicillin+ clavulanic acid and cefpodoxime+clavulanic acid among beta-lactamase positive clinical isolates of gram-positive and gram-negative pathogens. J Indian Med Assoc 2008; 106: 545-548.

58. Rawat D, Hasan AS, Capoor MR, Sarma S, Nair D, Deb M, et al. In vitro evaluation of a new cefixime-clavulanic acid combination for gram-negative bacteria. Southeast Asian J Trop Med Public Health 2009; 40: 131-139.

59. Mohanty S, Gaind R, Ranjan R, Deb M. Use of the cefepime-clavulanate ESBL Etest for detection of extended-spectrum beta-lactamases in AmpC co-producing bacteria. J Infect Dev Ctries 2009; 4: 24-29.

60. Chandra A, Dhar P, Dharap S, Goel A, Gupta R, Hardikar JV, et al. Cefoperazone-sulbactam for treatment of intra-abdominal infections: results from a randomized, parallel group study in India. Surg Infect (Larchmt) 2008; 9: 367-376.

DERMATOLOGY

PITYRIASIS RUBRA PILARIS

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Abstract: *Pityriasis rubra pilaris even though mentioned as a rare disorder in children has increased in the recent past and is characterized by keratotic papules, scaly erythematous patches that coalesce to form plaques and palmoplantar thickening. Five types are described apart from the disorder associated with HIV and out of this type 3,4 and 5 are in children. Type 3 and 5 disappears in the course of disease where as type 4 can persist for life. Conditions like seborrhoeic dermatitis and psoriasis may mimic like PRP.*

Keywords: *Keratotic papules, Erythematous patches*

Synonym: Lichen ruber pilaris, Devergie's disease, Lichen ruber acuminatus

Pityriasis rubra pilaris (PRP) was first described by Claudius Tarral in 1835 as a variant of psoriasis and later Devergie in 1856 described it as pityriasis pilaris and later name was modified to pityriasis rubra pilaris by Besnier in 1889.[1]

As the name suggests pityriasis means brawny scales, rubra means red and pilaris means hair follicle.

Even though mentioned as a rare disorder in children, the actual number of cases seen in office practice is on the rise. This is a group of conditions characterized by combination of keratotic follicular papules, scaly erythematous patches that coalesce to form plaques with palmoplantar thickening.[2]

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Epidemiology

Both males and females are equally affected. Majority of the cases are acquired and a few familial clustering has been reported.[3]

Aetiopathogenesis

The exact etiology of this condition is not known. Vitamin A deficiency was proposed and not substantiated. Due to good therapeutic response achieved by giving systemic retinoids a possible dysfunction of keratinization or Vitamin A metabolism has been proposed. Minor trauma to the skin, ultra violet exposure and infections have preceded the onset of PRP suggesting a physical trigger or superantigen. Autoimmune pathogensesis has also been thought of due to the association with autoimmune disease in few cases. PRP is diagnosed on clinical grounds and has been classified into five types (Table I).[4,5]

Table I. Types of Pityriasisrubrapilaris

Type 1	Classic type adult onset
Type 2	Atypical type adult onset
Type 3	Classical type juvenile onset
Type 4	Localised or circumscribed juvenile onset
Type 5	Atypical type juvenile onset

Some authors have proposed a sixth type of PRP which is associated with HIV infection in adults and children.[6] Type 3, Type 4 and Type 5 are the one which needs pediatricians attention.

Type 3 and type 5 manifest in the first decade of life and type 5 is present at birth or may develop a few years later.

Clinical features

Type 3 PRP

The condition develops during the first decade and starts as scaly, erythematous macules and papules and a few may coalesce. Usually starts over the face, neck and scalp; spreads in a cephalo-caudal direction involving the trunk and limbs over a period of several weeks to several months. Pruritus may be present during the evolution of the lesions. The whole skin surface is not involved but there are areas of normal skin in between called as islands of sparing. On the face, ectropion may be seen with palms and soles showing orange yellow coloured thick scaly skin. Scalp shows scaling which may resemble seborrhoeic dermatitis or psoriasis and thickening of nail is seen in the later stage.

Type 4

This is characterized by scaly thickened plaques over the elbows and knees. Palms and soles may show thickening in few patients.

Type 5

Present at birth or a few years of life with widespread scaly erythema with prominent hair follicular papules. Thickening of palms and soles may vary from mild thickening to pronounced thickening. There may be associated arthralgia.

Diagnosis

This condition is diagnosed clinically and no biochemical or laboratory investigations help.

Differential diagnosis

Psoriasis is one of the close differential diagnosis as this condition also shows elbows and knee involvement with scaling over the scalp and palms and soles involvement. The red orange thickening of palms and soles with grouped papules with islands of normal skin in between will differentiate psoriasis from PRP.

