Chapter 18

Endocrine and Metabolic Disorders

PSN Menon ❍ Anurag Bajpai ❍ Vandana Jain ❍ Rajni Sharma

GENERAL PRINCIPLES

Endocrine glands play a crucial role in the maintenance of body physiology and homeostasis. The hypothalamic–pituitary axis (HPA) regulates most endocrine organs, and growth, puberty, and mineral and water homeostasis.

Structure and Mechanism of Action

Hormones are derived from amino acids (e.g. peptide hormones, glycoproteins, thyroxine and epinephrine) or cholesterol (e.g. steroid hormones, vitamin D, adrenal and gonadal steroids). The peptide hormones (e.g. parathyroid hormone, growth hormone and insulin) do not bind to circulating binding proteins resulting in their rapid elimination with a short half-life. The steroid hormones, on the other hand, bind to circulating proteins, and have a longer half-life.

The peptide hormones act via receptors on the cell membrane. Binding of hormone to its receptor results in the release of second messengers that induce structural changes in intracellular proteins, culminating in the hormone effect. Steroids and thyroxine act on intracellular receptors. The hormone–receptor complex binds to the hormone response elements in the target gene, resulting in regulation of transcription.

Regulation and Metabolism

Hormone secretion is regulated by a feedback system that includes regulatory hormones, hormone levels, and their effects. The feedback operates at the level of the endocrine gland as well as the HPA. Plasma enzymes rapidly inactivate the peptide hormones, shortening their duration of action.

Activation of hormones (e.g. androgen to estrogen, testosterone to dihydrotestosterone and calcidiol to calcitriol) is vital for the action of some hormones. Inactivation of hormones at the site of their action prevents their excess effects (e.g. inactivation of cortisol by 11β-hydroxysteroid dehydrogenase prevents its action on mineralocorticoid receptor). Peripheral conversion also plays an important role in hormone function (e.g. conversion of thyroxine to triiodothyronine).

Assessment of Hormone Action

Endocrine assessment relies on the estimation of basal hormone levels (e.g. for thyroid disorders), and in some cases on their metabolites (e.g. urinary metabolites in adrenal disorders), or their effects (e.g. insulin-like growth factor-1 (IGF-1) levels in growth hormone (GH) deficiency and urinary osmolality for diabetes insipidus). Stimulation tests are often needed in deficiency states (e.g. GH deficiency and adrenal insufficiency) and suppression tests in excess states (e.g. GH excess and Cushing syndrome).

The feedback mechanism also guides the assessment of endocrine disorders. For example, thyroid-stimulating hormone is elevated in primary hypothyroidism. Conversely, low or low-normal pituitary hormone levels with hormone deficiency suggest hypothalamic or pituitary dysfunction.

DISORDERS OF THE PITUITARY GLAND

Physiology

The principal hormones produced by the anterior pituitary are growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL). These hormones regulate the actions of their target organs. Their secretion in turn is regulated by hypothalamic peptides—growth hormone-releasing hormone (GHRH), growth hormone-inhibiting hormone (GHIH or somatostatin), dopamine, gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH), and also by hormones produced by the target glands. Posterior pituitary hormones (arginine, vasopressin and oxytocin) are secreted by neurons in the hypothalamic nuclei.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) is caused by congenital malformations of central nervous system (CNS), genetic defects or acquired neurological insults **(Table 18.1)**.

Children with congenital GHD usually have normal anthropometry at birth. Growth retardation becomes apparent by the age of one year. These children have an immature round facies with prominent forehead and midfacial hypoplasia (deep set eyes and depressed nasal bridge) **(Fig. 18.1)**.

Micropenis and/or undescended testis and mild obesity are common clinical features. Body proportions are normal. The eruption of teeth is delayed. Bone age is delayed. Newborns and infants may occasionally present with hypoglycemic seizures due to severe GHD alone, and concomitant ACTH deficiency.

Resistance to GH action (GH insensitivity or Laron syndrome) presents with a similar phenotype with severe growth retardation and elevated baseline GH levels.

Approach to Diagnosis of Short Stature and GHD

Growth failure may be a part of any long-standing systemic illness. Chronic systemic disorders and nutritional deficiencies have predominant effect on weight, and height is less affected initially, therefore, body mass index (BMI) is usually low. On the contrary, endocrine causes (GHD and hypothyroidism) mainly affect height with a relatively normal BMI (*see* Chapter 2).

Evaluation

History: Perinatal events, birth weight and length give clues about the etiology. Birth asphyxia, breech presentation, neonatal hypoglycemia, micropenis and prolonged jaundice suggest the possibility of GHD. Features of chronic infections, chronic systemic disorders especially cardiopulmonary disorders, malabsorption and raised intracranial tension should be looked for in all short children. Presence of polyuria and polydipsia suggests diabetes insipidus, diabetes mellitus and/or renal tubular acidosis. Constipation, delayed milestones, lethargy and cold intolerance indicate hypothyroidism. Family history of short stature and/or delayed puberty suggests the possibility of familial short stature (FSS) or constitutional delay of growth and puberty (CDGP).

Table 18.1: Etiology of growth hormone deficiency

Congenital

Genetic defects

Isolated GH deficiency

- Defect in *GH1* gene
  - Type I: Autosomal recessive
  - Type II: Autosomal dominant
  - Type III: X-linked recessive
- Defect in *GHRHR* (GH-releasing hormone receptor) gene: Type IV

Multiple pituitary hormone deficiency

- Type I: Autosomal recessive
- Type II: X-linked recessive

Developmental defects: Pituitary aplasia or hypoplasia, holoprosencephaly, septo-optic dysplasia, anencephaly

Acquired

Tumors: Hypothalamic, pituitary or other intracranial tumors

Irradiation

Infections: Encephalitis, meningitis, tuberculosis, toxoplasmosis

Infiltration: Histiocytosis, hemochromatosis, sarcoidosis

Injury: Perinatal insult (breech), head injury, surgery

Vascular: Aneurysm, infarction

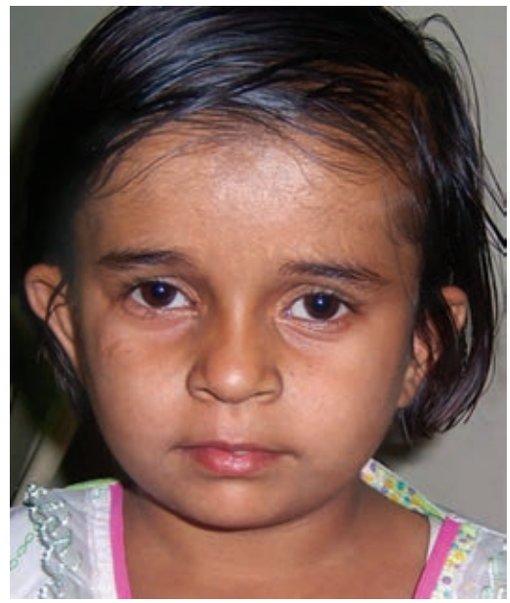

Fig. 18.1: A 6-year-old girl with short stature due to congenital growth hormone deficiency. Note the immature facies, midfacial hypoplasia and cherubic appearance

Examination: Anthropometry (weight, height, weight for height, BMI and head circumference) provides crucial inputs for the diagnosis. Body proportions help in identifying skeletal dysplasia—increased upper to lower segment (US:LS) ratio is observed in achondroplasia **(Fig. 18.2)** and rickets, while reduced US:LS ratio is seen in Morquio syndrome and spondyloepiphyseal dysplasia.

The clinician should also look for deformities and dysmorphism, and for specific phenotypes of an underlying etiology such as GHD, hypothyroidism (dull look, sallow complexion, dry skin, sparse hair, eyebrows and eyelashes, periorbital puffiness, and goiter in some cases), Turner syndrome (some girls may have webbed neck, cubitus valgus, low posterior hairline, etc.), and rickets. Pubertal staging (sexual maturity rating) is an essential part of evaluation.

Investigations: Laboratory evaluation of short stature is guided by the history and examination, and best done by a stepwise application of diagnostic tests to determine the etiology **(Fig. 18.3)**. Also *see* Chapter 2 **(Table 2.10)**.

Step 1: Rule out common treatable causes such as malnutrition, chronic systemic illnesses and recurrent infections, and estimate the bone age of the child.

Step 2: Rule out hypothyroidism, celiac disease and Turner syndrome.

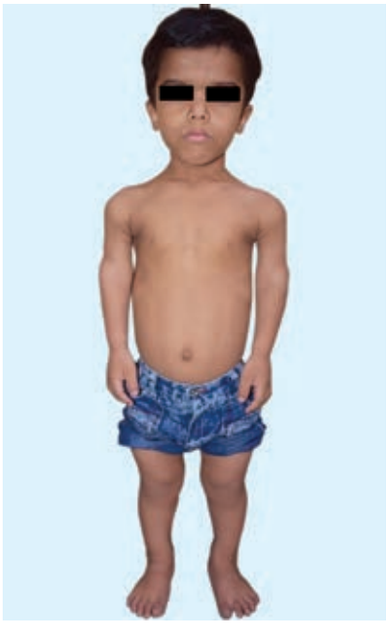

Fig. 18.2: Achondroplasia. Note the short stature with disproportionately short lower segment, short proximal limbs (rhizomelia) and characteristic facies (*Courtesy:* Dr. Neerja Gupta, AIIMS, Delhi)

Step 3: Evaluate for GH-IGF axis, after excluding common causes of short stature listed in steps 1 and 2. Measuring random or fasting blood GH level is not helpful as GH secretion is pulsatile. The diagnosis of GHD requires stimulation tests. GHD is suspected when the peak level of GH is less than 7 ng/mL following stimulation. The common provocative agents used are insulin, glucagon, clonidine or GHRH. IGF-1 and IGF binding protein-3 (IGFBP-3) are screening tests for the evaluation of GH-IGF axis, but are affected by malnutrition and systemic disorders. Low IGF-1 in the presence of high GH level suggests GH insensitivity (Laron syndrome).

GHD may be associated with other pituitary hormone deficiencies and investigations should be carried out to detect deficiency of these hormones, if GHD is present. Magnetic resonance imaging (MRI) of hypothalamic and pituitary region is essential to rule out developmental or acquired neurological lesions.

Management

General measures: Management of short stature involves correction of the underlying cause and provision of adequate nutrition. Nutritional deficiencies should be corrected, if present.

Specific therapy: Specific treatment is effective in restoring growth in hypothyroidism (thyroxine), celiac disease (gluten-free diet) and renal tubular acidosis (bicarbonate supplements). A short course of testosterone helps boys with CDGP.

Growth hormone: GH therapy results in increase in final height by 20–30 cm from pretreatment levels. The treatment is given as daily night-time injections (25–50 µg/kg/day) till epiphyses close. GH therapy is monitored by assessment of growth velocity and bone age. Lab parameters are not routinely used to monitor GH therapy. IGF-1 levels may be checked, if the response is suboptimal or the child is on a high dose. The treatment is expensive and all efforts should be made to ensure that treatment is given regularly. The role of GH is expanding with the increasing use in other disorders with short stature such as Turner syndrome, chronic renal failure, small for gestational age infants who fail to catch-up by 2 to 3 years of age, Russell-Silver syndrome, Prader-Willi syndrome and idiopathic short stature **(Table 18.2)**.

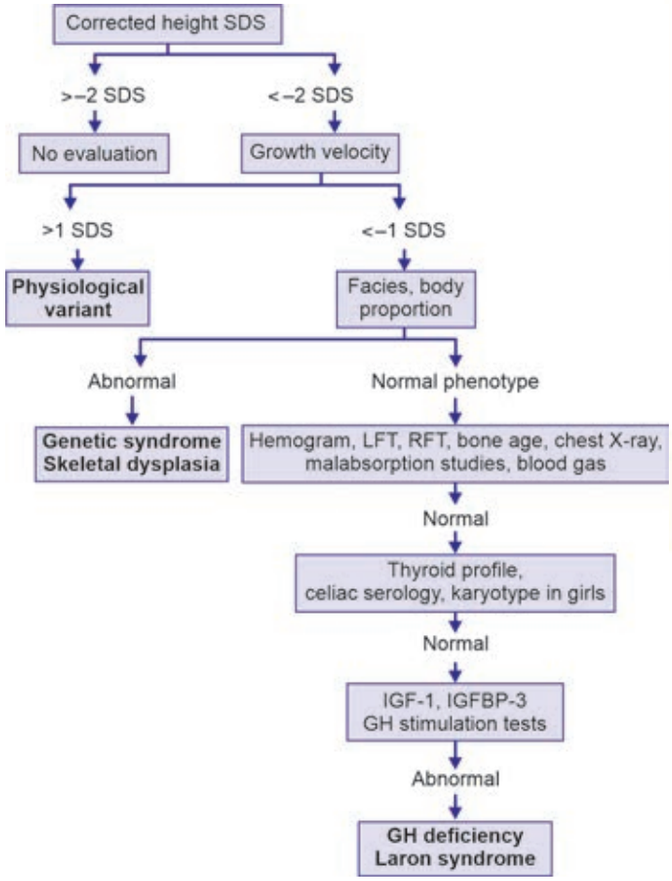

Fig. 18.3: Approach to a child with short stature. GH growth hormone; IGF-1 insulin-like growth factor-1; IGFBP-3 IGF binding protein-3; LFT liver function tests; RFT renal function tests; SDS standard deviation score

Growth Hormone Excess

Excess of GH during childhood may result in somatic overgrowth or gigantism. Increased GH secretion after

Table 18.2: Indications for growth hormone therapy

Growth hormone deficiency in children and adults
Turner syndrome
Chronic renal insufficiency
Prader-Willi syndrome
Small for gestational age who fail to catch-up in growth by 2–3 years of age
SHOX gene mutations and Leri-Weill dyschondrosteosis
Noonan syndrome
Idiopathic short stature

the fusion of skeletal epiphyses causes acromegaly (coarse features with prominent jaw, broad nose, large tongue, bushy eyebrows, thick skin and dorsal kyphosis). Headache and visual field defects (bitemporal hemianopia and enlargement of the blind spot) are common.

Diagnosis: IGF-1 is the best screening test for GH excess. Non-suppressible GH levels after a glucose challenge confirm the diagnosis. MRI of brain helps to confirm and determine the extent of the tumor.

Management: Resection of pituitary adenoma is the treatment of choice. Medical management involves the use of long-acting somatostatin analogs such as octreotide. The GH receptor antagonist, pegvisomant is also useful in treatment.

Diabetes Insipidus

Polyuria (urine output above 5 mL/kg/hr or 2 L/m^2/day) may result from increased solute load or impaired renal concentrating capacity (Table 18.3). Diabetes insipidus (DI) is an important cause of polyuria. DI presents with low urine osmolality (<600 mOsm/kg) in association with high plasma osmolality (>300 mOsm/kg or serum sodium >146 mEq/L). DI may be due to decreased production of AVP (central DI) or its action (nephrogenic DI). Dehydration is unusual unless there is an abnormality of thirst mechanism. Infants are at a high risk of developing hypernatremic dehydration.

Central DI: This is commonly associated with an intracranial pathology **(Table 18.3)**. Craniopharyngioma may present with DI, growth retardation and skull calcification. Germinoma located in the pituitary stalk may be missed on routine brain scans, and need repeat neuroimaging.

Nephrogenic DI: This results from inherited or acquired resistance to AVP. Congenital nephrogenic DI due to mutations in vasopressin receptor (V2) presents in infancy with failure to thrive, recurrent fever and dehydration. Hypokalemia and hypercalcemia are important causes of acquired nephrogenic DI.

Table 18.3: Causes of polyuria

Increased fluid load
Iatrogenic
Compulsive water drinking
Increased solute load
Osmotic diuresis: Diabetes mellitus, mannitol treatment
Salt loss: Adrenal insufficiency, diuretics, cerebral salt wasting, aldosterone resistance
Impaired urinary concentration
Deficiency or inefficient action of AVP (diabetes insipidus, DI)
• Central DI (neurogenic DI)
– Genetic defects
– Malformations: Septo-optic dysplasia, holoprosencephaly, anencephaly
– CNS insults: Head trauma, neurosurgery, infection, brain death
– Infiltrative disorders: Sarcoidosis, histiocytosis
– Space occupying lesions: Craniopharyngioma, germinoma
• Nephrogenic DI
– Genetic: X-linked (V2 receptor), AR and AD (aquaporin defect)
– Acquired: Hypokalemia, hypercalcemia, obstructive uropathy, nephrocalcinosis
Tubulopathy
• Renal tubular acidosis
• Bartter syndrome
• Gitelman syndrome

AD autosomal dominant; AVP arginine vasopressin; AR autosomal recessive; CNS central nervous system; DI diabetes insipidus

Evaluation

Urine output in excess of 2 L/m^2/day or 5 mL/kg/hr confirms polyuria **(Fig. 18.4)**.

Clinical: **Table 18.4** lists some pointers to the diagnosis of polyuria.

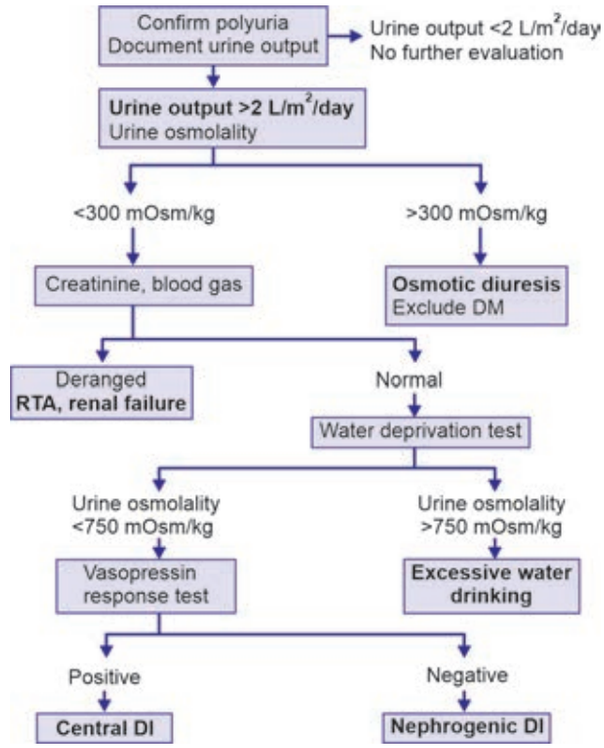

Fig. 18.4: Approach to a child with polyuria. DI diabetes insipidus; DM diabetes mellitus; RTA renal tubular acidosis

Table 18.4: Pointers to diagnosis of polyuria

Feature	*Diagnosis*
Cleft lip, cleft palate	Hypopituitarism
Metabolic bone	Renal tubular acidosis (RTA), renal disease failure
Growth failure	Nephrogenic diabetes insipidus, RTA, congenital adrenal hyperplasia, Bartter syndrome
Rash, ear discharge	Histiocytosis
Pigmentation	Adrenal insufficiency
Genital ambiguity	Congenital adrenal hyperplasia

Investigations: Initial investigations include testing urine glucose and early morning urine specific gravity and osmolality. Blood gases, urea, electrolytes, glucose, calcium and creatinine should be estimated. High plasma osmolality (>300 mOsm/kg or sodium >146 mEq/L) with low urine osmolality (<300 mOsm/kg and urine specific gravity <1.005) suggest the diagnosis of DI, which needs further classification on the basis of response to AVP. Patients with normal plasma osmolality and low urine osmolality (<300 mOsm/kg) should undergo water deprivation test. Urinary osmolality >300 mOsm/kg (specific gravity >1.010) excludes the possibility of complete DI.