Early PRP of the scalp may mimic seborrhoeic dermatitis of the scalp (Dandruff). Seborrhoeic dermatitis may respond well to routine measures whereas scalp scaling may not respond. Dermatomyositis Wong type may also mimic early PRP. Children with acute onset of PRP may be misdiagnosed as having Kawasaki disease. Erythrokeratoderma and non bullous ichthyosiform erythroderma may be the other close differential diagnosis.

Treatment

Topical therapy is the treatment of choice for mild type 3 and type 4 PRP.

Mild type 3 PRP: Emollients are applied twice daily immediately after bath to decrease the symptoms of dryness and tightness of the skin.

Severe form of type 3 PRP: Acitretin with a dose of 0.5-0.75mg/kg per day is the drug of choice.[7] When using acitretin regular monitoring of blood lipids and liver function test done regularly. It has been found that acitretin may shorten the duration of the disease.

Mild form of type 4 PRP: Emolients along with retinoids(0.05%) topically may improve the condition.

Type 4 PRP: Emollients and oral acitretinare the drug of choice. Other drugs which could be used for PRP are methotrexate and cyclosporine.[8] Calcipotriol ointments may help to bring down the thickness of palms and soles.[9]

Prognosis

Large doses of oral vitamin A has resolved many PRP lesions along with vitamin B and D. In type 3 and type 4 PRP, spontaneous clearance occurs in a majority of patients. Type 4 PRP persists through out life.

Points to remember

- ***Many children with PRP are seen in office practice nowadays and one has to look for the typical lesions.***
- ***Seborrhoeic dermatitis and Psoriasis may mimic PRP.***
- ***Reassurance and emollients with vitamin A orally in large doses help in PRP and most of them resolve spontaneously within 3-5 years except type 4 which may persist life long.***

References

1. Besnier E: Du Pityriaisrubrapilaire. Ann Dermatol Syphiligr Paris 1889; 10:253.
2. Peter A Hogan. Papulosquamous disease, Pityriasis rubra pilaris. In: Schachner LA, Hansen RC, Eds. Pediatric Dermatology. 3rd Edn. Mosby, 2003;pp676-680
3. Griffiths WAD. Pityriasis rubra pilaris. Clin Exp Dermatol 1980; 5:105-112.
4. Grifiths WA. Pityriasis rubra pilaris – an historical approach. 2. Clinical features Clin Exp Dermatol 1976;1:37-50.
5. Griffith WA. Pityriasisrubrapilaris. J Am Acad Dermatol 1984;10:1086-1088.
6. Menni S, Brancaleone W, Grimalt R. Pityriasis rubra pilaris in a child seropositive for the human immunodeficiency virus. J Am Acad Dermatol 1992;27.1009.
7. Brook M, Lowe NJ. Pityriasis rubra pilaris: further observation of systemic retinoid therapy. J Am Assoc of Dermatol 1990;22:792.
8. Rosenbach A, Lowe NJ. Pityriasis rubra pilaris and cyclosporine. Arch Dermatol 1993; 129:1346-1348.
9. Van de kerhoff PCM. Steijlen PM. Topical treatment of pityriasis rubra pilaris with calcipotriol. Br J Dermatol 1994;130:675-678.

BOOK REVIEW

Name	**:**	Pediatric Clinical Methods
Editor	**:**	Meharban Singh
Review	**:**	The Fourth Edition of Pediatric Clinical Methods by Prof. Meharban Singh by Sagar publications is a wonderful update of the earlier editions with the same title. This edition of the book is better formatted. The initial chapters covering history taking and initiating clinical examination are very informative exercise which will benefit the post graduate students. Photographs are updated and new and they convey what is needed for the text description with clarity. The nice quotes given at the beginning of every chapter is a treat. A good handbook for post graduate students and beginners in pediatrics.
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RADIOLOGIST TALKS TO YOU

PARASELLAR MASSES-2

** Vijayalakshmi G*
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***** Elavarasu MD*

We will continue with parasellar masses in this issue. The lesions presented here are rare, but interesting. The parasellar region does not have specific boundaries and we have seen the long list of anatomic structures that are included. Now we will see some lesions around the third ventricle.

The third ventricle is seen as a fluid space placed centrally. Inferior to this is the hypothalamus. On either side are the thalami. Fig.1. shows a thalamic mass with marked surrounding edema. The commonest mass involving the deep grey matter is the astrocytoma which may be of varying pathological grade. Depending on their grade they show enhancement in both CT and MRI which is most intense in the grade 3 or 4 masses. Their central location provides little room for expansion so that there is distortion and displacement of the third ventricle and early gross hydrocephalus. They will invade the basal ganglia and extend downwards to involve the hypothalamus. The commonest cell type of gliomas in the thalami, hypothalami and basal ganglia is the fibrillary type.