MRI of the hypothalamic–pituitary region and anterior pituitary hormone evaluation should be done in central DI. Evaluation of nephrogenic DI includes renal imaging and estimation of serum electrolytes.

Water deprivation test: This test is indicated in children with polyuria with low urinary osmolality and normal plasma osmolality. The aim is to increase plasma osmolality above 300 mOsm/kg (or serum sodium above 146 mEq/L) to allow the opportunity for maximal renal concentration. Water deprivation test is not required in the presence of hypernatremia.

Water deprivation should be done on an inpatient basis as there is a risk for dehydration. It is started early in the morning. The child is weighed and target weight loss calculated (5% of total body weight). Body weight, urine output and urine and blood osmolality are monitored hourly. The test is stopped when urine osmolality increases above 750 mOsm/kg or specific gravity is more than 1.010, excluding DI. The test is also discontinued when serum sodium goes above 146 mEq/L (target achieved) or weight loss is more than 5% (risk of dehydration). Urine osmolality below 300 mOsm/kg in the presence of plasma osmolality above 300 mOsm/kg confirms DI and needs evaluation by a formal vasopressin test.

Vasopressin response test: This test helps to differentiate central DI from nephrogenic DI. Urine osmolality is measured one hour after a vasopressin injection (0.1 unit/kg). An increase in urine osmolality by more than 50% of baseline level is diagnostic of central DI while a smaller increase suggests nephrogenic DI.

Management

Central DI: Central DI is managed with a vasopressin analog. Desmopressin (DDAVP), a vasopressin analog, has high potency and prolonged duration of action. It can be given by intranasal (2.5–10 µg 12 hourly), sublingual or oral (50–200 µg 12 hourly) route, to be titrated according to urine output. Patients with idiopathic DI should be monitored for an evolving brain tumor. Desmopressin is avoided in infants, as it may lead to hyponatremia.

Nephrogenic DI: The combination of hydrochlorothiazide and amiloride reduces urine output by 40%. Addition of indomethacin to this regimen reduces urine output by 50–70%. This should be combined with salt restriction and reduction in solute load.

Suggested Reading

1. Desai MP, Parikh R. Growth hormone deficiency and insensitivity. In: Desai MP, Menon PSN, Bhatia V, Seth A, (eds). Pediatric Endocrine Disorders, 4th edition. Hyderabad; Universities Press India Ltd. 2022; 94–109.
2. Godbole T, Menon PSN. Polyuria, diabetes insipidus and syndrome of inappropriate secretion of ADH. In: Gupta P, Menon PSN, Ramji S, Lodha R (eds). PG Textbook of Pediatrics, 3rd edn. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2021, pp 2678–82.
3. Grimberg A, DiVall SA, Polychronakos C, et al. Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016;86:361–97.
4. Patel R, Bajpai A. Evaluation of short stature in children and adolescents. Indian J Pediatr 2021;88(12):1196–1202.

DISORDERS OF THE THYROID GLAND

Physiology

Biosynthesis of thyroid hormones involves interactions of iodine, tyrosine, thyroglobulin and the enzyme, thyroid peroxidase. These processes are regulated by TSH, which is under the direct control of TRH and feedback control of thyroxine. Thyroid hormones bind to intracellular receptors and activate transcription factors. Most triiodothyronine (T_3) in the circulation is produced by peripheral conversion of thyroxine (T_4) by the enzyme monodeiodinase.

Thyroid hormones play an active role in the regulation of somatic and intellectual growth, intermediary metabolism and thermoregulation. There is a critical phase in the early neonatal period for the effect of thyroid hormone on intellectual development. This underscores the need for early diagnosis and management of congenital hypothyroidism. TSH levels increase immediately after birth, resulting in increase in T_3 and T_4 levels, and reach their peak by 24 hours. Their levels fall to normal in the next few weeks. TSH levels should thus be estimated after 48 hours of birth during neonatal screening for congenital hypothyroidism.

Assessment of Thyroid Function

Thyroid function is assessed by serum TSH and T_4 and T3 levels. TSH is the most sensitive indicator of primary (thyroidal) hypothyroidism. Serum T_4 level is a better indicator of thyroid status than serum T_3 due to increased conversion of T_4 to T_3 during thyroid-depleted states. Considering the variability in the levels of circulating thyroxine-binding globulin (TBG), estimation of free thyroid hormones is superior to total hormone levels in the diagnosis of hypothyroidism. Low free T_4 (FT_4) and low or normal TSH suggest central hypothyroidism, while low FT_4 levels and high TSH indicate primary hypothyroidism. Persistent elevation of TSH in the presence of normal FT_4 suggests subclinical hypothyroidism. Elevated free T_3 (FT_3) and/or FT_4 and undetectable TSH levels imply a hyperthyroid state.

Competencies: **PE33.1; PE33.2; PE33.3**

Hypothyroidism

Hypothyroidism results from defects in the hypothalamic–pituitary axis (central hypothyroidism), or thyroid gland (primary hypothyroidism) **(Table 18.5)**. It may be congenital or acquired.

Congenital Hypothyroidism

Congenital hypothyroidism (CH) is the most common preventable cause of intellectual disability, with an approximate prevalence of 1 in 2,000 newborns. The reported incidence in India is much higher.

Etiology: Thyroid dysgenesis is the most common cause of CH in India (75% of all cases) as well as most parts of the world. The disorder encompasses a spectrum ranging from agenesis to ectopic thyroid. Biosynthetic defects include disorders affecting iodine transport, peroxidation, thyroglobulin synthesis and deiodination. Pendred syndrome, a disorder of the pendrin gene, is associated with decreased intracellular transport of iodine and deafness. Nongoitrous CH is known to be associated with *TSHR*, *PAX8* and *TSHB* gene defects.

Clinical features: Features of CH are nonspecific and often difficult to identify in the neonatal period. They become prominent as the child grows older. Unfortunately, the window period for intervention would have elapsed in most children by that time. This underscores the need for universal neonatal screening for CH. Clinical manifestations in infancy include hoarse cry, facial puffiness, umbilical hernia, hypotonia, mottling of skin and lethargy **(Fig. 18.5)**. Prolonged jaundice, constipation and unexplained hypothermia may also be present. Open posterior fontanel is an important indicator of CH **(Table 18.6)**.

Evaluation: History of a maternal thyroid disease or ingestion of antithyroid medications to mother should be probed. Family history of hypothyroidism suggests dyshormonogenesis. Residence in iodine deficient area may suggest the diagnosis of iodine deficiency. Goiter is common in disorders of thyroid hormone biosynthesis. Hypoglycemia, micropenis and midline facial defects suggest a hypothalamic–pituitary etiology.

Investigations: Initial investigations in a neonate include serum TSH and FT_4 levels. Those with high TSH and low FT_4 levels need evaluation by radionuclide scan and ultrasound of thyroid to confirm agenesis, ectopia or dysgenesis of thyroid. Children with undetectable thyroid on radionuclear scan but normal thyroid on ultrasound may have defects in iodine transport, TSH receptor abnormalities or transplacental passage of TSH blocking antibody. Children with low TSH and FT_4 levels should be worked up for pituitary-hypothalamic defects.

Table 18.5: Etiology of hypothyroidism

Primary (thyroid, >95%)
Autoimmune thyroiditis
Enzyme defects: Trapping, organification, thyroglobulin synthesis, deiodination
Iodine deficiency: Endemic goiter
Dysgenesis: Aplasia, dysplasia, ectopia
Thyroid injury: Surgery, radiation, infection
Goitrogens: Thiocyanates, thionamides, lithium, amiodarone
Transient causes: Maternal TSH receptor blocking antibody, iodine excess, maternal antithyroid drug
Secondary or tertiary (hypothalamus or pituitary, <5%)
Malformations: Septo-optic dysplasia, holoprosencephaly
Genetic defects
CNS insults: Trauma, surgery, radiation, infection
CNS tumors: Craniopharyngioma, germinoma
Peripheral (extremely rare)
Resistance to thyroxine

CNS central nervous system; TSH thyroid-stimulating hormone

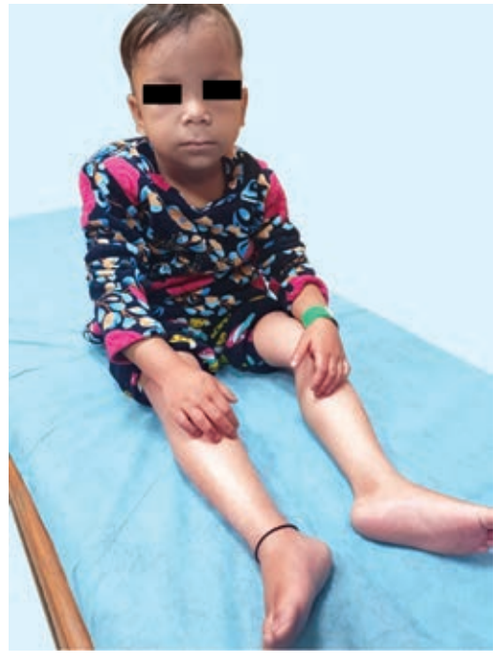

Fig. 18.5: A 7-year-old girl with untreated congenital hypothyroidism. Note the dull look, sallow complexion, puffiness around the eyes, sparse eyebrows, and 'edematous' lower limbs

Table 18.6: Clinical features of hypothyroidism

Congenital	*Acquired*
Open posterior fontanel	Myopathy and pseudohypertrophy of limb muscles
Umbilical hernia	Enlarged sella
Delayed neurodevelopment	Pseudotumor cerebri
Large tongue	
Common to both congenital and acquired forms	
Growth retardation	
Sallow edematous facies	Pallor
Delayed skeletal maturation	Hypothermia
Delayed dental development	Rough dry skin
Delayed puberty	Hypotonia
Constipation	Protuberant abdomen

Management: Thyroxine replacement is started immediately after diagnosis of CH. In central hypothyroidism, cortisol replacement should precede thyroid replacement as it may precipitate adrenal insufficiency. Thyroxine is initiated at a dose of 10–15 µg/kg/day. FT_4 and TSH levels are expected to normalize over one week and one month, respectively. FT_4 and TSH levels should be measured at each visit preferably every 2 months in the first year. Thyroxine dose should be adjusted to achieve FT_4 levels in the upper normal range for the age. Lifelong thyroxine replacement is required in most cases. In newborns with suspected transient CH, thyroxine replacement should be stopped for one month at the age of 3 years and retested. Treatment is not required, if follow-up thyroid functions are normal.

Outcome: Early diagnosis and treatment following neonatal screening has resulted in normal intellectual outcome. Outcome is, however, poor in children with CH who have been diagnosed beyond early infancy. Neurocognitive disability and short stature are common sequels.

Screening: Difficulty in early identification of CH and the disastrous consequences of delayed diagnosis have led to the practice of universal neonatal screening for CH. Screening programs use dried blood spot (DBS) sample collected at the postnatal age of 2 to 4 days. Cord blood is used, if postnatal DBS sample is not feasible. The most commonly used strategy screens first for TSH. TSH levels above 40 mU/L in the first week, 20 mU/L between 7 and 21 days and above 10 mU/L beyond 21 days suggest the need for treatment. Treatment should be started after sending a confirmatory venous sample for measurement of FT_4 and TSH. TSH-based screening has higher sensitivity compared to T_4-based approach. However, TSH-based approach may not identify central hypothyroidism. T_4-first approach can identify these children, but has the disadvantage of missing cases with compensated hypothyroidism.

Acquired Hypothyroidism

Etiology: Autoimmune thyroiditis (AIT), also called Hashimoto thyroiditis, is the most common cause of acquired hypothyroidism. Anti-thyroperoxidase (anti-TPO) antibodies are usually present. AIT may be associated with other autoimmune endocrinopathies (adrenal insufficiency, type 1 diabetes mellitus and hypoparathyroidism). Rarely, thyroid dysgenesis (ectopia) or an inborn error of thyroid hormone synthesis may become evident in older children and adolescents. Iodine deficiency and goitrogens are other causes of primary hypothyroidism in older children.

Clinical features: Features of acquired hypothyroidism are subtle compared to CH **(Table 18.6)**. Often short stature may be the only manifestation. Cold intolerance, lethargy, constipation, delayed dentition and poor school performance may be present. Delayed puberty is common; uncontrolled long-standing hypothyroidism may present with peripheral sexual precocity due to functioning ovarian cysts in girls. Children with Down syndrome, Turner syndrome, celiac disease and type 1 diabetes should be periodically screened for hypothyroidism even in the absence of symptoms.

Evaluation: Severe short stature and intellectual disability suggest missed CH. A firm and non-nodular goiter implies iodine deficiency or a disorder of thyroid hormone synthesis; firm nodular goiter indicates AIT. Children with central hypothyroidism should be evaluated for other pituitary hormone deficiencies and MRI of the hypothalamic–pituitary region. Anti-TPO antibodies should be estimated in acquired primary hypothyroidism.

Management: Thyroxine in a dose of 100 µg/m^2/day is recommended. In long-standing cases, treatment is started at 25–50% of the dose with a gradual build up every 3–4 weeks. Thyroxine is given on empty stomach in the morning, at least 30 minutes before breakfast, and at least 6 hours before iron or calcium supplements. Follow-up is done every 3 months during the first 2 years of therapy and six-monthly thereafter. The doses should be modified to maintain FT_4 and TSH levels in the normal range. Most children require lifelong therapy.

Subclinical Hypothyroidism

Mild elevations of TSH (below 10 mU/L) with normal FT_4 levels are frequently observed in children especially with obesity. In most cases, these findings reverse over a period of 3 to 6 months. Treatment should be considered in children with thyromegaly, presence of anti-TPO antibodies, or family history of hypothyroidism.

Goiter

Goiter refers to the enlargement of the thyroid gland.

Etiology: Goiter may be associated with diminished, normal or increased thyroid function. Thyroid enlargement may be diffuse or nodular, and may represent increase in size in response to compensatory TSH secretion (hypothyroidism), infiltration (AIT, neoplasms or hemochromatosis), or presence of TSH receptor stimulating antibodies (Graves disease) **(Table 18.7)**. Important causes of congenital goiter include maternal antithyroid medications, dyshormonogenesis and iodine deficiency. AIT is the most common cause in older children, followed by iodine deficiency.

Evaluation: Goiter may be diffuse or nodular. Investigations should include thyroid function tests. Anti-TPO antibodies should be measured to identify AIT. Presence of anti-TPO antibodies indicate acquired hypothyroidism. Ultrasound and fine needle aspiration cytology may help in diagnosis.

Management: Treatment should be directed to the cause (antithyroid medications in Graves' disease; thyroxine in hypothyroidism). Suppressive thyroxine therapy for euthyroid goiter is of limited benefit and is best avoided. Surgery is indicated, only if goiter is large enough to cause respiratory embarrassment.

Solitary Thyroid Nodule

Identification of solitary thyroid nodule in children should alert to the possibility of thyroid malignancy. A well-circumscribed, cystic nodule is usually benign. Pointers towards malignancy include a firm nodule with limited

Table 18.7: Causes of thyromegaly in children

Diffuse

- Thyroiditis
  - Autoimmune thyroiditis: Hashimoto thyroiditis, Graves disease
  - De Quervain's subacute thyroiditis, Reidel thyroiditis
- Environmental goitrogens: Iodine deficiency (endemic goiter), dietary goitrogens
- Dyshormonogenesis
  - Pendred syndrome
  - Mutations in genes encoding thyroid peroxidase, thyroglobulin
- Resistance to thyroid hormones
- Idiopathic

Nodular

- Multinodular goiter (due to long-standing simple goiter or autoimmune thyroiditis or dyshormonogenesis)
- Solitary nodule
  - Hyperfunctioning (toxic) nodule
  - Hypofunctioning (cold) nodule
    - ◊ Follicular adenoma
    - ◊ Cyst, abscess
    - ◊ Thyroid cancer

mobility and associated lymph node enlargement. Children with solitary thyroid nodule should undergo ultrasound-guided fine needle aspiration cytology to exclude an underlying malignancy.

Competencies: **PE13.8; PE13.9**

Iodine Deficiency Disorders

The term 'iodine deficiency disorders (IDD)' refers to the wide-spectrum of effects of iodine deficiency on growth and development. These include endemic goiter, endemic cretinism and impaired mental function in children and adults with goiter and increased rates of stillbirths and perinatal and infant mortality. Correcting iodine deficiency can prevent these conditions. Endemic goiter is present when the prevalence of goiter in a defined population exceeds 5%. Endemic goiter is graded by the method suggested by World Health Organization (WHO) **(Table 18.8)**. Screening of estimates of iodine intake are usually derived from 24-hour urinary iodine excretion values or urinary iodine concentration expressed in relation to creatinine concentration as given in **Table 18.9**.