The hypothalamic hamartoma is a developmental malformation consisting of hypothalamic nerve cells and glial cells. There are two clinico-anatomical subsets. a) The intrahypothalamic hamartoma lies within the hypothalamus. It is seen as a sessile mass distorting the third ventricle and is associated with gelastic seizures. b) The other type is the parahypothalamic type that is pedunculated and attached to the floor of the hypothalamus. This is the mass that is seen in Fig.2, a hamartoma of the tuber cinereum. The tuber cinereum is the part of the hypothalamus that projects downwards between the chiasma and the mammillary bodies. This child had precocious puberty which is associated with this type, rather than gelastic seizures. On CT (Fig.2) it is seen as a well defined mass projecting into the suprasellar cistern. It is homogenous and does not enhance. In MRI, on T1 it is isointense or mildly hypointense and on T2 images it is hyperintense (Fig.3). There is no enhancement and no calcification.

The pineal gland is situated behind the third ventricle. Most of the pineal region neoplasms are highly malignant lesions. These include the germ cell tumors like the pineal germinoma. Germinomas are a type of tumor arising from germ cells that originate from yolk-sac endoderm, migrate widely and settle in the gonadal ridges of the embryo. Normally, the nongonadal cells disappear. Failure of these cells to involute in

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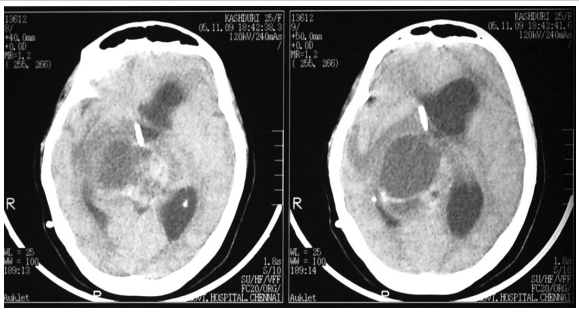

Fig.1. Thalamic glioma. A shunt tube is also seen.

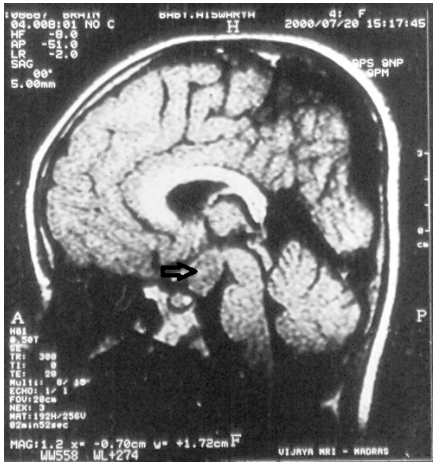

Fig.3. Hamartoma of the tuber cinereum(arrow)- MRI

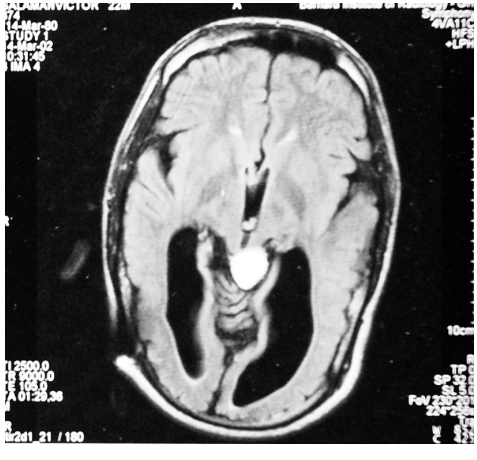

Fig.5. Dermoid cyst near the aqueduct

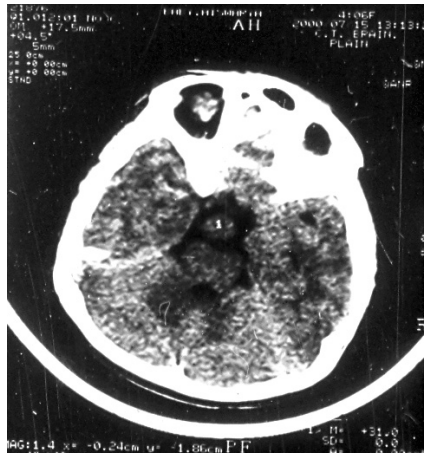

Fig.2. Hamartoma of the tuber cinereum (1) - CT film.