Table 18.8: Estimation of thyroid size by palpation

Stage 0	No goiter
Stage 1A	Goiter detectable only by palpation and not visible even when the neck is fully extended
Stage 1B	Goiter palpable but visible only when the neck is fully extended (this stage also includes nodular glands, even if not goitrous)
Stage 2	Goiter visible when the neck is in normal position; palpation not needed for diagnosis
Stage 3	Very large goiter, which can be recognized at a considerable distance

Table 18.9: Severity of iodine deficiency in a defined area

Iodine deficiency	*None*	*Mild*	*Moderate*	*Severe*
Median urine iodine, µg/L	>100	50–99	20–49	<20
Goiter prevalence	<5%	5–20%	20–30%	>30%
Neonatal TSH, >5 mU/L whole blood	<3%	3–20%	20–40%	>40%
Cretinism	None	None	Present	Present

WHO. Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers. 3rd edn. 2007.

Endemic goiter: This does not differ from nontoxic diffuse sporadic goiter and the diagnosis is established by epidemiologic criteria. Usually, TSH is elevated with low T_4 and T_3 levels.

Endemic cretinism: This is associated with endemic goiter and severe iodine deficiency. Two types of endemic cretinism are described. Neurological cretinism is characterized by deaf–mutism, squint, proximal spasticity and rigidity and severe intellectual disability. Myxedematous cretinism is characterized by less severe intellectual impairment, severe short stature, coarse facial features and myxedema. Iodine deficiency is also associated with poor school performance in children.

Prevention and control: Iodine deficiency disorders are best prevented as treatment is usually ineffective. Iodinated salt or iodized oil are highly efficacious in preventing iodine deficiency. Treatment of endemic cretinism may eliminate signs of hypothyroidism but neuromotor and intellectual deficiency are irreversible. Surgical removal of large goiters is indicated only to relieve airway obstruction or for cosmetic reasons.

The 'National Goiter Control Programme' of the Ministry of Health and Family Welfare in India began in 1962 with establishment of salt iodination plants. The program is directed towards control of iodine deficiency disorders and ensuring that only iodized salt is used in India. The recommended daily intake of iodine is 40–120 µg for children up to the age of 10 years, 150 µg for older children and adults and an additional 25 µg and 50 µg during pregnancy and lactation, respectively. Based on an assumption of a mean intake of salt of 5 g/day, the recommended level of iodination is one part of iodine in 25,000 to 50,000 parts of salt.

Hyperthyroidism

Hyperthyroidism is relatively uncommon in children. It is most commonly seen in young girls, caused by Graves disease **(Table 18.10)**.

Clinical features: Hyperthyroidism is suspected in children with weight loss with increased appetite, tremors, diarrhea, warm extremities, increased sweating and anxiety. Inability to concentrate, personality changes, mood instability and poor school performance are common. Examination reveals firm homogeneous goiter.

Eye signs are relatively uncommon compared to adults and are related to sympathetic overactivity (lid lag, ophthalmoplegia, absence of wrinkling) or autoimmune

Table 18.10: Etiology of hyperthyroidism

Infancy
• Transplacental passage of thyroid antibodies
• TSH receptor activating mutation
After infancy
• Graves disease (TSH receptor stimulating antibody)
• Toxic thyroid nodule, toxic multinodular goiter
• Pituitary resistance to T3
Transient:
• Release of preformed thyroid hormone in viral or bacterial infections of the thyroid (acute or subacute thyroiditis)
• During early phase of Hashimoto thyroiditis (Hashitoxicosis)
• Iatrogenic

infiltration (chemosis or proptosis). Tachycardia, cardiac arrhythmia and high output cardiac failure may occur.

Diagnosis: The diagnosis is confirmed by the demonstration of elevated serum FT_4 and FT_3 levels. The presence of goiter, infiltrative eye signs and hyperthyroidism are suggestive of Graves disease. Absence of goiter should raise the possibility of transient hyperthyroidism as part of AIT. Differentiating thyrotoxicosis from thyroiditis is important, as antithyroid drugs are not required in children with AIT who may progress to hypothyroidism. Diffusely increased radiotracer uptake is suggestive of Graves disease while reduced uptake is characteristic of AIT.

Management: Treatment should be started with methimazole (0.5–1.0 mg/kg/day) in 3–4 divided doses. Propylthiouracil is contraindicated in children due to hepatotoxicity. Beta-blockers (propranolol 2 mg/kg/day in 2–3 divided doses) are effective in ameliorating sympathetic symptoms. Prednisolone (1–2 mg/kg/day) inhibits peripheral conversion of T_4 to T_3 and is useful in treatment of hyperthyroid storm. Surgery and radioiodine ablation should be considered in patients with failure of medical management or relapse after stopping medication. Patients with large or toxic nodular goiter require partial or total thyroidectomy. Radioiodine (^{131}I) is now increasingly used in the management of childhood Graves disease.

Neonatal Hyperthyroidism

One percent of babies born to mothers with Graves disease show fetal thyrotoxicosis and cardiac failure. This usually occurs within the first week of life but may be delayed, if mother is on antithyroid medications or has concomitant TSH receptor blocking antibody. Treatment should include antithyroid drugs, propranolol and corticosteroids.

Suggested Reading

1. Desai MP, Sharma R, Riaz I, et al. Newborn screening guidelines for congenital hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)-Part 1: Screening and confirmation of diagnosis. Indian J Pediatr 2018;85:440–47.
2. Kahaly GJ, Bartalena L, Hegedüs L, et al. European Thyroid Association guideline for the management of Graves' hyperthyroidism. Eur Thyroid J 2018;7:167–86.
3. Sudhanshu S, Riaz I, Sharma R, et al. Newborn screening guidelines for congenital hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)-Part II: Imaging, treatment and follow-up. Indian J Pediatr 2018;85:448–53.

Competency: **PE13.12**

DISORDERS OF BONE AND MINERAL METABOLISM

Physiology

Serum calcium, especially free ionized calcium, plays an important role in cell membrane stability, myocardial function and neurotransmission. Calcium homeostasis involves interaction of gastrointestinal absorption, bone resorption and renal excretion. Parathyroid hormone (PTH), vitamin D and calcitonin are the key regulators of calcium metabolism (*see* Chapter 8; **Fig. 8.3**). These help to maintain serum total calcium in the range of 8–10 mg/dL and ionized calcium in 4.6–5.1 mg/dL.

The calcium-sensing receptors present in the parathyroid gland and kidney sense the extracellular calcium levels. Low serum calcium reduces the activity of these receptors leading to increased PTH secretion from the parathyroid glands and decreased calcium excretion from the kidneys. PTH increases serum calcium by three mechanisms:

1. Stimulates osteoclastic bone resorption and release of calcium from bone.
2. Stimulates the activity of renal 1α-hydroxylase enzyme with increased calcitriol production.
3. Inhibits renal calcium excretion from distal tubules.

At the same time, PTH increases phosphate excretion from the proximal renal tubules leading to low serum phosphate levels.

Calcitriol (1,25-dihydroxyvitamin D) is the active form of vitamin D (*see* Chapter 8: Vitamin D metabolism). It increases intestinal calcium and phosphate absorption. Vitamin D is activated first in the liver (25-hydroxylation) and then kidney (1α-hydroxylation) to produce calcitriol.

The diagnosis and management of calcium and magnesium disorders are also discussed in Chapter 6.

Hypocalcemia

Hypocalcemia is defined as serum total calcium <8.5 mg/dL) and ionic calcium <4.4 mg/dL (<1.1 mmol/L).

Clinical Features

In infancy, hypocalcemia is characterized by subtle clinical features like lethargy, jitteriness and poor feeding. Seizures are common and hypocalcemia is one of the most common biochemical abnormalities associated with neonatal seizures.

Beyond infancy, the commonest presentation is tetany. This is most commonly observed in hands (adduction of thumbs along with extension of interphalangeal joints) and feet (flexion and internal rotation of lower limbs) resulting in carpopedal spasm. Latent tetany is detected by tapping the facial nerve at the angle of jaw resulting in contraction of facial muscles (Chvostek sign). Inflating blood pressure

cuff above the systolic blood pressure for more than 5 minutes triggers spasm of the hand muscles (Trousseau sign). Hypocalcemia should be considered in children with seizures, dilated cardiomyopathy and stridor (due to laryngospasm).

The diagnosis is supported by the demonstration of prolonged QT interval on ECG, as suggested by QTc more than 0.45 seconds, where $QT_c = Q_oT \div \sqrt{RR}$

(Q_oT = Interval from beginning of Q wave to beginning of T wave; RR = RR interval)

Etiology

Hypocalcemia is most commonly caused by deficiency or inefficient action of PTH or vitamin D and occasionally by chelation of calcium (*see* **Table 6.9**).

PTH related: Decreased production of PTH (hypoparathyroidism) and inefficient PTH action (pseudohypoparathyroidism) caused by receptor dysfunction are important causes of chronic hypocalcemia. These disorders are characterized by low serum calcium and high serum phosphate levels due to impaired phosphaturic action of PTH. Autoimmune hypoparathyroidism is the most common cause of acquired hypoparathyroidism in older children and is frequently associated with autoimmune polyendocrinopathy (APS type 1).

DiGeorge syndrome is an important cause of congenital hypoparathyroidism and is characterized by abnormal development of third and fourth pharyngeal pouches due to deletion of a part of chromosome 22q. Activating mutation of calcium-sensing receptor (CaSR) is associated with low PTH secretion, low serum calcium levels and paradoxically increased urinary calcium excretion (familial hypercalciuric hypocalcemia).

Maternal hyperparathyroidism may result in chronic fetal hypercalcemia, suppression of fetal parathyroid function and manifest as neonatal hypoparathyroidism after birth.

Hypomagnesemia should be excluded in children with refractory hypocalcemia.

PTH resistance (pseudohypoparathyroidism, PHP): This is caused by an inactivating mutation in the gene encoding for stimulatory subunit of G protein (Gsα). This presents with clinical features of hypoparathyroidism but elevated PTH levels. PHP may be associated with the phenotype of Albright hereditary osteodystrophy (AHO) such as round facies, brachydactyly, short stature, obesity, short fourth and fifth metacarpals (brachymetacarpia), osteodystrophy and heterotopic ossification.

Vitamin D related: Vitamin D deficiency (lack of sunlight, nutritional and malabsorption), increased inactivation of vitamin D (antiepileptic drugs), decreased 1α-hydroxylase action (renal failure and vitamin D-dependent rickets, VDDR type I), and calcitriol resistance (VDDR type II) are associated with hypocalcemia. In vitamin D related disorders, low serum calcium stimulates parathyroid glands to release PTH. Compensatory increase in PTH may raise the serum calcium levels to normal range when vitamin D deficiency is not severe. High PTH levels may also result in low serum phosphate levels due to increased renal phosphate excretion.

Nutritional vitamin D deficiency is the most common cause of hypocalcemia in children and is associated with clinical and biochemical findings of rickets (*see* Chapter 8). Maternal vitamin D deficiency results in reduced calcium and vitamin D stores in newborns at birth. As breastmilk is also low in vitamin D in mothers with vitamin D deficiency, it is recommended to supplement breastfed infants with vitamin D. Vitamin D-dependent rickets type I and II present with early onset severe hypocalcemia and rickets.

Increased chelation: High serum phosphate levels due to renal failure or release of intracellular phosphate (due to hemolysis, tumor lysis or rhabdomyolysis) bind to serum calcium and result in extracellular deposition of calcium and low serum levels. Cow milk and certain commercial formulations have high phosphate loads that can chelate calcium and lead to hypocalcemia in the newborn period. Metabolic or respiratory alkalosis increases albumin binding of calcium resulting in low ionized calcium and features of hypocalcemia.

Evaluation

Clinical: Detailed history of the age of onset, presenting features, frequency of episodes of hypocalcemia and family history should be obtained. Neonates should be screened for prematurity, birth asphyxia, maternal hyperparathyroidism and initiation of top feeds. Congenital heart disease, towards recurrent infections and abnormal facies may point towards DiGeorge syndrome.

Investigations: Initial evaluation should include serum phosphate levels, renal and liver function tests and serum alkaline phosphatase **(Table 18.11)**. Phosphate regulation is dependent on PTH, and inefficient PTH action results in hyperphosphatemia. Hypocalcemia due to decreased vitamin D action is associated with secondary hyperparathyroidism and low phosphate levels. Thus hypocalcemia with hyperphosphatemia in the absence of phosphate load (exogenous or tissue lysis) and

Table 18.11: Laboratory features of common causes of hypocalcemia

Disorder	*Phosphate*	*25-hydroxyvitamin D*	*Parathyroid hormone (PTH)*
Vitamin D deficiency	Low, normal	Low	High
Renal failure	High	Normal	High
Hypoparathyroidism	High	Normal	Low
Pseudohypoparathyroidism	High	Normal	High
Hypomagnesemia	Low, normal	Normal	Low

normal renal function suggests parathyroid insufficiency. Hypomagnesemia should be considered in patients with refractory hypocalcemia and normal or low phosphate levels. 25-hydroxyvitamin D levels should be measured in children with rickets to identify vitamin D deficiency.

Management

In children with severe hypocalcemia, parenteral calcium should be administered (2 mL/kg of calcium gluconate, 9 mg calcium per mL) intravenously over 5–10 min after obtaining a blood sample for calcium. Care should be taken to administer the drug slowly under cardiac monitoring (to prevent cardiac arrhythmias) and avoid extravasation (to prevent skin necrosis).

Parenteral calcium should be started at a dose of 80 mg/kg/day and should be gradually tapered over 2 days. The management of nutritional and refractory rickets is given in Chapter 8.

Hypercalcemia

Hypercalcemia (serum calcium >11 mg/dL) is rare in children. Its causes include increased bone resorption (hyperparathyroidism, malignancy and immobilization) or excessive vitamin D action (iatrogenic excess and increased 1α-hydroxylase activity).

Etiology: Hyperparathyroidism is the commonest cause of chronic hypercalcemia in children. Homozygous inactivating mutations of the calcium-sensing receptor present with severe neonatal hyperparathyroidism and hypocalciuria. Parathyroid adenoma is rare before the age of 10 years, but may be a feature of inherited endocrine disorders like multiple endocrine neoplasia type 1 (MEN type 1) especially with a positive family history. Rarely, hypercalcemia may be associated with other conditions, e.g. Williams syndrome (supravalvular aortic stenosis and abnormal facies) or hypophosphatasia (inactivating mutation of alkaline phosphatase). Vitamin D-related hypercalcemia occurs in children receiving parental vitamin D or inadvertently high doses of oral vitamin D. Increased 1α-hydroxylase activity may occur in patients with granulomatous diseases (tuberculosis and sarcoidosis) or fat necrosis.

Clinical features: These are nonspecific, including muscular weakness, anorexia, nausea, vomiting, constipation, polydipsia and polyuria. Ectopic calcification in the kidney, basal ganglia and skin are common. Bony deformities and pathological fractures may be present. Infants present with failure to thrive, poor feeding, hypotonia and seizures.

Diagnosis: Serum total and ionized calcium levels are elevated with low levels of phosphate. Hyperparathyroidism is associated with elevated levels of PTH while the levels are low in vitamin D toxicity or malignancy.

Management: Treatment of acute hypercalcemia involves high fluid intake followed by diuresis (furosemide 1 mg/kg). Bisphosphonates are drugs which block osteoclastic bone resorption and decrease serum calcium. They are indicated, if there is no response to these measures. Hemodialysis may be required in refractory cases. Short course of glucocorticoids (prednisolone 2 mg/kg/day for 3 weeks) is indicated in children with iatrogenic vitamin D excess or increased 1α-hydroxylase action (fat necrosis or sarcoidosis).

Suggested Reading

1. Brandi ML, Bilezikian JP, Shoback D, et al. Management of hypoparathyroidism: Summary statement and guidelines. J Clin Endocrinol Metab. 2016;101:2273–83.
2. Chinoy A, Mughal Z, Padidela R. Hypocalcemia, hypercalcemia and disorders of the parathyroid glands. In: Desai MP, Menon PSN, Bhatia V, Seth A, eds. Pediatric Endocrine Disorders, 4th edn. Hyderabad: Universities Press (India) 2022;473–84.
3. Davies JH, Shaw NJ. Investigation and management of hypercalcemia in children. Arch Dis Child 2012;97:533–38.

DISORDERS OF ADRENAL GLANDS

Physiology

Adrenal cortex produces three important groups of hormones—glucocorticoids, mineralocorticoids and androgens. The process of steroidogenesis involves conversion of cholesterol to steroid hormones through a series of enzymatic processes **(Fig. 18.6)**. Cholesterol is transferred into the mitochondria in a process mediated by the steroidogenic acute regulatory protein (StAR), an ACTH- dependent protein.

Cortisol, the major glucocorticoid hormone has an important role in intermediary metabolism causing increased blood glucose levels and enhanced catabolism of proteins and lipids.

Aldosterone acts on distal renal tubules and collecting ducts of kidneys to promote sodium and fluid reabsorption. Aldosterone deficiency causes urinary salt-wasting resulting in salt-wasting crisis (hyponatremia, hyperkalemia and metabolic acidosis).

Adrenal androgens are necessary for the development of pubic and axillary hair in girls.

Regulation of adrenal cortical hormone synthesis: ACTH is the major regulator of glucocorticoid and androgen synthesis. Aldosterone synthesis is regulated by intravascular volume, renin–angiotensin system and serum potassium levels. ACTH secretion is stimulated by hypothalamic CRH and suppressed by cortisol.

Adrenocortical Hyperfunction—Cushing Syndrome

The most common disorder of adrenocortical hyperfunction is Cushing syndrome. The term Cushing disease refers to hypercortisolism caused by an ACTH-producing pituitary tumor. Classic features of Cushing syndrome such as central obesity, striae, moon facies and buffalo hump are less common in children **(Fig. 18.7)**. Growth failure and obesity are more common; other features include hypertension, hirsutism, delayed puberty, behavioral problems, bone pain and muscle weakness.