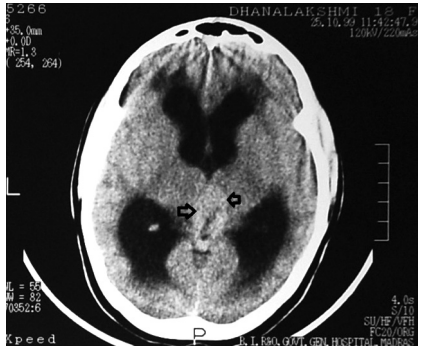

Fig.4. Germ cell tumor in the pineal region(arrows)

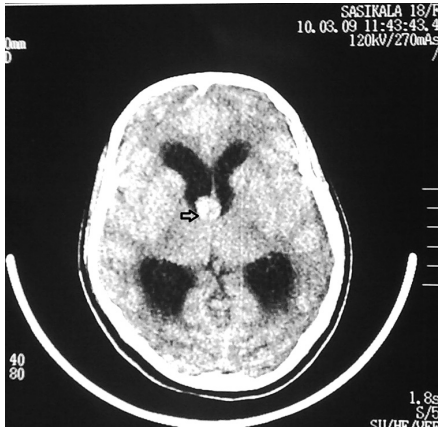

Fig.6. Colloid cyst - CT.

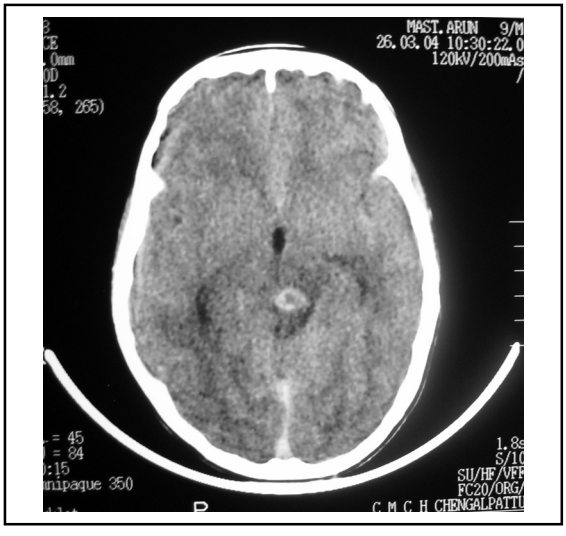

Fig.7. Ring lesion in the hypothalamus

the retroperitoneum, sacrococcygeal region, mediastinum, cerebral hemisphere or pineal and suprasellar region give rise to this group of tumors. Synchronous germ cell tumors in the pineal gland and other locations are known to occur and this requires an extensive search in the suprasellar region and spine. Other germ cell tumors are choriocarcinoma, endodermal sinus tumor, embryonal cell carcinoma and malignant teratoma. The non-germ cell malignancies are pineoblastoma, glioblastoma, metastatic tumor and sarcoma. Germ cell tumors are seen predominantly in males from infancy to 20 years of age. Fig.4 is a CT image of germ cell tumor in an 18 year old girl. There is a slightly hyperdense midline mass behind the third ventricle which in turn is compressed causing hydrocephalus. CT scan is sensitive for picking up calcification. The presence of pineal calcification in children less than 6 years of age should lead to suspicion of mass. In MRI, they are iso or hypointense in T1 images and iso or hyperintense in T2 images. On administration of gadolinium there is intense homogenous enhancement, a fact that is made use of in the search for spinal seeding.

Fig.5 shows a bright or hyperintense midline round mass near the hypothalamus compressing the aqueduct. The increase in intensity is due to fat content. The fat content that is so characteristic of a dermoid is brought out very well with MRI. In CT the dermoid is seen as a well circumscribed mass with a decreased attenuation value of 20 to 40 because of its fat content. Contrast enhancement is rarely seen in the wall. There is no enhancement within the dermoid. The sebaceous glands that are included in the cyst go on secreting so that the dermoid cyst grows and rupture is a possibility later in life. Rupture is seen as hyperintense droplets in the cisterns or in the ventricles.

Colloid cysts are epithelial lined collections of mucoid fluid that usually occur in the antero-superior third ventricle close to the foramen of Munro. Here they cause symptoms by obstructing CSF flow. Colloid cysts contain blood products, macrophages, cholesterol crystals and numerous metallic ions. The last mentioned ingredient gives the colloid cyst its classic hyperdensity (Fig.6). In MRI, there is a varied intensity, but commonly it is hyperintense on T1 images and hypo or iso-intense on T2 images. There is no calcification and no contrast enhancement.

In conclusion, let us not forget the granuloma or abscess that can occur anywhere in the brain and cause surrounding edema and hydrocephalus as in Fig.7.

CASE STUDY

MELIOIDOSIS IN A NEW BORN

*** *Anand Kalaskar***

Abstract: *Melioidosis is the name given to all diseases caused by the bacterium Burkholderia pseudomallei. Melioidosis incidence has been constantly increasing in the last decade, owing to the increasing number of immunocompromised in the community. Melioidosis is an infection which mainly affects adults but here we report melioidosis in a neonate, its clinical presentation, microbial diagnosis, possible mode of transmission and outcome.*

Keywords: *Melioidosis, Burkholderia pseudomallei*

Melioidosis is a tropical disease and prevails in parts of Southeast Asia, northern Australia, and Central and South America. In India cases of melioidosis have been reported from West Bengal, Tamil Nadu, Tripura, Maharashtra and Kerala.[1]

Case Report

A pre-term male baby (34 weeks), appropriate for gestational age, born by spontaneous vaginal delivery to a multiparous and immunized mother, developed respiratory distress soon after birth. Pre-natal history was normal and mother had no infections, medications or trauma during pregnancy. There was a history of spontaneous pre-mature rupture of membranes.

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The neonate's Apgar scores were 5 and 8 at 1 and 5 min, respectively, and he weighed 2.2 kg at birth. On examination, the child was febrile (38.6 ^{o} C), had grunting and was lethargic. His respiratory rate was 88/min, heart rate was 164 with a low pulse volume and poor peripheral perfusion. The child was provisionally diagnosed to have pneumonia with sepsis and was shifted to the neonatal intensive care unit (NICU) for respiratory support, pre-term care and monitoring.

Laboratory investigations revealed leukopenia (total leukocyte count 4500 /µl), normal blood glucose, electrolytes and liver and renal function tests. The micro erythrocyte sedimentation rate was normal. Chest X-ray revealed reticulogranular appearance with a patch of pneumonia in the left lung.

The neonate was given surfactant and put on ventilator soon after admission in the NICU. He was given intravenous fluids and ceftriaxone with gentamicin. Since the pulse volume was low, the child was given a normal saline bolus and started on dopamine infusion. On the second day, antibiotics were empirically changed to meropenem and vancomycin as the baby's condition was deteriorating. Fresh frozen plasma (30 ml) was given twice on the second and fifth days.

Blood culture in biphasic BHI (brain heart infusion) agar medium revealed motile, Gram negative bacilli with bipolar staining. Sub-culture on blood agar showed greyish white, smooth colonies with a slight metallic sheen and a distinctive musty odour. Growth on

MacConkey Agar revealed non-lactose fermenting colonies, which turned pink after 48 hours. Ashdown's medium, a selective medium showed 3-4 mm bluish purple colonies, characteristic of B. pseudomallei. The isolate was identified as B. pseudomallei based on bipolar appearance, growth on Ashdown's medium and characteristic biochemical reactions, including positive oxidase reaction, nitrate reduction, arginine dihydrolase activity and oxidation of glucose and lactose.

Antibiotic susceptibility testing was performed by disk diffusion test according to the Clinical Laboratory Standards Institute guidelines. The isolate was susceptible to ceftazidime, cotrimoxazole and meropenem, but resistant to gentamicin, amikacin, ciprofloxacin and polymyxin B (300 µg/disc). The unusual antibiotic susceptibility pattern was also suggestive of B. pseudomallei.

After two days, baby's condition improved. Dopamine was tapered and stopped and the baby was slowly weaned off from the ventilator on third day. Gradually baby was started on gavage feeds and on the 7th postnatal day baby was put on supervised breast feeding. Meropenem was continued for 14 days. On the 18th postnatal day, baby was discharged. At the time of discharge the baby was active, tolerating feeds and all the vital parameters were within normal limits.

After an interval of two weeks and later at the age of three months baby was reviewed in the out-patient department as part of follow up and was found that he was tolerating direct breast feeds well and gaining weight steadily, the neurological and developmental assessment was found to be normal for the corrected age of the child.

Investigations were conducted to determine the source of infection. B.pseudomallei was recovered from the vaginal swab of the mother.

Discussion

In India, melioidosis was reported first in a child from Maharashtra in 1990.[2] Recently, many cases of melioidosis have been reported from India among adults,[3,4] but there are only a few reports in children.[2,4] Neonatal cases have been reported from the United States of America, Thailand, Malaysia and United Kingdom and recently a case has been reported from Indian subcontinent.[5]

The infection is usually transmitted by inhalation of contaminated aerosols and ingestion of or direct contact of skin lesions with contaminated water or soil.[6] Perinatal transmission and transmission through breast milk have also been observed.[7] In humans, vertical transmission of this organism has been demonstrated.[8]

In our case, B. pseudomallei was recovered from the genital tract of the mother and so the newborn might have acquired the infection during birth.