Etiology: Cushing syndrome results from increased endogenous production or exogenous administration **(Table 18.12)**. Prolonged steroid treatment is the commonest

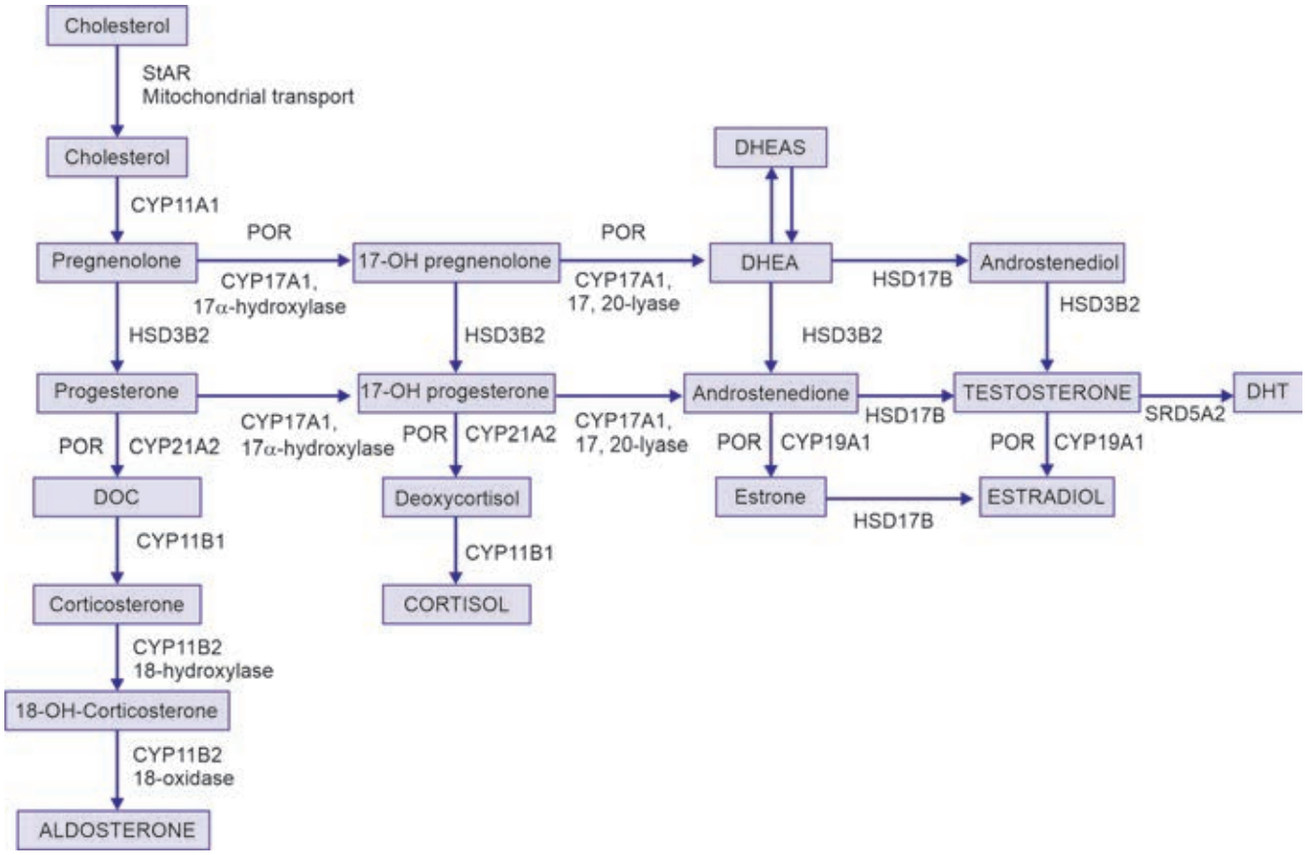

Fig. 18.6: Pathways of steroid biosynthesis. The key enzymes mediating synthesis of principal steroids are named according to their site of action and the nomenclature of cytochrome P450 enzymes. StAR steroidogenic acute regulatory protein; DOC deoxycorticosterone; DHEA dehydroepiandrosterone; DHEAS–DHEA sulfate; DHT dihydrotestosterone. The enzyme nomenclature: CYP11A1: P450 side chain cleavage enzyme, P450scc or 20,22-desmolase; HSD3B2: 3β-hydroxysteroid dehydrogenase type 2; CYP17A1: 17α-hydroxylase or17,20 lyase; CYP21A2: 21-hydroxylase; CYP11B1: 11β-hydroxylase; CYP11B2: This has 3 actions—11β-hydroxylase, 18-hydroxylase and 18-oxidase; POR: P450 oxidoreductase; CYP19A1: Aromatase; HSD17B: 17β-hydroxysteroid dehydrogenase; SRD5A2: 5α-reductase type 2

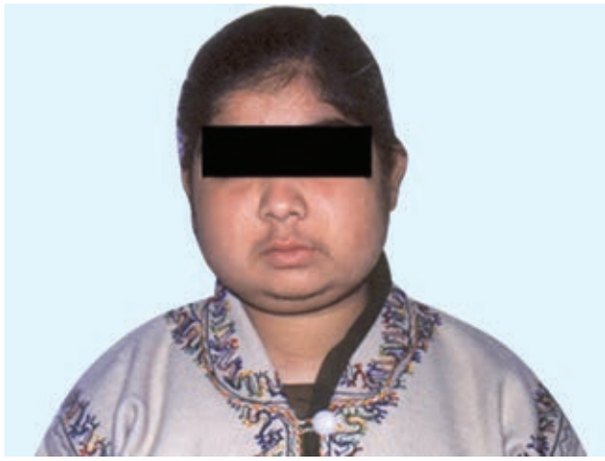

Fig. 18.7: Cushing disease secondary to pituitary adenoma. Note the moon face and hypertrichosis over forehead and upper lip

cause of childhood Cushing syndrome. Adrenal pathology is more likely in young children, while pituitary causes are more likely in older children and adolescents. Ectopic ACTH production is rare in children.

Evaluation: Investigations are directed towards confirming the diagnosis of Cushing syndrome and finding the etiology.

Table 18.12: Etiology of Cushing syndrome

ACTH-dependent causes
• *Hypothalamic lesions:* Increased corticotropin production
• *Pituitary lesions:* Microadenoma, macroadenoma
• *Ectopic lesions:* Neuroblastoma, carcinoid tumor, Wilms tumor
ACTH-independent causes
• Adrenal carcinoma, adenoma
• Pigmented nodular hyperplasia
• McCune-Albright syndrome
Exogenous administration
• Glucocorticoids
• ACTH

ACTH adrenocorticotropic hormone

Commonly used screening tests include assessment of diurnal cortisol rhythm, overnight single midnight dose of dexamethasone 0.03 mg/kg; maximum dose 1 mg) and 24-hour urine free cortisol **(Table 18.13)**. The diagnosis is confirmed with low dose dexamethasone suppression test (serum cortisol after dexamethasone 5 µg/kg every 6 hours for two days).

The most important part of evaluation of a child with Cushing syndrome is to differentiate ACTH-dependent

Table 18.13: Screening tests for Cushing syndrome

Test	*Sensitivity*	*Specificity*	*Cut-off level*	*Comments*
Morning cortisol	Low	Low	>10 µg/dL	Not recommended
Overnight dexamethasone suppression test	High	Low	>1.8 µg/dL	Screening test
Urine free cortisol	High	High	>75 µg/m²/day	Screening test*
Low dose dexamethasone suppression test	High	High	>1.8 µg/dL	Diagnostic test

*Diagnostic of Cushing syndrome, if level is greater than 3 to 4 times the normal range

Table 18.14: Laboratory findings in common causes of Cushing syndrome

Disorder	*Urinary free cortisol*	*High dose dexamethasone suppression test*	*Adrenocorticotropic hormone (ACTH)*
Adrenal lesion	High	Not suppressed	Low
Pituitary lesion			
Microadenoma	High	Suppressed	High
Macroadenoma	High	Not suppressed	High
Ectopic ACTH	High	Not suppressed	High
Exogenous	Low	Not suppressed	Low

causes from autonomous adrenal steroid production (Table 18.14). ACTH levels differentiate ACTH- independent (ACTH levels <5 pg/mL) from ACTH-dependent conditions (ACTH levels >15 pg/mL). Ectopic ACTH production should be suspected in children with extremely high ACTH levels (>100 pg/mL). High dose dexamethasone suppression test is based on the principle that high doses of dexamethasone suppress ACTH production in individuals with pituitary lesions but not in those with ectopic ACTH production.

Adrenal tumors in children are usually large and identifiable on ultrasound. Magnetic resonance imaging of the hypothalamic–pituitary region should be performed in children with ACTH-dependent Cushing syndrome. Inferior petrosal sinus sampling can identify the source of ACTH production and should be performed in children with ACTH-dependent Cushing syndrome with normal neuroimaging.

Management: Resection of adrenal lesion is recommended for adrenal adenoma and carcinoma. Prolonged cortisol excess causes suppression of the normal contralateral adrenal gland. This mandates close monitoring for adrenal insufficiency in the perioperative period. Adrenal carcinoma is highly malignant and has a high rate of recurrence. Pigmented nodular hyperplasia should be treated with bilateral adrenalectomy. Trans-sphenoidal resection of pituitary adenoma is recommended for Cushing disease.

In refractory cases, medical management of Cushing syndrome with inhibitors of steroidogenesis (ketoconazole, aminoglutethimide, cyproheptadine, metyrapone and mitotane) has been tried with variable results.

Aldosterone Excess

Hyperaldosteronism is associated with fluid and sodium retention along with increased urinary loss of potassium. The chief clinical features of primary hyperaldosteronism are hypertension and hypokalemic alkalosis. Primary hyperaldosteronism due to increased adrenal aldosterone production is extremely rare. Secondary hyperaldosteronism results from factors that activate the renin–angiotensin system (Table 18.15).

Table 18.15: Etiology of hyperaldosteronism

Primary hyperaldosteronism
- Adenoma, hyperplasia
- Glucocorticoid remediable hyperaldosteronism (chimeric fusion of promoter of CYP11B1 with coding region of CYP11B2, resulting in regulation of aldosterone synthesis by ACTH)

Secondary hyperaldosteronism
- Renal artery stenosis, renin-secreting tumor
- Cardiac failure, nephrotic syndrome, liver disease

Other causes of excessive mineralocorticoid action
- Apparent mineralocorticoid excess (deficiency of 11β-hydroxy-steroid dehydrogenase type 2 in the kidneys)
- Liddle syndrome
- Congenital adrenal hyperplasia due to deficiency of 17α-hydroxylase or 11β-hydroxylase

Evaluation: Aldosterone excess should be suspected in a child with hypertension, hypokalemic alkalosis, and low plasma renin levels on investigations. High aldosterone level in this setting is suggestive of primary hyperaldosteronism or glucocorticoid remediable hyperaldosteronism (GRA). Decrease in aldosterone levels and resolution of clinical and laboratory features after dexamethasone suppression suggests GRA; no effect is seen in primary hyperaldosteronism. Diagnosis of primary hyperaldosteronism should be confirmed by adrenal imaging.

Management: Hyperaldosteronism should be managed with salt restriction and aldosterone antagonist (spironolactone or eplerenone). Physiological hydrocortisone replacement suppresses ACTH secretion in GRA. Surgery is the treatment of choice for adrenal adenoma.

Pheochromocytoma

Pheochromocytoma is a catecholamine-secreting tumor, arising from chromaffin cells of adrenal medulla. It can also

arise from the abdominal sympathetic chain, peri-adrenal area, or in the thoracic cavity. It is rare in children. Unlike adults, in children, pheochromocytoma is more likely to be bilateral, and associated with underlying genetic syndromes such as neurofibromatosis, von Hippel-Lindau disease and multiple endocrine neoplasia type 2 (MEN type 2).

Clinical features: Excessive secretion of catecholamines results in hypertension, which is usually sustained and occasionally paroxysmal. The clinical symptoms include headache, palpitation, pallor, sweating, nausea, vomiting, visual disturbances and occasionally convulsions.

Evaluation: It is important to rule out common causes of childhood hypertension such as renal parenchymal disorders, renal artery stenosis and coarctation of aorta. Diagnosis is established by demonstration of increased urinary excretion of catecholamines and their derivatives.

Ultrasound, CT scan, MRI scan and ^{123}I metaiodobenzylguanidine (MIBG) scintigraphy are used for localization of the tumor. Occasionally, the tumors are multiple.

Management: Surgery is the treatment of choice. Transabdominal exploration of all the sites with removal of tumors is advocated. Preoperatively alpha-blockade is done using phenoxybenzamine and prazosin, followed by beta-blocking agents.

Adrenal Insufficiency

Adrenal insufficiency may be related to adrenal defects (primary adrenal insufficiency; autoimmune destruction, infection, steroidogenic defects, hemorrhage), decreased ACTH production (secondary adrenal insufficiency) or ACTH resistance.

Etiology: Autoimmune adrenal dysfunction is the commonest cause of primary adrenal failure (Addison disease) beyond infancy. Autoimmune adrenal failure is often associated with autoimmune polyendocrinopathy (APS) types 1 and 2. Infections due to tuberculosis and human immunodeficiency virus (HIV) may result in primary adrenal failure. Adrenal hemorrhage in the setting of meningococcal and other bacterial infections (Waterhouse-Friderichsen syndrome) is an important cause of adrenal insufficiency. Tuberculosis is still an important cause of adrenal insufficiency (caseous necrosis of adrenals) in developing countries. Congenital adrenal hyperplasia (CAH) due to deficiency of 21-hydroxylase or 3β-hydroxysteroid dehydrogenase and deficient steroidogenesis due to defective steroidogenic acute regulatory protein (StAR; causing lipoid CAH) are the chief causes in the neonatal period. Adrenal hypoplasia congenita due to a defect in *DAX*1 gene causes early onset adrenal insufficiency with small adrenals. This is an X-linked condition, with affected infants often having unilateral or bilateral cryptorchidism presenting with hypogonadotropic hypogonadism later.

Secondary (central) adrenal insufficiency is caused by congenital malformations (holoprosencephaly and midline defects), genetic defects or acquired insults (neurosurgery, tumor or radiation). This is usually associated with other anterior pituitary hormone deficiencies as well. In secondary adrenal insufficiency, mineralocorticoid function is preserved, as ACTH does not regulate aldosterone secretion. Thus, salt-wasting is not observed. Prolonged steroid treatment is associated with suppression of the hypothalamic–pituitary axis resulting in adrenal insufficiency even after discontinuation of medications. Again, mineralocorticoid activity is preserved in these patients. ACTH resistance due to ACTH receptor defects (familial glucocorticoid deficiency) presents with isolated cortisol deficiency, pigmentation, and normal potassium levels.

Clinical features: Adrenal insufficiency presents with slowly progressive lethargy, vomiting, salt craving, fatigue, postural hypotension, hypoglycemia and episodes of shock during severe illness. The concomitant presence of shock, hyponatremia, hyperkalemia and hemoconcentration is characteristic of acute adrenal insufficiency and warrants immediate steroid replacement. Primary adrenal insufficiency is characterized by hyperpigmentation due to elevated levels of melanocyte-stimulating hormone (MSH). Hyperpigmentation is present in sun-exposed areas such as elbows and palmar creases and areas that are normally hyperpigmented such as areola and genitalia. Pigmentation is absent in children with secondary adrenal insufficiency.

Evaluation: All patients suspected to have adrenal insufficiency should undergo immediate testing for serum electrolytes and blood glucose. Basal levels of cortisol are low (<5 µg/dL), but these have low specificity, as they can be low even in healthy non-stressed individuals. The next step in evaluation of adrenal insufficiency is estimation of serum ACTH levels. In children presenting with salt-wasting and hyperpigmentation, presence of elevated plasma ACTH levels and low basal cortisol levels is sufficient to make the diagnosis of primary adrenal insufficiency. If plasma ACTH levels cannot be assessed due to nonavailability of the test, or are low, an ACTH stimulation test (cortisol estimation 60 minutes after 0.25 mg of intramuscular or intravenous ACTH injection) is the best test for adrenocortical reserve. Serum cortisol levels lower than 18 µg/dL are suggestive of adrenal insufficiency.

In children with low cortisol after ACTH stimulation test and low plasma ACTH levels, a pituitary defect is likely. Elevated plasma renin activity (PRA) indicates mineralocorticoid deficiency. Further evaluation of primary adrenal insufficiency includes abdominal CT scan and work-up for tuberculosis.

Management: The initial management of salt-wasting crisis includes correction of shock by fluid boluses. Hydrocortisone is given immediately in a dose of 50 mg/m^2, followed by 100 mg/m^2/day in four divided doses. Frequent monitoring of hemodynamic parameters, urine output and serum electrolytes are required. Once the child is hemodynamically stable, hydrocortisone is tapered to the physiological dose (10–12 mg/m^2/day given in three divided doses). Fludrocortisone acetate (0.1 mg/day once daily) is added when hydrocortisone dose is <50 mg/m^2/day.

Long-term management of adrenal insufficiency requires lifelong replacement of glucocorticoids and

mineralocorticoids. Parents should be educated about the need for increasing the dose during periods of stress. The dose of glucocorticoid should be increased 2–3 times in conditions of minor stress (fever and mild infection) and 4–5 times in severe stress (severe infection or surgery). These doses should continue throughout the period of stress. Patients with secondary adrenal insufficiency require lower dose of glucocorticoids (6–10 mg/m^2/day); mineralocorticoid replacement is not necessary.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), a group of autosomal recessive defects in steroid synthesis, is characterized by the deficiency of adrenocortical hormones on one hand and the excess of steroid precursors on the other **(Fig. 18.6)**. CAH is the commonest adrenal disorder in childhood.

21-hydroxylase Deficiency

21-hydroxylase deficiency is the commonest form of CAH accounting for over 90% of all cases. This disorder is associated with diminished synthesis of the cortisol and aldosterone. Low cortisol levels stimulate ACTH synthesis. Elevated ACTH level causes accumulation of steroid precursors (e.g. dehydroepiandrosterone [DHEA], androstenedione and 17-hydroxyprogesterone [17-OHP]). Depending on the severity of enzyme deficiency, the disease forms a spectrum of presentations detailed below.

Salt-wasting form: These patients are the most severely affected due to almost absent enzyme activity and present in the neonatal period with salt-wasting and virilization. Abnormal genital appearance should prompt the diagnosis in girls. Diagnosis is often missed in boys as they lack specific clinical features and genital ambiguity. They present after second week of life with failure to thrive, polyuria, hyperpigmentation and shock. Early diagnosis is mandatory to prevent mortality. 21-hydroxylase deficiency should be suspected in neonates with ambiguous genitalia, polyuria, shock, recurrent vomiting and features of sepsis with negative septic screen. The diagnosis is confirmed by measurement of blood levels of 17-OHP.

Simple virilizing form: A subset of patients with 21-hydroxylase deficiency (25%) synthesizes enough aldosterone to prevent adrenal crisis. These patients have features of androgen excess in the form of virilization in girls and peripheral precocious puberty in boys **(Fig. 18.8)**.

Non-classic form: This disorder is associated with partial 21-hydroxylase deficiency. Clinical manifestations are related to mild hyperandrogenism that presents with hirsutism, acne and menstrual irregularity in adolescents.

Diagnosis: Diagnosis of the salt-wasting form is established by demonstration of extreme elevations of 17-OHP levels (10000–20000 ng/dL, normal <200 ng/dL) in the presence of clinical and laboratory features of adrenal insufficiency. 17-OHP levels are elevated to a lesser extent in those with simple virilizing and non-classic forms. The best method of diagnosing these patients is the estimation of 17-OHP levels before and 60 minutes after an intramuscular injection of ACTH (0.25 mg).

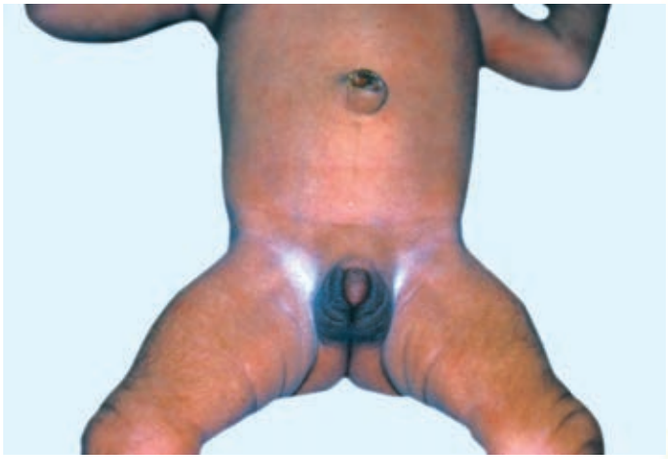

Fig. 18.8: Congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency in a 46,XX newborn. Note the clitoral hypertrophy, hyperpigmentation and increased rugosity of the labial folds giving a male appearance to the female genitalia. Testes were absent.

Management: These patients require lifelong steroid replacement therapy. Patients with salt-wasting and virilizing forms are treated with hydrocortisone (10–15 mg/m^2/day) and fludrocortisone (0.1 mg/day). After completion of growth and pubertal development, long-acting glucocorticoid preparations (dexamethasone or prednisolone) can be used.

Other Variants

Enzyme deficiencies other than 21-hydroxylase deficiency account for less than 10% of cases of CAH **(Table 18.16)**. Patients with 11-hydroxylase deficiency and 17- hydroxylase deficiency present with hypertension and are managed with hydrocortisone alone. Deficiencies of StAR and 3β-hydroxysteroid dehydrogenase manifest as salt-wasting crisis and require therapy with mineralocorticoid.

Suggested Reading

1. Bajpai A, Menon PSN. Congenital adrenal hyperplasia. In: Gupta P, Menon PSN, Ramji S, Lodha R, Eds. PG Textbook of Pediatrics, 3rd edn. New Delhi; Jaypee Brothers, 2022; pp 2918–22.
2. Brandão Neto RA, de Carvalho JF. Diagnosis and classification of Addison disease. Autoimmune Rev 2014;13:408–11.
3. Greaves RF, Jevalikar G, Hewitt JK, Zacharin MR. A guide to understanding the steroid pathway: new insights and diagnostic implications. Clin Biochem 2014;47:5–15.
4. Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:4133–60.

Competencies: **PE11.1; PE11.2; PE11.3; 11.4; PE11.5; PE11.6**

OBESITY

The incidence of childhood obesity has increased rapidly in the last decade. The prevalence of overweight and/or obesity in urban Indian children is around 20% posing significant risk of lifestyle diseases in future.

Table 18.16: Comparison of common variants of congenital adrenal hyperplasia

Enzymes deficient	*Androgen levels*	*Blood pressure*	*Clinical presentation*		*Laboratory diagnosis*	*Treatment*
			Boys	*Girls*		
21-hydroxylase						
Salt-wasting	High	Low	Precocious puberty	Atypical genitalia	17-OHP*	Hydrocortisone Fludrocortisone
Simple virilizing	High	Normal	Precocious puberty	Atypical genitalia	17-OHP*	Hydrocortisone Fludrocortisone@
Non-classic	High	Normal	Normal	Hirsutism	17-OHP*	Hydrocortisone
11β-hydroxylase	High	High/Normal$	Precocious puberty	Atypical genitalia	DOC	Hydrocortisone Spironolactone
3β-hydroxysteroid dehydrogenase	Variable#	Low	Atypical genitalia	Atypical genitalia	ACTH stimulation test**	Hydrocortisone Fludrocortisone
17α-hydroxylase/ 17-lyase	Low	High$	Atypical genitalia	Delayed puberty	DOC	Hydrocortisone^
StAR	Low	Low	Atypical genitalia	Delayed puberty	Low 17-OHP	Hydrocortisone Fludrocortisone

DOC deoxycorticosterone; StAR steroidogenic acute regulatory protein; 17-OHP 17-hydroxyprogesterone
*Basal and ACTH stimulated
$BP is high due to mineralocorticoid effect of DOC; however, BP may be normal
#Due to peripheral conversion of dehydroepiandrosterone (DHEA)
**Ratio of pregnenolone, progesterone, 17-hydroxypregnenolone to 17-OHP and DHEA to androstenedione following ACTH stimulation test
@Flurocortisone is useful in few patients with simple virilizing CAH, but not needed in most
^Few patients may need spironolactone

Criteria for Diagnosis of Obesity

Obesity implies excessive fat and not merely excess weight. As methods of measuring body fat are cumbersome and expensive, several clinical and anthropometric parameters are used as markers of obesity.

Body mass index: Body mass index (BMI) is the most widely used parameter to define obesity. It takes into account weight as well as the height. It is calculated by the formula:

$$\text{BMI} = \text{Weight (kg)} \div \text{Height (m}^2\text{)}$$

BMI is a good indicator of body fat but is unreliable in short muscular individuals. As the aim of assessing BMI is to identify individuals at risk for metabolic complications, lower BMI cutoffs are recommended for Indian adults (23 kg/m^2 for overweight and 27 kg/m^2 for obesity). The IAP 2015 growth charts extrapolate 23rd and 27th adult equivalent centiles of BMI for diagnosis of overweight and obesity respectively, in children above 5 years of age. The 23rd adult equivalent centile corresponds to approximately 0.55 SDS (71st centile) for males and 0.67 SDS (75th centile) for females; while the 27th adult equivalent centile corresponds to 1.33 SDS (90th centile) and 1.63 SDS (95th centile), respectively, in males and females.

Weight for height: This compares the child's weight to the expected weight for his/her height and is useful in children below 5 years of age (*see* Chapter 2, **Table 2.4**).

In children below 5 years, the cutoffs, for overnutrition are based on WHO MGRS charts, are as follows:
Overweight: Weight for length/height > +2 SDS
Obesity: Weight for length/height > +3 SDS

Skinfold thickness: Skinfold thickness measured over the subscapular, triceps or biceps regions is an indicator of subcutaneous fat. Age-specific percentile cutoffs should be used.

Waist circumference, waist–hip ratio and waist circumference to height ratio: Waist circumference is a good indicator of abdominal adiposity. Waist circumference >75th centile for age or >80 cm in girls and >90 cm in boys is a good marker of risk for metabolic and cardiovascular effects of obesity. Waist circumference to height ratio of >0.5 is a better age-independent method to identify those at increased health risk.

Etiology

In most children with obesity, lifestyle and hereditary factors play the major role **(Table 18.17)**. A specific etiology is identified in a few cases (<5%).

Constitutional or exogenous obesity: Most children with obesity do not have an organic cause. Excessive weight gain is caused by an imbalance in energy intake and expenditure. They are tall for their age and with reference to their midparental height, a factor that differentiates them from pathological obesity.

Endocrine causes: Endocrine causes are rare (about 2–3%) in children referred for evaluation of overweight. An important clue to endocrine etiology is the deceleration or cessation of linear growth—height below the centile expected for the genetic potential. Cushing syndrome is characterized by central obesity, hypertension, and purple striae with delayed skeletal maturation. In GH deficiency and pseudohypoparathyroidism, growth retardation and

Table 18.17: Etiology of obesity

Constitutional
Environmental factors (95% cases)
Pathological
Endocrine: Cushing syndrome, growth hormone deficiency, hypothyroidism, pseudohypoparathyroidism
Hypothalamic: Head injury, infection, brain tumor, radiation, chemotherapy, following neurosurgery, ROHHAD(NET)*
Drugs: Antiepileptic drugs, steroids, antidepressants, estrogen
Genetic syndromes: Prader-Willi, Bardet-Biedl, Laurence-Moon, Beckwith-Wiedemann, Alström, Carpenter syndromes
Monogenic disorders: Leptin deficiency, or resistance (leptin receptor defect), abnormalities of melanocortin-4 receptor and proconvertase
Psychological: Personal or parental stress, binge eating

*ROHHAD(NET) Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation, and neural crest tumors

hypocalcemia respectively are dominant clinical features and abdominal obesity is less prominent. Hypothyroidism is associated with mild weight gain, coarse skin and characteristic facies. However, mildly elevated TSH levels (up to 10 mU/L) seen in children with obesity, represent the effect and not the cause of obesity.

Genetic syndromes: Several genetic syndromes have obesity as their major clinical feature.

Hypothalamic obesity: CNS insults due to surgery, radiation, tumors and trauma result in rapid-onset obesity. Excessive appetite and features of CNS involvement and hypothalamic–pituitary defects are usually present. Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation (ROHHAD) is a rare disease that presents with rapid weight gain, most commonly between 2 and 4 years of age, with associated features, and neuroendocrine tumors in approximately 50% of affected children.

Monogenic obesity: Monogenic obesity is rare and more likely when the obesity is morbid, and has onset in infancy, with a strong family history of obesity. Leptin deficiency was the first monogenic cause of obesity identified. Inefficient leptin action (receptor deficiency or resistance) results in uncontrolled appetite and obesity. Melanocortin-4 receptor (*MC4-R*) defects are the commonest monogenic form of obesity and are associated with growth acceleration.

Drugs: Commonly used drugs associated with obesity include corticosteroids, antipsychotics (olanzapine and risperidone), antidepressants (paroxetine) and antiepileptics (valproic acid and lamotrigine).

Evaluation

Initial evaluation is guided to differentiate exogenous (constitutional) from endogenous (pathological) obesity. Normal growth, generalized pattern of obesity and the lack of developmental delay or dysmorphism imply constitutional obesity.

History: Details of physical activity, dietary recall and sedentary habits help in diagnosis. Increased appetite in a child with recent-onset obesity may indicate the possibility of a hypothalamic lesion. Features of raised intracranial tension along with history of neurologic infection, head trauma or neurosurgery suggest an underlying neurologic cause for obesity. Intake of drugs linked with development of obesity should be probed.

Examination: Look for features of endocrinopathies, dysmorphic syndromes and complications such as hypertension and acanthosis nigricans **(Fig. 18.9)**. Emphasis should be given to sexual maturity and ocular examination. Hypogonadism is an important feature of obese children with Laurence-Moon, Bardet-Biedl and Prader-Willi syndromes **(Figs 18.10, 18.11** and **Table 18.18)**. Parents of obese girls are often concerned about premature thelarche.

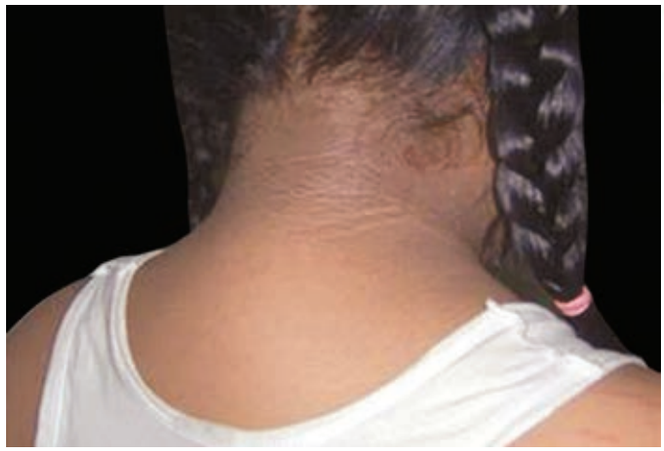

Fig. 18.9: Acanthosis nigricans on the back of neck in a girl with obesity

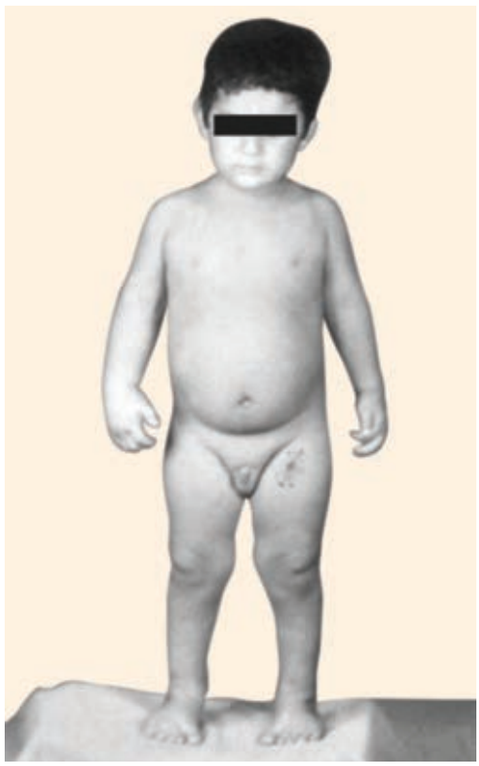

Fig. 18.10: Bardet-Biedl syndrome. Note the central obesity and hypoplastic genitalia

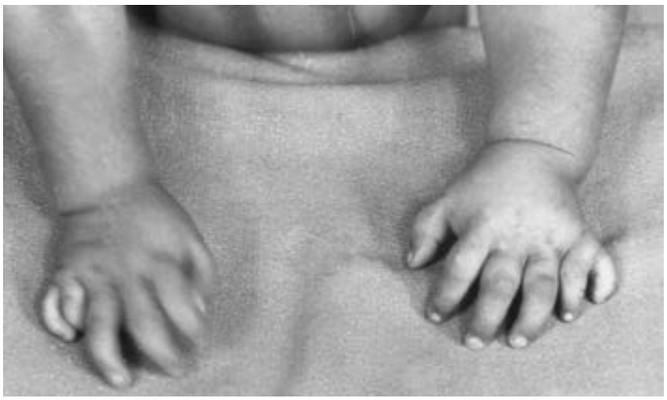

Fig. 18.11: Bardet-Biedl syndrome. Note the polydactyly

While this may reflect central isosexual precocious puberty caused by obesity, it is most likely due to increased fat. These conditions are distinguished by approximating the thumb and index finger around the nipple. Lack of resistance during this procedure indicates lipomastia while breast nodule can be felt as an area of resistance. Obese boys frequently present with concerns of small penile size. This is usually due to penis being buried in the suprapubic pad. Stretched penile length should be measured after pressing the suprapubic pad of fat to ascertain the actual size of penis.

Investigations: No workup for etiology is required in children with normal growth, facies and pubertal development. Thyroid profile and evaluation for Cushing syndrome should be done in the presence of growth failure and/or characteristic clinical features. Mildly elevated TSH levels with normal FT_4 are common in obese children. This is not the cause of obesity and should not be treated unless TSH is persistently elevated. Cortisol levels may be mildly elevated in obese children and should not be mistakenly diagnosed as Cushing syndrome. Genetic testing for Prader-Willi syndrome should be done in the presence of facial features, history of infantile hypotonia and growth failure. Monogenic causes of obesity should be considered only in the presence of clinical features or pointers to diagnosis.

Complications

Childhood obesity is associated with significant complications. These are summarized in **Table 18.19**, and the more important ones are discussed below.

Endocrine and metabolic: Endocrine complications are the most important adverse effects of childhood obesity. Central to this is the development of insulin resistance caused by overspill of fat and its deposition in liver and skeletal muscle. Insulin resistance predisposes to development of type 2 diabetes, polycystic ovarian disease, metabolic syndrome and non-alcoholic fatty liver disease (NAFLD). Hyperandrogenism is a common feature in obese girls. Obesity has also been associated with accelerated growth, skeletal maturation and early puberty in girls.

Cardiovascular system: Children with obesity have a higher prevalence of dyslipidemia, hypertension and atherosclerosis. Childhood obesity is associated with increased risk of adult coronary disease.

Non-alcoholic fatty liver disease (NAFLD): It is present in up to 60% of children with obesity, and in a small proportion it can progress to steatohepatitis and fibrosis.

Table 18.18: Distinguishing features of endogenous causes of obesity

Disorder	*Characteristic features*
Prader-Willi syndrome	Low birth weight, feeding difficulties, infantile hypotonia, hyperphagia starting around 1 year of age, almond-shaped eyes, short stature, acromicria (small hands and feet), hypogonadism, cognitive impairment and behavioral abnormalities
Bardet-Biedl (BB) and Laurence-Moon (LM) syndromes	Obesity by 1 year of age, visual impairment due to retinitis pigmentosa, polydactyly (BB), syndactyly (LM), notch between tragus and antitragus of ear (LM), spasticity (LM), hypogonadism, renal abnormalities and intellectual disability
Beckwith-Wiedemann syndrome	Macrosomia at birth, organomegaly, ear lobe creases, macroglossia, abdominal wall defects and hemihypertrophy
Alström syndrome	Obesity, short stature, retinal degeneration, sensorineural hearing loss, dilated cardiomyopathy, type 2 diabetes mellitus
Carpenter syndrome	Severe intellectual disability, syndactyly, brachydactyly, clinodactyly, lower limb deformities, undescended testes and cardiac defects
Cushing syndrome	Hirsutism, central obesity, growth retardation, striae, buffalo hump, hypertension and myopathy
Hypothyroidism	Growth retardation, coarse facies, dry skin and developmental delay
Pseudohypoparathyroidism with Albright hereditary osteodystrophy	Obesity, short stature, round face, short neck, short and wide long bones of hands, PTH resistance and hypocalcemic tetany
Leptin and leptin receptor deficiency	Infantile onset severe obesity, hyperphagia, hypogonadism, hypothalamic hypothyroidism and adult short stature
Mineralocortin-4 deficiency	Infantile onset severe obesity, hyperphagia, increased linear growth and bone mass and subclinical hypothyroidism
Hypothalamic obesity	History of brain tumor, radiation or chemotherapy, squint and pituitary hormone defects

Table 18.19: Complications of obesity

Category	*Complications*
Metabolic	Insulin resistance, type 2 diabetes, metabolic syndrome, hyperandrogenism
Cardiovascular	Hypertension, dyslipidemia, atherosclerosis
Gastrointestinal	Non-alcoholic fatty liver disease, gallstones, gastroesophageal reflux
Skeletal	Blount's disease, slipped capital femoral epiphysis, fractures
Respiratory	Obstructive sleep apnea, hypoventilation syndrome
Neurological	Benign intracranial hypertension
Psychological	Mood disorders, low self-esteem, risk of being bullied or teased, depression

Assessment of Complications

Table 18.20 summarizes the recommendations for screening for various complications of obesity in children.