This report of neonatal melioidosis is to alert the pediatricians and microbiologists to the possibility of this infection even among neonates.

Since the organism was recovered from the vagina, routine vaginal swab culture is necessary before all deliveries.

References

1. Baveja CP Pseudomonas, Burkholderia. In: Text Book of Microbiology, 2nd Edn, New Delhi, Arya publications 2006;p299.
2. Raghavan KR, Shenoi RP, Zaer F, Aiyer R, Ramamoorthy P, Mehta MN. Melioidosis in India. Indian Pediatr 1991;28:184-188.
3. Dhodapkar R, Sujatha S, Sivasangeetha K, Prasanth G, Parija SC. Burkholderia pseudomallei infection in a patient with diabetes presenting with multiple splenic abscesses and

abscess in the foot: A case report. Cases J 2008;1:224.

4. Vidyalakshmi K, Shrikala B, Bharathi B, Suchitra U. Melioidosis: An under-diagnosed entity in western coastal India: A clinico-microbiological analysis. Indian J Med Microbiol 2007;25:245-248.
5. Noyal MJC, Harish BN, Bhat V, Parija V. Neonatal melioidosis: A case report from India. Indian J Med Microbiol. 2009;27, 3: 260-263.
6. Pitt TL, Dance DA. Burkholderia spp. and related genera. In: Borriello SP, Murray PR, Funke G, editors. Topley and Wilson's Microbiology and Microbial infections. 10th Edn, London: Hodder Arnold; 2005; pp 1607-1648.
7. Ralph A, McBride J, Currie BJ. Transmission of Burkholderia pseudomallei via breast milk in northern Australia. Pediatr Infect Dis J 2004;23:1169-1171.
8. Abbink FC, Orendi JM, de Beaufort AJ. Mother-to-child transmission of Burkholderia pseudomallei. N Engl J Med 2001;344: 1171-1172.

CASE STUDY

INFANT PRESENTING WITH DIFFUSE SWELLING OF ARM – A DIAGNOSTIC DILEMMA

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**** Shanthi P*
***** Parthiban B*

Abstract: *Infant who presented with progressive swelling of arm with deforming lesions invited many differential diagnoses like skin tuberculosis, rhabdomyosarcoma and Kimura's disease, later diagnosed as Basidiobolomycosis.*

Keywords: *Infant, Subcutaneous swelling, Zgomycosis.*

Basidiomycosis is caused by an environmental saprophyte. Basidiobolus rananem belonging to zyconycosis can cause chronic subcutaneous infection which responds to potassium iodide, as well as fulconazole.

Case Report

Seven months old female infant was admitted with complaints of swelling of right upper limb of 3 months duration. The swelling was insidious in onset and slowly progressed to involve right side of chest. The child was evaluated by a private practitioner with fine needle aspiration cytology. (FNAC). Since granulomatous inflammation was reported, antituberculous therapy (ATT) was empirically started. As the swelling continued to be increase in size, the anxious parents brought the child to ICH for further management.

As the child's condition inspite of ATT was progressive, the child was referred to the Department of Pulmonology suspecting drug resistant TB. On examination, the infant was afebrile and vitals were stable. Diffuse swelling of the entire right upper limb extending to the right side of chest was present (Fig.1). The mid arm circumference was 25cm against the normal value (12.5 cm) for the age. The skin of the right upper limb showed minimal hyperpigmentation. Other systems were clinically normal. Except for microcytic hypochromic anemia, the blood counts and immunoglobulin profile were normal. FNAC from the swelling was not contributory. Gastric lavage for Zeihl Neilson stain and Mantoux were negative. Blood culture did not reveal any growth. Computerized tomogram of the right upper arm and chest revealed multiple lobulated hypodense lesions, especially in right axilla causing severe lymphedema of right arm (Fig.2). A provisional diagnosis of soft tissue tumour probably rhabdomyosarcoma was made and the infant was subjected to biopsy from the swelling in the arm.

Histopathological examination was initially reported as findings suggestive of Kimura's disease. However a more representative sample was requested. The second sample revealed dense infiltration with eosinophils forming

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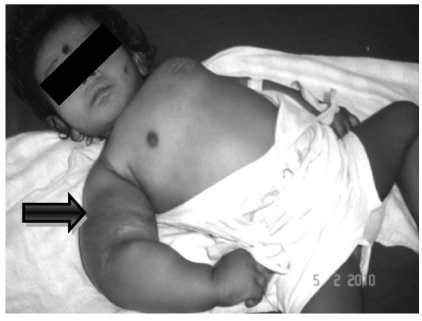

Fig.1. Infant with diffuse swelling of right upper limb with areas of hyper-pigmentation

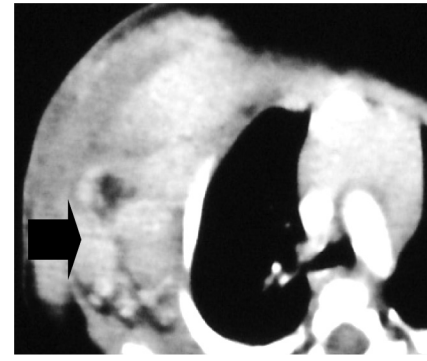

Fig.2. CT chest showing multiple lobulated subcutaneous swellings

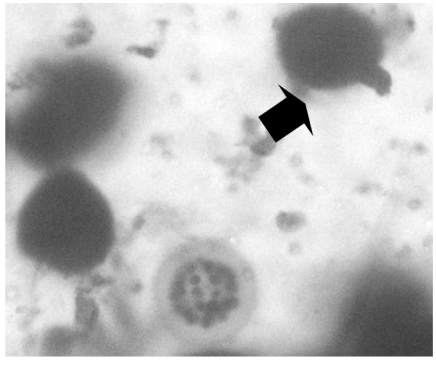

Fig.3. Zygospheres with lateral protuberances of gametogonial beaks

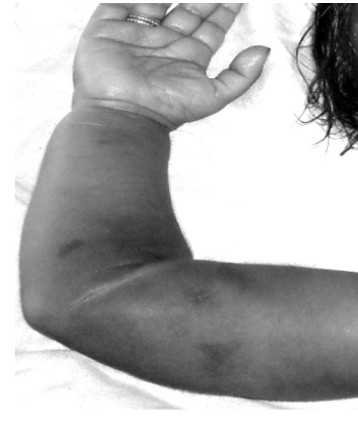

Fig.4. Significant reduction of lesion after treatment

microabcesses and numerous giant cells, foreign body granulomas and Periodic Acid Schiff (PAS) stain showing fungal hyphae-suggestive of subcutaneous zygomycosis (Fig.3). The culture in Sabourad's dextrose agar grew Basidiobolus species.

The infant was treated initially with oral fluconazole and subsequently saturated solution of potassium iodide (SSKI) as per the advice of dermatologist. After one month there was marked reduction in the size of the swelling and the right arm was near normal in size (Fig.4).

Discussion

The above case has been presented for its diagnostic difficulties and rarity in the infancy. Basidiobolomycosis is most commonly reported in children and this may be one of the youngest (7 months) cases reported so far.[3] The child had many differential diagnoses like skin tuberculosis, rhabdomyosarcoma and Kimura's disease before confirmation as a fungal infection. The host inflammatory reaction is composed mostly of mononuclear cells with abundant eosinophils and foreign body

granulomas which misled the practitioner for starting ATT.[4]

Of the two, the first HPE was misleading probably due to the dense eosinophilic infiltrates which are seen in both Kimura's and subcutaneous zygomycosis, but Kimura's disease demonstrates proliferation of lymphoid follicles and vascular endothelium which are not a feature in subcutaneous zygomycosis.[5] However further treatment was not attempted for Kimura's disease because of the second sample report.

Basidiobolomycosis is a form of zygomycosis caused by the fungus Basidiobolus ranarum an environmental saprophyte. Subcutaneous zygomycosis, the commonest clinical form of Basidiobolomycosis, is endemic in South India and the present case hails from Andhra Pradesh.[4] Basidiobolus is a true pathogen, not opportunistic one causing infections in immunocompetent host. The characteristic features of subcutaneous phycomycoses like lobulated swelling with rounded edges that can be raised up by inserting the fingers underneath could not be demonstrated in the present case as the overlying skin was stretched due to severe lymphedema.[6]

The portal of entry of the organism is unknown, but few cases following insect bites have been reported, which correlates with the subsequent detailed history given by the mother.[7, 8] Basidiobolomycosis is characterized not only by its granulomatous nature and formation of hard, non ulcerating subcutaneous masses in the limbs, chest, back, and buttock, but also known for its slow progression over weeks and months, as seen in this case.