Prevention and Management of Overweight and Obesity

Prevention and management of obesity constitute a continuum of efforts aimed at reducing the imbalance between energy intake and output at one end to creating a negative energy balance at the other end. A stepwise approach is suggested, wherein the interventions are scaled up gradually, depending on the severity of obesity, presence of complications, and the response to interventions. The focus is on modifications in diet and lifestyle, but the intensity of the interventions (dietary and physical activity-related) increases at each successive level, with closer supervision, multi-disciplinary care with more frequent contacts with the healthcare team, and need for more committed involvement of the family **(Table 18.21)**.

Pharmacotherapy for Obesity

Orlistat is approved for use in children with obesity. The drug inhibits gastric lipase resulting in reduced absorption of fat. However, side effects like abdominal pain, bloating and steatorrhea lead to discontinuation of treatment by most patients. Glucagon-like peptide-1 (GLP1) analogs, e.g. liraglutide, have been recently approved for pediatric obesity and type 2 diabetes. Metformin should be used only in the presence of diabetes or polycystic ovarian disease. Overall, pharmacotherapy for obesity has limited utility.

Specific Management

Specific treatment is initiated in children with hypothyroidism, GH deficiency and Cushing syndrome. Children with mildly elevated TSH level do not need treatment. Children with Prader-Willi syndrome and growth failure may benefit from GH therapy.

Table 18.20: Screening for complications of pediatric overweight and obesity

Complication	*Age for screening*	*Tests and their interpretation*			
Prediabetes	Clinical screen at first visit, lab screen for >10 years	HbA1c 5.7 to <6.5% Impaired fasting glucose: Fasting plasma glucose ≥100 but <126 mg/dL			
Diabetes	Older than 10 years	HbA1c ≥6.5% Fasting plasma glucose ≥126 mg/dL 2 hr plasma glucose ≥200 mg/dL during an oral glucose tolerance test			
Dyslipidemia	First visit, then every 2 years	*Fasting lipids (mg/dL)*	*Normal*	*Borderline*	*Abnormal*
		Triglycerides			
		0–9 years	<75	75–99	≥100
		10–19 years	<90	90–129	≥130
		LDL-cholesterol	<110	110–129	≥130
		HDL-cholesterol	>45	40–45	<40
Hypertension	Children older than 3 years at every visit	BP is checked and compared against age, gender and height-based charts. • Normal BP: <90th percentile for age and gender in 1–13-yr-old children, and <120/<80 mm Hg in adolescents ≥13 yr. • Elevated BP: ≥90th to <95th percentile in 1–13-yr-old, and 120/<80 to 129/<80 mm Hg in adolescents ≥13 yr. • Stage 1 hypertension: BP ≥95th to <95th percentile + 12 mm Hg in 1–13-yr-old children; and 130/80 to 139/89 mm Hg in ≥13 yr. • Stage 2 hypertension: BP ≥95th percentile +12 mm Hg in 1–13-yr-old children, and ≥140/90 mm Hg in adolescents ≥13 yr.			
NAFLD	Older than 10 years	ALT >25 U/L (boys), >22 U/L (girls) are considered elevated. Ultrasonography or fibroscan is used for screening for fatty liver.			
Others	*Testing to be done as per symptoms*				
Sleep apnea	Polysomnography, if there is snoring, daytime somnolence, lethargy, difficulty in sleeping supine				
Hyperandrogenism	Testosterone, LH, SHBG, if there is hirsutism, acne and menstrual irregularities in girls				
Psychological	Psychological review, if features of depression, eating disorders, bullying, etc.				
Musculoskeletal	Orthopedic review for bone pains, bowing, etc.				

ALT alanine transaminase; BP blood pressure; HDL high-density lipoprotein; LDL low-density lipoprotein; LH luteinizing hormone; SHBG sex hormone binding globulin; NAFLD non-alcoholic fatty liver disease

Table 18.21: Key interventions for prevention and management of obesity in children

Dietary interventions

- Exclusive breastfeeding for first 6 months
- Continued breastfeeding till 2 years
- Home-based complementary feeding starting at 6 months of life, with avoidance of sugar-sweetened beverages and packaged foods in the first 2 years
- Avoid force feeding, overfeeding, skipping of meals and frequent snacking
- Traffic light approach—green to be eaten often, yellow in moderation and red sparingly
  - Green (low energy, high nutrient foods)—fruits and vegetables
  - Yellow (moderate energy foods)—grains, pulses
  - Red (high energy, low nutrient foods)—sweets, sweetened beverages, fried foods
- Structured and timely meals with appropriate portion size
- Increase water intake

Physical activity

- Reduction of sedentary habits
- At least 60 minutes/day of moderate to vigorous physical activity (sports, running, dancing, etc.)

Behavioral interventions

- Education to family about importance of healthy diet and activity
- Mindful eating, avoid distractions, and avoid grazing
- Sleep hygiene (adequate duration and without electronic devices)
- Role modeling of desirable behaviors by parents
- Positive reinforcements, praise and rewards
- Recognize and manage psychosocial co-morbidities (depression, anxiety, etc.)
- Limitation of non-academic screen time

Treatment of Complications

Complications should be treated early to avoid long-term adverse effects. Metformin is indicated in children with insulin resistance and type 2 diabetes, and polycystic ovarian disease. Statins are the drug of choice for children with persistent dyslipidemia. Children with symptomatic or stage 2 hypertension should receive antihypertensives (enalapril or amlodipine). Treatment of NAFLD includes the use of metformin, vitamin E and pioglitazone. Girls with polycystic ovarian syndrome may benefit from lifestyle modifications, metformin, oral contraceptives and antiandrogens. Medroxyprogesterone acetate is beneficial in children with obesity-hypoventilation syndrome while continuous positive airway pressure may be used in obstructive sleep apnea.

Surgical Management

Bariatric surgery is considered in severe obesity when other measures fail. The intervention is preferred after achieving final height to avoid potential adverse growth effects. Laparoscopic adjustable banding is the recommended procedure in children.

Suggested Reading

1. Mittal M, Jain V. Management of obesity and its complications in children and adolescents. Indian J Pediatr 2021;88:1222–34.
2. Ranjani H, Mehreen TS, Pradeepa R, et al. Epidemiology of childhood overweight & obesity in India: A systematic review. Indian J Med Res 2016;143:160–74.
3. Styne, Arslanian SA, Connor EL, et al. Pediatric obesity–Assessment, treatment and prevention: An Endocrine Society clinical practice guidelines. J Clin Endocrinol Metab 2017;102:709–57.

Competencies: **PE33.8; PE33.10**

DISORDERS OF THE GONADS

Puberty

Puberty is the phase of life when secondary sexual characteristics appear and mature, and the capability of reproduction is attained.

Physiology

Puberty involves development of primary (testicular and penile growth in boys and ovarian and uterine growth in girls) and secondary sexual characteristics (pubic and axillary hair growth, change of voice in boys, acne and axillary odor). Sex hormones (estrogen in girls and testosterone in boys) play an important role in the development of primary sexual characteristics, while adrenal androgens are involved in the development of secondary sexual characteristics in girls.

Kisspeptin, a hypothalamic peptide, is the key regulator of puberty. Acting as the 'on-off switch' of puberty, kisspeptin initiates GnRH pulses. Initially, GnRH pulses occur only during nights followed by secretion during both day and night. This leads to increase in the levels of gonadotropins, and thereby, sex hormones. The hypothalamic– pituitary–gonadal axis is under feedback control. Thus secretion of LH is inhibited by testosterone produced by the Leydig cells in boys, and estrogen produced by the theca cells in girls. FSH is inhibited by inhibin produced by the Sertoli cells in boys, and granulosa cells in girls.

Patterns of Pubertal Development

Puberty starts at around the age of 10 years in girls (range 8–12 years) and is completed over 3–5 years. Breast enlargement (thelarche) is the first event followed by the development of pubic hair (pubarche) and onset of menstrual cycles (menarche). Breast development may be asymmetrical in the initial phase. Menarche usually occurs 2 years after thelarche during stage III or IV. Average age at menarche in Indian girls is about 12 years.

Pubertal development is closely linked to the remaining growth potential of the child. Thus, a girl is expected to gain around 20 cm from breast stage II development and 6–10 cm after menarche. Discordant pubertal development (menarche within one year of thelarche) suggests a hyperestrogenic state with withdrawal bleeding.

In boys, puberty starts with testicular enlargement at 11.5 years (range 9 to 14 years). This is followed by penile enlargement and pubarche; spermarche occurs by 14 years. Peak growth velocity correlates to testicular volume of 10 mL.

Assessment of Puberty

Pubertal development is assessed using Tanner staging system (*see* Chapter 5, **Figs 5.1, 5.2**). Breast development beyond Tanner II in girls and testicular volume equal or greater than 4 mL indicate the onset of puberty. Maximum growth spurt occurs during early puberty in girls (Tanner II–III) compared to boys where it occurs later (Tanner III–IV). Menstrual periods are irregular in the first few years before attainment of regular ovulatory cycles. It is important to differentiate adrenarche (pilosebaceous development related to increase in adrenal steroids causing pubarche and change in odor) from gonadarche (genital development related to increase in GnRH causing breast development) in girls.

Precocious Puberty

Pubertal onset before the age of 8 years in girls and 9.5 years in boys is suggestive of precocious puberty. Precocious puberty may be due to stimulation of the hypothalamic– pituitary axis (gonadotropin-dependent or central precocious puberty) or autonomous sex hormone production (gonadotropin-independent or peripheral).

Precocious Puberty in Girls

Precocious puberty is common in girls and may represent a normal variation in the age at onset of puberty. In most cases, puberty is slowly progressive with no long-term adverse effect. Endocrine workup should be restricted to girls with progressive forms of puberty.

Gonadotropin-dependent precocious puberty (central precocious puberty, CPP) is much more common than gonadotropin-independent precocious puberty **(Table 18.22)**. In more than 90% cases, no underlying cause is identified. It may be caused by a variety of pathologies of the central nervous system. Hypothalamic hamartoma, a neuronal migration defect, is the commonest cause of organic CPP. The disorder presents with early onset and rapid progression of puberty, seizures and uncontrolled laughter episodes (gelastic epilepsy).

Table 18.22: Etiology of precocious puberty in girls

Gonadotropin-dependent or central precocious puberty
Idiopathic (in more than 90%)
Tumors: Hypothalamic glioma
Infections: Neurotuberculosis, meningitis
Injury: Head trauma, neurosurgery, cranial irradiation
Malformation: Hypothalamic hamartoma, arachnoid cyst, hydrocephalus, septo-optic dysplasia
Gonadotropin-independent or peripheral precocious puberty
Hypothyroidism
Ovarian estrogen: McCune-Albright syndrome, cyst, tumor, aromatase excess
Adrenal estrogen: Estrogenic adrenal adenoma
Exogenous estrogen exposure
Incomplete variants
Isolated thelarche
Isolated pubarche (adrenarche)
Isolated menarche

Gonadotropin-independent precocious puberty (peripheral precocious puberty, PPP) is rare and usually caused by estrogenic ovarian cysts. Fluctuating pubertal development and early vaginal bleeding (due to hyperestrogenic state) is common. Recurrent ovarian cysts should raise the possibility of McCune-Albright syndrome, a somatic activating mutation of stimulatory G protein, which presents with a constellation of cutaneous (multiple café au lait spots), skeletal (multiple fibrous dysplasia) and endocrine abnormalities (hyperthyroidism, rickets and GH excess). Precocious puberty occurs at an early age and is rapidly progressive. Prolonged untreated primary hypothyroidism may induce early puberty due to action of TSH on FSH receptor. Delayed bone age and growth are characteristic features.

Evaluation

Clinical: History should include the onset, progression and extent of puberty. Exposure to steroids, estrogens and androgens should be enquired. Family history of precocious puberty and early menarche points towards idiopathic CPP. Features of hypothyroidism should be assessed. Advanced growth is characteristic of precocious puberty; growth retardation indicates hypothyroidism or concomitant GH deficiency **(Fig. 18.12)**.

Abdominal examination for adrenal or ovarian mass should be done. Features of McCune-Albright syndrome include café au lait spots, polyostotic fibrous dysplasia, bony deformities and polyendocrinopathy.

Investigations: Assessment of pubertal status is based on basal or stimulated gonadotropin levels. Pooled gonadotropin levels are preferred due to their pulsatile secretion. LH is a better indicator compared to FSH, since the former increases significantly during puberty. LH levels in the pubertal range (basal >0.3 mU/L or stimulated >6 mU/L with LH/FSH ratio >1) is suggestive of development of puberty.

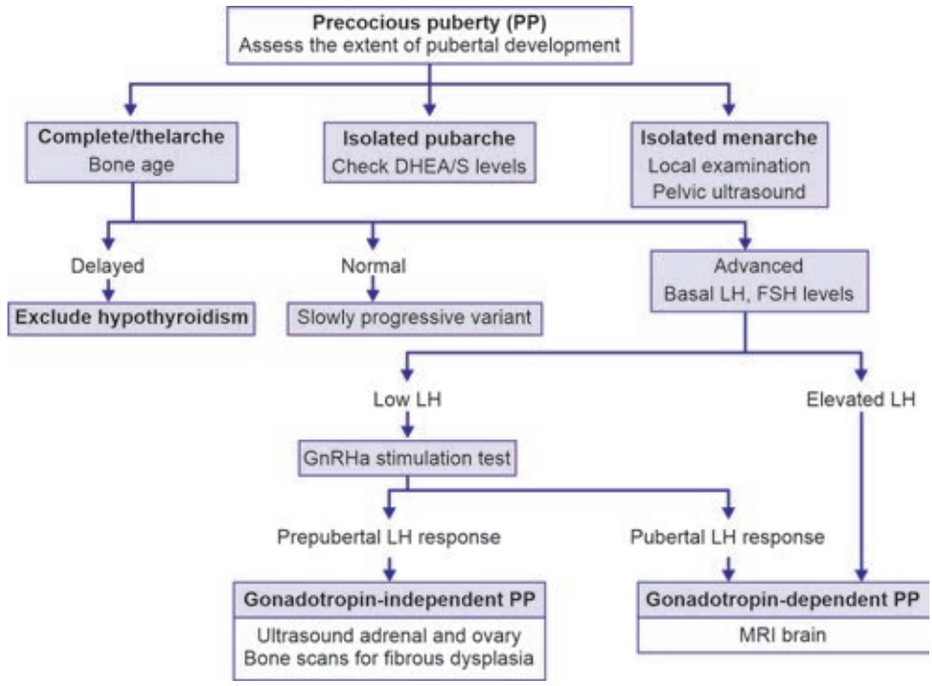

Fig. 18.12: Approach to precocious puberty in girls. DHEA/S dehydroepiandrosterone sulfate; FSH follicle-stimulating hormone; GnRHa gonadotropin-releasing hormone agonist; LH luteinizing hormone; MRI magnetic resonance imaging

Bone age is typically advanced, and helps in assessing the height compromise and in predicting final height. Short stature with delayed skeletal maturation suggests the possibility of hypothyroidism and associated GH deficiency. Thyroid function should be assessed to rule out hypothyroidism in these girls.

MRI of brain should be done in girls with onset of puberty before 6 years of age, rapid progression and associated neurological features. Ultrasound of abdomen and pelvis helps in diagnosing follicular cysts and ovarian and adrenal mass. Girls with prepubertal LH levels should undergo ultrasound of ovary and adrenals (for ovarian cyst and adrenal tumor) and skeletal survey (to assess for fibrous dysplasia).

Management

Aims of management include treatment of underlying cause, management of associations, puberty suppression and achievement of target height potential. The significant long-term consequence of rapidly progressive precocious puberty is short stature. Growth is accelerated at presentation. This is associated with disproportionately advanced bone age resulting in premature epiphyseal fusion culminating in compromised final height.

CPP: Long-acting GnRH analogs are effective in improving height outcome in CPP. They cause sustained stimulation and desensitization of pituitary leading to reversal of pubertal changes. GnRH analogs should be considered in girls with early onset (before 6 years of age) rapidly progressive puberty and height compromise (predicted adult height below the target height range). The treatment is discontinued at the chronological age of 11 years and bone age of 12.5 years.

Other drugs used for pubertal suppression include depot medroxyprogesterone acetate (MPA), and cyproterone. MPA does not improve height outcome and may be considered in girls with intellectual disability as a temporary measure to stop or postpone menstruation.

PPP: Thyroxine replacement reverses the pubertal changes of hypothyroidism. Treatment for McCune-Albright syndrome is directed towards inhibiting estrogen production (aromatase inhibitors—anastrazole, letrozole) or estrogen action (estrogen receptor antagonist—tamoxifen, fulvestrant). Size and morphological features guide treatment of ovarian cysts.

Incomplete Variants of Precocious Puberty

These disorders represent normal variants and do not require specific treatment. Their identification helps in restricting the extent of diagnostic workup and counseling.

Isolated thelarche: Isolated breast development may represent isolated thelarche or first manifestation of CPP. Bone age, gonadotropin levels and pelvic ultrasound help in differentiating the two conditions. Normal growth, prepubertal LH, age-appropriate bone age and small uterine size suggest isolated thelarche. These children usually present around the age of 1–2 years and show gradual regression of thelarche by 5 years of age.