Though the swelling was progressive, other systems were not involved (blood for fungal culture was negative). Systemic and gastrointestinal infection have been reported but the present case did not show any evidence of such involvement.[9,10] Although a reliable diagnosis of Basidiobolomycosis can be made from the histological characteristics, fungal culture is necessary for definite evidence as reported in our study.[9] The culture shows thick-walled zygospore with conical projection (tubular protuberances), a characteristic feature of Basidiobolus ranarum.[11]

Though saturated solution of potassium iodide (SSKI) is widely used in the tropics for the management of Basidiobolomycosis, recent studies favour the use of itraconozole or fluconazole.[12, 13] SSKI is given in the dose of 1g/day in three divided doses along with milk increasing the dose by 1-1.5g/wk upto 3-6g/day for 16 weeks in adults. [In children 33-50% of the adult dose given].

In conclusion, subcutaneous fungal infection should be kept in mind in the differential diagnosis of progressive soft tissue swelling with non caseating granulomas. Adequate sample for culture from the appropriate site culture in appropriate medium is essential to clinch the diagnosis which goes a long way in early diagnosis, avoiding unnecessary treatment.

The undersigned authors certify that the article is original, is not under consideration by any other journal and has not been previously published.

References

1. Mathew R, Kumaravel S, Kuruvilla S, Varghese RG. Successful treatment of extensive basidiobolomycosis with oral itraconazole in a child. Int J Dermatol. 2005.;44:572-575.
2. Debabrata B, Satyendra NC, Basidiobolomycosis successively treated with fluconazole. Ind J Dermatol 1996; 41: 134 -135.
3. Krishnan SG, Sentamilselvi G, Kamalam A, Das KA. Mycoses. Entomophthoromycosis in India—a 4-year study. Mycoses 1998; 41:55-58.

4. Sujatha S, Sheeladevi C, Khyriem AB, Parija SC, Thappa DM. Subcutaneous zygomycosis caused by Basidiobolus ranarum: A case report. Indian J Med Microbiol 2003; 21: 205-206.

5. Kimura T, Yoshimura S, Ishikawa E. On the unusual granulation combined with hyperplastic changes of lymphatic tissues. Trans Soc Pathol Jpn. 1948;37:179-180.

6. Prasad PV, Paul EK, George RV, Ambujam S, Viswanthan P. Subcutaneous phycomycosis in a child. Indian J Dermatol Venereol Leprol 2002;68:303-304.

7. Sugar AM. Agents of mucormycosis and related species. In: Mandell GL, Bennett JE, Dolin R, Eds. Mandell, Douglas and Bennetts's principles and practice of infectious diseases. 6th Edn. Philadelphia, USA: Elsevier; 2005; 2973-2984.

8. Rippon JW. The pathogenic fungi and the pathogenic actinomycetes. Medical Mycology: 3rd Edn. WB Saunders Philadelphia 1988; 681 – 693.

9. Guido EL van den Berk, L Arnold Noorduyn, Ruud J van Ketel, Jeannouel van Leeuwen et al A fatal pseudo-tumour: disseminated basidiobolomycosis. BMC Infect Dis 2006;6: 140.

10. Yusuf NW, Assaf HM, Rotowa NA. Invasive gastrointestinal Basidiobolus ranarum infection in an immunocompetent child. Pediatr Infect Dis J 2003; 22:281-282.

11. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000;13:236-301.

12. Richardson MD, Warnock DW 6th Edn. Entomophthoramycosis. Fungal infection: diagnosis and management. 3rd Ed. Blackwell Publishing 2003;pp293 - 297.

13. Sethuraman G, Susan K, Lenikumar J. Subcutaneous zygomycosis – Basidiobolomycosis. Indian J Dermatol 2001; 46:242 - 244.

CLIPPINGS

Bryan D. Upham, Cynthia J. Mollen, Richard J. Scarfone, Jeffrey Seiden, Amber Chew, Joseph J. Zorc.

Nebulized Budesonide Added to Standard Pediatric Emergency Department Treatment of Acute Asthma: A Randomized, Double-blind Trial, Academic Emergency Medicine. 2011; 18:665-673

The goal was to determine if adding inhaled budesonide to standard asthma therapy improves outcomes of pediatric patients presenting to the emergency department (ED) with acute asthma. The authors conducted a randomized, double-blind, placebo-controlled trial in a tertiary care, urban pediatric ED. Patients 2 to 18 years of age with moderate to severe acute asthma were randomized to receive either a single 2-mg dose of budesonide inhalation suspension (BUD) or normal sterile saline (NSS) placebo, added to albuterol, ipratropium bromide (IB), and systemic corticosteroids (SCS). The primary outcome was the difference in median asthma scores between treatment groups at 2 hours. Secondary outcomes included differences in vital signs and hospitalization rates. The study concluded that for children 2 to 18 years of age treated in the ED for acute asthma a single 2-mg dose of budesonide added to standard therapy did not improve asthma severity scores or other short-term ED-based outcomes.

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