Isolated adrenarche: Premature adrenarche refers to development of pubic hair and acne in the absence of breast development or menarche. Most cases are physiological variants. Rarely, androgen excess due to adrenal (21-hydroxylase deficiency, 11β-hydroxylase deficiency and adrenal tumor) or ovarian (tumor and polycystic ovarian disease) causes may be identified. DHEAS levels above 150 μg/dL suggest a pathological cause. Normal bone age and absence of virilization suggest premature adrenarche and no treatment is required.

Isolated menarche: Vaginal bleeding in the absence of thelarche is against the diagnosis of CPP. Vaginal bleeding occurs early in course of estrogen excess states like ovarian cysts, hypothyroidism and McCune-Albright syndrome. Vaginal bleeding without breast development requires evaluation of local causes (infection, foreign body, sexual abuse or tumors).

Precocious Puberty in Boys

Precocious puberty is less common in boys, but when present is usually associated with a significant pathology. This mandates prompt evaluation and treatment of all boys with precocious puberty.

Etiology

Gonadotropin-dependent and independent precocious puberty accounts for similar number of cases **(Table 18.23)**.

CPP: The etiology is similar to girls, except that organic neurologic causes are common. Hypothalamic hamartoma, glioma, hydrocephalus and tubercular meningitis are important causes **(Figs 18.13 and 18.14)**. These disorders are associated with an increase in testicular volume and elevated basal and GnRH-stimulated LH.

PPP: This results from increased androgen production by testes and adrenals, with prepubertal LH levels. Adrenal overproduction due to CAH due to 21-hydroxylase deficiency is a common cause of PPP in boys; adrenal tumors are rare. Human chorionic gonadotropin (hCG) secreting tumors of the liver, mediastinum or brain may present with precocious puberty. Testotoxicosis (familial male-limited precocious puberty), associated with constitutional activation of LH receptor, presents with early onset PPP. Androgen-secreting testicular tumors present with precocious puberty and unilateral testicular enlargement.

Evaluation

Evaluation is directed towards confirming the diagnosis and establishing the underlying cause.

Clinical: History should include the age at onset and progression of puberty, neurological features, family history of precocious puberty and androgen exposure. Detailed anthropometric and neurological examination is performed. Features of CAH (hyperpigmentation and hypertension) should be identified. Estimation of testicular volume is an integral part of assessment. Prepubertal testicular volume (<4 mL) is characteristic of PPP due to CAH and adrenal tumors; unilateral enlargement is seen in testicular tumors.

Investigations: Initial investigations include baseline LH, FSH and testosterone levels, stimulated LH (if required) and bone age. All patients with pubertal LH levels should undergo MRI of brain. In the presence of prepubertal LH levels, imaging for adrenals (preferably CT scan) and 17-OHP levels should be done. The levels of hCG should be estimated, if these investigations are noncontributory **(Fig. 18.15)**.

Table 18.23: Etiology of precocious puberty in boys

Gonadotropin-dependent or central precocious puberty
Idiopathic
Central nervous tumors: Craniopharyngioma, glioma
Infections: Tubercular meningitis
Injury: Head trauma, surgery, radiation
Malformation: Hamartoma, arachnoid cyst, hydrocephalus
Gonadotropin-independent or peripheral precocious puberty
Congenital adrenal hyperplasia: 21-hydroxylase deficiency, 11β-hydroxylase deficiency
Adrenal tumors: Adenoma, carcinoma
Testicular tumors: Seminoma, germinoma
Testotoxicosis: Activation of LH receptor
hCG secreting tumor: Germinoma, hepatoblastoma
Exogenous androgen exposure: Testosterone cream

hCG human chorionic gonadotropin, LH luteinizing hormone

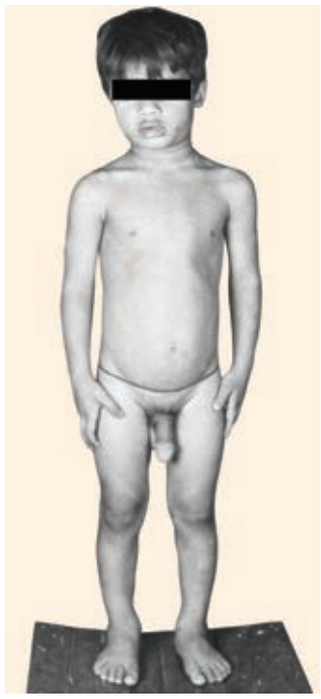

Fig. 18.13: Central precocious puberty secondary to hypothalamic hamartoma

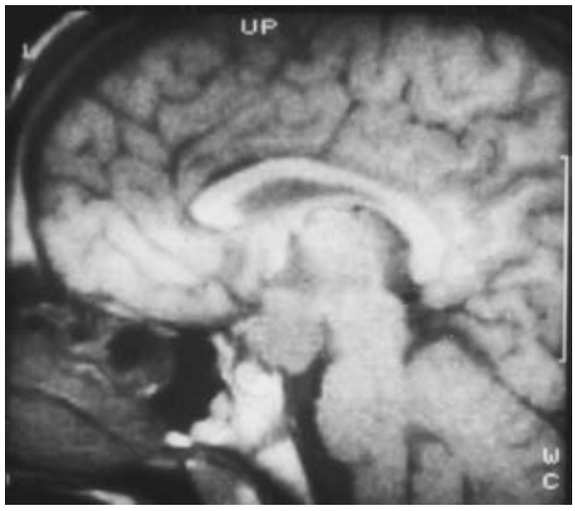

Fig. 18.14: MRI scan showing an isointense mass suggestive of hypothalamic hamartoma

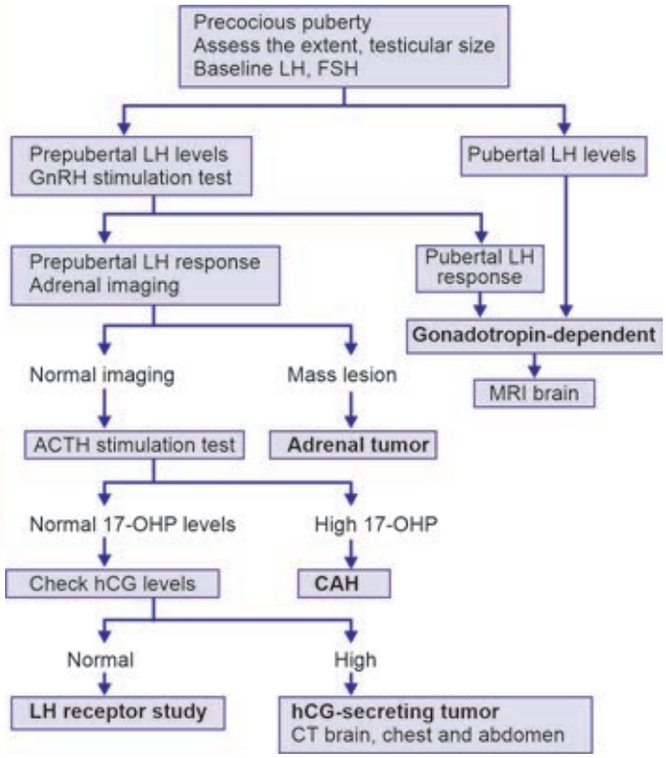

Fig. 18.15: Approach to precocious puberty in boys. ACTH adrenocorticotropic hormone; CAH congenital adrenal hyperplasia; CT computed tomography; FSH follicle-stimulating hormone; GnRH gonadotropin-releasing hormone; hCG human chorionic gonadotropin; LH luteinizing hormone; MRI magnetic resonance imaging; 17-OHP 17-hydroxyprogesterone

Management

Management of CPP includes treatment of the underlying pathology and GnRH analog therapy. GnRH analog should be continued till the age of 12 years. CAH is managed with hydrocortisone and fludrocortisone. Surgery is the treatment of choice for adrenal and testicular tumors, while radiotherapy is effective in hCG-secreting tumors. Aromatase inhibitors and antiandrogens are indicated in testotoxicosis.

Delayed Puberty

Delayed puberty is more common in boys than in girls. Most children with delayed puberty have constitutional delay emphasizing the need for watchful monitoring and a conservative approach.

Delayed Puberty in Girls

Delayed puberty in girls is defined as lack of secondary sexual characteristics by the age of 13 years. Absence of menarche by the age of 16 years, or 5 years after onset of puberty indicates pubertal delay.

Etiology

Delayed puberty may be caused by defects in the hypothalamic–pituitary axis, ovaries or genital tract (Table 18.24). Defects in the hypothalamic–pituitary axis are associated with low gonadotropin levels (hypogonadotropic hypogonadism). This may be related to reversible causes such as systemic diseases, malnutrition, eating disorders, hyperprolactinemia and hypothyroidism or a self-limited form that improves over time. Irreversible defects include destruction of the hypothalamic–pituitary axis by infection, surgery, radiation or tumor. Defective smell sensation, low GnRH levels and hypogonadotropic hypogonadism characterize Kallmann syndrome, a neuronal migration

Table 18.24: Etiology of delayed puberty

Hypogonadotropic hypogonadism

Transient

- *Self-limited delayed puberty (constitutional delay): Most common cause in boys, less frequent in girls*
- *Systemic disorders:* Renal failure, liver disease, celiac disease, renal tubular acidosis, cystic fibrosis
- *Nutritional disorders:* Malnutrition, anorexia nervosa
- *Endocrine disorders:* Hypothyroidism, hyperprolactinemia, type 1 diabetes

Permanent

- *Isolated hypogonadotropic hypogonadism*
  - *Genetic: KAL1, GnRH* receptor, *LH, FSH, CHD7, DAX1 gene mutations*
  - *Dysmorphic syndromes:* CHARGE, Prader-Willi, Laurence-Moon, Bardet-Biedl
- *Multiple pituitary hormone deficiencies*
  - *Malformations:* Holoprosencephaly, septo-optic dysplasia, midline defects
  - *Genetic disorders: PROP1, LH* gene deletions
  - *Brain tumors:* Craniopharyngioma, germinoma, glioma
  - *Brain injury:* Surgery, infection, radiation, trauma
  - *Infiltrative disorders:* Histiocytosis, autoimmune disorders

Hypergonadotropic hypogonadism

In girls

- *Gonadal dysgenesis:* Turner syndrome, 46,XY with *SRY* deletion, trisomy 18, 13, 21
- *Steroidogenic defects:* StAR, 17α-hydroxylase, 17β-hydroxysteroid dehydrogenase or aromatase deficiency
- *Ovarian insults:* Surgery, radiation, alkylating agents, infections
- *Autoimmune ovarian failure:* Autoimmune polyendocrinopathy
- *Gonadotropin resistance:* LH and FSH receptor mutations

In boys

- *Chromosomal abnormalities:* Klinefelter syndrome, gonadal dysgenesis
- *Steroidogenic defects:* StAR, 17α-hydroxylase, 17β-hydroxysteroid dehydrogenase deficiency, Smith-Lemli-Opitz syndrome
- *Testicular insults:* Radiotherapy, chemotherapy, trauma, torsion, infections
- *Malformations:* Vanishing testis syndrome, cryptorchidism
- *Inefficient testosterone action:* 5α-reductase deficiency
- *Resistance to testosterone action:* Androgen insensitivity syndrome

Isolated amenorrhea in girls

- *Structural malformations:* Müllerian agenesis, vaginal septum, imperforate hymen
- *Inefficient androgen action:* 46,XY with complete androgen insensitivity syndrome

DAX1 dosage sensitive sex reversal; FSH follicle-stimulating hormone; GnRH gonadotropin-releasing hormone; LH luteinizing hormone; *KAL1* kallmann syndrome gene 1; StAR steroidogenic acute regulatory protein; *SRY* sex determining region on Y chromosome

defect due to mutation in one of the several genes associated with this syndrome. Hypergonadotropic hypogonadism is associated with defective estrogen production by ovaries and elevated gonadotropin levels. Causes include Turner syndrome, ovarian failure and enzymatic defects in estrogen synthesis.

Evaluation

Goals of evaluation include identification of constitutional delay, organic etiology requiring neuroimaging and decision regarding treatment.

Clinical: Family history of delayed puberty provides a clue to constitutional delay in puberty. Patients are screened for chronic systemic or neurological diseases, Turner syndrome or hypothyroidism, and poor olfactory sensation. Amenorrhea with normal secondary sexual characteristics indicates anatomical defects.

Investigations: Workup is directed towards screening for systemic disorders (liver, renal or gastrointestinal disease), followed by estimation of FSH levels and karyotype. Steroidogenic defects are likely, if karyotype and pelvic ultrasound are normal. In patients with low/normal FSH levels, prolactin and thyroid profile is measured to exclude reversible causes. Neuroimaging and pituitary function tests should be done, if these levels are normal.

Management

All patients with hypergonadotropic hypogonadism and irreversible hypogonadotropic hypogonadism need hormone replacement. Hormone replacement should be deferred till the bone age of 12 years to avoid deleterious effects on height. The goal of treatment is to initiate and maintain sexual characteristics and to prevent osteoporosis. Treatment should be started with low dose estrogens (2 µg ethinyl estradiol, 0.3 mg conjugated estrogen or 0.25 mg estradiol valerate everyday) and gradually increased every 3 months till adult doses (20 µg of ethinyl estradiol, 1.25 mg of conjugated estrogen or 2 mg estradiol valerate daily by 2 years) are reached. Medroxyprogesterone acetate (5–10 mg from day 11 to 21) should be added two years after initiation of treatment or when withdrawal bleeding occurs.

Delayed Puberty in Boys

Delayed puberty is more common in boys than girls and is usually due to a constitutional delay. Lack of pubertal changes by the age of 14 years is suggestive of delayed puberty in boys.

Etiology

Constitutional delay in growth and puberty is the commonest cause of delayed puberty in boys **(Table 18.25)**. They have growth retardation and delayed bone age. Family history of delayed puberty is present. Gonadotropin levels are prepubertal similar to hypogonadotropic hypogonadism.

Hypogonadotropic hypogonadism: This may be reversible due to systemic illnesses or permanent due to neurological insult (e.g. infection, surgery, radiation or tumor). Kallmann syndrome is an important cause of isolated gonadotropin deficiency and presents with impaired smell sensation.

Table 18.25: Features suggestive of Turner syndrome

Age group	*Features*
Intrauterine period	Increased neck translucency, cystic hygroma
Infancy	Cystic hygroma, lymphedema, coarctation of aorta, partial anomalous pulmonary venous return (PAPVR)
Childhood and adolescence	Growth failure, hearing defect, delayed puberty, skeletal abnormalities
Adulthood	Secondary amenorrhea, infertility

Hypergonadotropic hypogonadism (testicular failure) may be due to chromosome abnormalities (e.g. Klinefelter syndrome), partial gonadal dysgenesis, steroidogenic defects and acquired testicular injury (infection, radiation, or chemotherapy) **(Fig. 18.16)**.

Evaluation

Clinical: Family history of delayed puberty suggests constitutional delay in puberty. History of delayed growth spurt with continued growth in adult years and late onset of shaving in father and brothers is common. Patients are examined for features of systemic disease(s); history of head injury, neurosurgery and intracranial space occupying lesions suggest a defect in the hypothalamic–pituitary axis.

Investigations: Initial step includes estimation of LH, FSH and testosterone levels. Elevated gonadotropin levels (hypergonadotropic hypogonadism) should be followed by karyotype (Klinefelter syndrome) and evaluation for biosynthetic defects. Boys with low LH and FSH levels may have constitutional delay in puberty

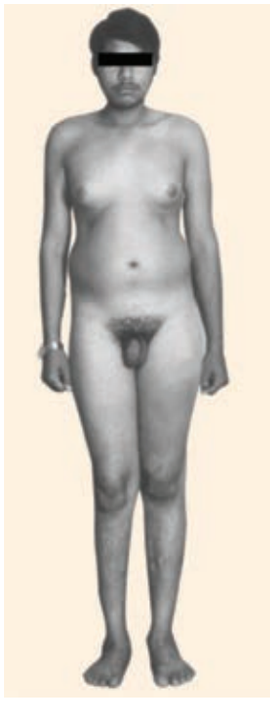

Fig. 18.16: Klinefelter syndrome. Note the tall stature and gynecomastia

or hypogonadotropic hypogonadism. Testicular volume below 1 mL points towards a permanent form of delayed puberty, while serum Inhibin B levels above 100 pg/mL are suggestive of constitutional delay. Adolescents with constitutional delay are likely to show a response on stimulation testing with hCG or GnRH. However, these tests are nondiscriminatory in most cases and follow-up after a course of testosterone is the best strategy. Patients with hypogonadotropic hypogonadism should undergo evaluation of hypothalamic–pituitary axis and neuroimaging.

Management

Testosterone treatment should be deferred till the age of 14 years and bone age of 13.5 years. Boys with suspected constitutional delay in puberty should receive three-monthly injections of testosterone enanthate (50 mg). This should be repeated, if adequate response is not achieved. Serum testosterone levels should be estimated three months after the last dose of the drug. Low testosterone levels indicate hypogonadotropic hypogonadism and the need for continued treatment. Gonadotropin treatment is effective in inducing fertility in hypogonadotropic hypogonadism.

Turner Syndrome

Turner syndrome is the most important cause of hypergonadotropic hypogonadism in girls. The disorder affects 1 in 2500 newborn phenotypic females. Features in childhood include cubitus valgus (wide carrying angle), shield chest with widely spaced nipples, web neck and short fourth metacarpal **(Table 18.25)**. Cardiac associations such as coarctation of aorta, mitral valve prolapse and aortic stenosis are common. Renal malformations such as horseshoe kidney, duplication of renal pelvis and agenesis may be present. Endocrine associations include hypothyroidism and diabetes mellitus **(Table 18.26)**. The condition is discussed in detail in Chapter 23.

Suggested Reading

1. Bangalore KK, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: Update by an international consortium. Horm Res Pediatr 2019;91:357–72.
2. Fuqua JS. Treatment and outcomes of precocious puberty: an update. J Clin Endocrinol Metab 2013;98:2198–207.
3. Menon PSN, Paulose A. Precocious puberty. In: Desai MP, Menon PSN, Bhatia V, Seth A (eds). Pediatric Endocrine Disorders, 4th edn. Hyderabad: Universities Press Pvt Ltd; 2022, pp 153–69.
4. Watson S, Fuqua JS, Lee PA. Treatment of hypogonadism in males. Pediatr Endocrinol Rev 2014;11(Suppl 2):230–39.

Competencies: **PE33.7; PE33.8**

DIFFERENCES IN SEX DEVELOPMENT

Disorders or differences in sex development (DSD), previously termed as intersex disorders, are rare disorders of aberrant anatomical sexual differentiation.

Physiology

In utero, normal sexual development proceeds in an orderly manner from genetic to gonadal to genital differentiation. Foremost, the sexual differentiation is determined by the karyotype of the fetus. The Y chromosome contains the SRY gene (sex-determining region of the Y chromosome), which encodes a transcription factor that is essential for the development of testes.

Gonadal differentiation: Germ cells arise from the celomic epithelium of hindgut and migrate to the gonadal ridge at 4–6 weeks of gestation. These cells combine with somatic cells to give rise to the undifferentiated gonad that is bipotential and can develop into testes or ovary. Certain genes such as Wilms tumor gene 1 (*WT1*) and steroidogenic factor 1 (*SF1* or *NR5A1*) are needed for gonadal differentiation in both males and females. In the presence of Y chromosome and SRY, testes development ensues. Other genes act in conjunction with *SRY*, namely, *SOX9* (a transcription factor on X

Table 18.26: Associations of Turner syndrome and their evaluation

System	*Association*	*Intervention*
Growth	Growth failure	GH, oxandrolone
Puberty	Delayed puberty, secondary amenorrhea, infertility	FSH estimation at 12 years, hormone replacement
Cardiovascular system	Coarctation of aorta, bicuspid aortic valve, partial anomalous pulmonary venous return (PAPVR), aortic dissection	Four limb blood pressure, ECG, ECHO at baseline, MRI at 18 years, imaging every 5 years
Ear	Otitis media, conductive and sensorineural hearing loss	Hearing assessment, otoscopic examination, hearing aid
Eye	Strabismus, ptosis, color blindness	Fundoscopy
Orthopedics	Scoliosis, lordosis, reduced cortical density, congenital dislocation of hip	Orthopedic review
Renal system	Collecting duct abnormality, horseshoe kidney, positional abnormality	Ultrasound kidney
Autoimmune disorders	Hypothyroidism, celiac disease	Thyroid function, tissue transglutaminase antibodies
Skin	Pigmented nevi	Monitoring for size

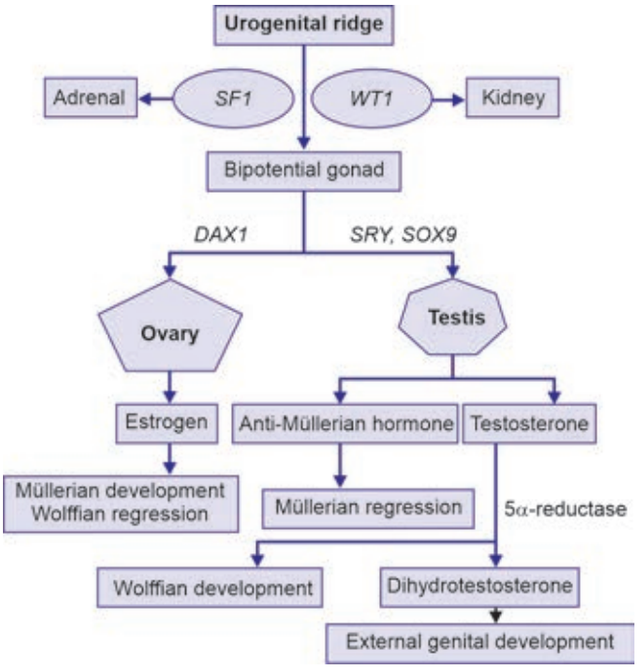

Fig. 18.17: The process of sex development (DSD) and its disorders. *DAX1* dosage sensitive sex reversal gene; *SF1* steroidogenic factor 1; *SOX9* transcription factor related to SRY; SRY sex-determining region on the Y chromosome; *WT1* Wilms tumor 1 gene

chromosome) and *DAX1* gene (dosage-sensitive sex reversal) to induce testes development **(Fig. 18.17)**. In the absence of *SRY*, the bipotential gonad develops into ovary. Gonadal differentiation is complete by 7–8 weeks of gestation.

Genital differentiation: The testes secrete anti-Müllerian hormone (AMH) and testosterone. AMH, produced by the Sertoli cells, leads to regression of Müllerian ducts. Testosterone produced by the Leydig cells is responsible for differentiation of Wolffian ducts into vas deferens and seminiferous tubules. Dihydrotestosterone (DHT), produced by the action of 5α-reductase on testosterone, is responsible for male external genital development (testicular descent, scrotal fusion and penile enlargement).

In the absence of testes and AMH production, Müllerian ducts differentiate into fallopian tubes, uterus and the upper two-thirds of the vagina. In the absence of testosterone, Wolffian ducts regress and external genitalia remain undifferentiated. Labioscrotal swellings and urethral folds do not fuse and give rise to labia majora and minora, respectively. The genital tubercle forms the clitoris while canalization of the vaginal plate creates the lower portion of the vagina. Prenatal exposure to androgens may lead to labioscrotal fusion, while exposure thereafter usually causes clitoromegaly alone and no labial fusion.

Classification

DSD is defined as a discrepancy among the chromosomal, gonadal and genital sex. DSD is classified based on the karyotype as sex chromosomal DSD, 46,XY DSD and 46,XY DSD **(Table 18.27)**.

Table 18.27: Karyotype based classification of differences in sex development (DSD)

46,XX DSD
- Androgen excess
  - Congenital adrenal hyperplasia
    - 21-hydroxylase deficiency
    - 11β-hydroxylase deficiency
    - 3β-HSD deficiency
    - POR deficiency
  - Placental aromatase deficiency
  - Maternal virilizing tumors
  - Maternal ingestion of androgenic drugs
- Abnormal gonadal developments
  - Ovotesticular DSDs
  - 46,XX testicular DSD (*SRY*+, *SOX9* duplication)

46,XY DSD
- Disorders of androgen synthesis or actions
  - *LHCGR* gene mutations
  - Congenital adrenal hyperplasia
    - StAR deficiency
    - 3β-HSD deficiency
    - 17-hydroxylase/17,20-lyase deficiency
    - POR deficiency
  - 17β-HSD deficiency
  - 5α-reductase deficiency: Types I and II
  - Androgen insensitivity syndrome: Complete or partial Smith-Lemli-Opitz syndrome
- Abnormal gonadal development
  - Gonadal dysgenesis: Complete or partial
  - Gonadal regression
- Other conditions
  - Persistent Müllerian duct syndrome

Sex chromosomal DSD
45,X (Turner syndrome and variants)
47,XXY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis)
46,XX/46,XY (chimeric, ovotesticular DSD)

HSD hydroxysteroid dehydrogenase; LHCGR luteinizing hormone/choriogonadotropin receptor; POR P450 oxidoreductase; StAR steroidogenic acute regulatory protein

Sex Chromosomal DSD

Sex chromosomal DSD includes patients with abnormal karyotype including mixed gonadal dysgenesis (mosaic karyotype 45,X/46,XY).

XY DSD

Among 46,XY individuals, defects in testicular differentiation (gonadal dysgenesis) androgen production or action may result in DSD.

Disorders of gonadal differentiation: These disorders are associated with abnormal gonadal development. The gonad is usually a streak (no functional gonadal tissue, also called complete gonadal dysgenesis) or partially functional (partial gonadal dysgenesis). *SRY* gene deletion in a 46,XY male results in development of ovary and

female phenotype. Causes of gonadal dysgenesis include mutations in genes involved in the testicular differentiation (*WT1, SF1, SOX9,* and *DAX1*). These disorders are associated with renal (*WT1* mutation), skeletal (*SOX9*) and adrenal abnormalities (*DAX1*). 46,XY gonadal dysgenesis is associated with the risk of development of gonadal malignancy (gonadoblastoma).

Vanishing testes syndrome consists of absent testes with normal or undervirilized external genitalia. The exact etiology of this condition is not known but postulated to be *in utero* ischemic insult to the testes.

Inefficient androgen production: Testosterone biosynthetic defects include deficiency of enzymes involved in steroid and androgen production like StAR, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase and 17β-hydroxysteroid dehydrogenase. These disorders may be associated with adrenal insufficiency depending on the enzyme that is deficient. Patients have low testosterone levels and testes fail to produce adequate testosterone after hCG injection.

Inefficient androgen action: These disorders result from decreased action of androgens. Androgen insensitivity syndrome (AIS) is an X-linked disorder that results from *AR* gene mutation and is characterized by absent or dysfunctional androgen receptor. AIS forms a clinical spectrum ranging from complete feminization to a boy with hypospadias, to a male with infertility. Children with complete AIS have feminized genitalia and may be diagnosed in childhood due to the presence of inguinal mass (palpable testes) or present at puberty with primary amenorrhea. These patients have normal thelarche (due to estrogen formed from high testosterone levels) but absent or sparse pubic and axillary hair.

Patients with 5α-reductase enzyme deficiency have normal testosterone but low levels of DHT leading to undermasculinization. The presentation ranges from female-looking genitalia to variable degrees of undermasculinization (micropenis, undescended testes, incomplete fusion of scrotum or hypospadias). Most children with 5α-reductase deficiency virilize during puberty due to increased testosterone levels. In classical cases, a 46,XY individual with 5α-reductase deficiency reared as a girl presents with spontaneous virilization and gender change at puberty.

46,XX DSD

Increased androgen production during the critical period of fetal development can result in virilization of a 46,XX individual, the most common cause being CAH due to 21-hydroxylase deficiency. It is characterized by deficiency of glucocorticoids and mineralocorticoids with excess androgens levels. Delay in diagnosis may result in fatal salt-wasting crisis, underscoring the importance of early detection. 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency and P450 oxidoreductase deficiency (POR) are the other forms of CAH that present with virilization of a 46,XX infant.

Rarely, transplacental transfer of androgens due to maternal medications or hyperandrogenism may lead to fetal virilization. These disorders are readily identifiable by history of virilization in mother. Placental aromatase enzyme converts fetal adrenal androgens to estrogen and deficiency of this enzyme may result in high levels of fetal androgens, virilization of mother during pregnancy and DSD in the newborn.

Other rare causes of 46,XX DSD include gonadal dysgenesis due to genes involved in gonadal development (*WT1* or *SF1*). These patients have normal female external genitalia but fail to undergo normal puberty due to lack of ovaries. Occasionally, an aberrant *SRY* gene translocation in a 46,XX individual can result in testicular development and typical male genitalia.

Ovotesticular DSD (previously called true hermaphroditism) is a condition in which both testes and ovary are present in the same individual. It results from mutations in certain genes involved in gonadal development. The most common karyotype is 46,XX and rarely 46,XY/46,XX or 46,XY/46,XXY chimerism. These patients have a variable presentation ranging from atypical genitalia to abnormal pubertal development.

Evaluation

The main clinical presentation of DSD consists of atypical genitalia generally noticed at birth (**Table 18.28**). Sometimes, the genitalia may be normal-looking but the child may present at a later age with inguinal masses (probable AIS) or atypical pubertal development: Virilization in children raised as girls (possible 5α-reductase deficiency), delayed puberty (probable gonadal dysgenesis) or primary amenorrhea (probable complete AIS).

Clinical: Family history of genital ambiguity is suggestive of genetic disorders such as 21-hydroxylase deficiency, 5α-reductase deficiency or AIS. CAH is likely, if there is a history of fetal losses and sibling deaths and family history of consanguinity. On the other hand, history of similar disorder in healthy 'genetically male' relatives (brothers, maternal uncles and sons of maternal aunts) is suggestive of an X-linked disorder such as AIS.

Intake of progestational drugs during first trimester and features of virilization in mother should be searched. Failure to thrive, polyuria and lethargy indicate 21-hydroxylase deficiency **(Table 18.29)**. Virilization during puberty is suggestive of 5α-reductase deficiency, while feminization (gynecomastia) indicates AIS.

General examination should include assessment for facial dysmorphism and hyperpigmentation. Maternal

Table 18.28: Definition of atypical genitalia in a newborn

• Apparent female with clitoromegaly >1 cm
• Apparent female with inguinal masses
• Apparent male with bilateral cryptorchidism
• Apparent male with micropenis (stretched penile length <2.5 cm)
• Apparent male with isolated severe degree of hypospadias (penoscrotal or perineal)
• Any degree of hypospadias associated with micropenis or undescended testes

Table 18.29: Clinical pointers to etiology of differences in sex development (DSD)

Pointer	*Likely diagnosis*
Pigmentation	Congenial adrenal hyperplasia, *SF1* defect, StAR defect
Polydactyly	Smith-Lemli-Opitz syndrome
Skeletal dysplasia	*SOX9* defect
Genital asymmetry	Mixed gonadal dysgenesis, ovotesticular DSD
Hypertension	11β- or 17α-hydroxylase defect
Hemihypertrophy	*WT1* mutation
Renal failure	Denys-Drash syndrome

examination for features of hyperandrogenism such as hirsutism, acne and change in voice should be done.

Genital examination: The most important step is identification of gonads. Bilaterally rounded structures below the inguinal canal are most likely testis. If they are present, the position of the testes (inguinal or scrotal) should be noted. Unilateral gonads are suggestive of mixed gonadal dysgenesis. The labioscrotal region should be evaluated for the extent of fusion and the presence of separate urethral and vaginal openings. The length of phallus and the position of urethra should be recorded for the presence of hypospadias. In virilized females, the genitalia is staged according to the classification proposed by Prader from grades I to V, with grade I representing female with clitoromegaly and V male-looking genitalia with cryptorchidism. Müllerian structures may be confirmed by rectal examination.

Investigations: Initial investigations for a child with DSD presenting with atypical genitalia should include karyotyping, estimation of serum electrolytes and 17-OHP, and pelvic ultrasound. Fluorescent *in situ* hybridization (FISH) is used to confirm the presence of Y chromosome. Ultrasound of pelvis helps to identify intra-abdominal gonads and Müllerian structures.

In girls with common urogenital sinus, a genitogram is helpful to determine the level of fusion of the vagina with the common urogenital sinus, which is of surgical importance. Further investigations are guided by clinical and laboratory evaluation.

Presence of clitoromegaly and no palpable gonads in a child with 46,XX karyotype as well as Müllerian structures on ultrasound indicate an androgen excess state and the need for estimation of serum 17-OHP to rule out CAH. Similarly absence of Müllerian structures in a child with 46,XY karyotype is suggestive of inefficient testosterone production or action with normal sertoli cell function and should be evaluated with estimation of testosterone and DHT. The presence of both Müllerian structures and palpable gonads indicates gonadal dysgenesis or ovotesticular DSD. Absent gonads and Müllerian structures may be caused by vanishing testis syndrome or dysfunctional intra-abdominal testis. Estimation of levels of AMH and hCG stimulation test are helpful in differentiating these two conditions. Children with vanishing testis will have low levels of AMH and low testosterone response to hCG stimulation.

Management

Management involves parental counseling, decision about sex of rearing, timing of surgical correction and gonadectomy.

Parental counseling: Birth of a child with DSD generates significant parental anxiety and stress. The most important aspect of counseling is reassurance of parents that the child is healthy and can be managed with appropriate surgical and/or medical treatment. Gender-specific connotation ('he or she', 'his or her', 'testis or ovary') should be avoided and neutral terms like 'child' or 'baby' and ' gonads' and 'phallus' be used during counseling.

Decision about gender of rearing: Gender assignment should depend on the potential for future sexual and reproductive function, anatomical status, feasibility of reconstructive surgery and social acceptance and norms. 46,XX girls with virilization disorders usually have potential for fertility and should be reared as females. Individuals with complete AIS should also be reared as females. Decision of gender of rearing is difficult in disorders of inefficient androgen production and action. This should depend on genital appearance, surgical feasibility and psychological evaluation.

Surgery: In virilized girls with CAH, most centers perform clitoroplasty at the age of 1 year with vaginoplasty later during puberty for girls with vaginal stenosis. Gonadectomy should be done in gonadal dysgenesis or ovotesticular DSD, if a Y cell line is present, as there is a risk of gonadal malignancy. In undervirilized males, hypospadias repair and chordee correction are generally done in early childhood.

Cryptorchidism (Undescended Testes)

Cryptorchidism is present in about 3% of full-term infants and 20% of premature infants. In most of these cases, testes descend spontaneously by the age of one year with a decrease in the prevalence to 1%. Spontaneous testicular descent is unlikely after the age of one year and the prevalence in adult population is 0.8%.

Etiology

Most children with undescended testis do not have an identifiable underlying cause. Endocrine causes account for only a small proportion. The possibility of salt-wasting 21-hydroxylase deficiency presenting with sex reversal should be considered in newborns with bilateral cryptorchidism. Undescended testis may be associated with hypopituitarism, dysmorphic syndromes and disorders of androgen production and action.

Evaluation

It is important to differentiate true undescended testis from retractile or ectopic testis due to therapeutic and prognostic implications. Poorly developed scrotum and inability to bring down the testis to the scrotal sack suggests true undescended testis. Retractile testis is an otherwise fully descended testis that has an active cremasteric reflex, which retracts it into the groin.

Penoscrotal hypospadias and genital ambiguity are suggestive of disorders of androgen production or action. The hCG stimulation test and serum AMH levels should be done in boys with bilateral nonpalpable testis to differentiate abdominal testis from anorchia.

Management

Undescended testis is associated with significant complications like torsion, trauma, inguinal hernia, testicular dysfunction and development of malignancy. These children should be treated early because of the increased risk for malignancy and infertility in later life. Surgery is the only approved therapy for undescended testis due to potential adverse effects of hCG on germ cells. Surgery should be done within the first year of life.

Micropenis

A penis whose length in stretched position is less than 2 SD below the mean for the age is termed micropenis. Most often it is the result of primary or secondary testicular failure.

Etiology

Micropenis results from decreased androgen action during fetal life. It may be due to hypogonadotropic hypogonadism as in Kallmann syndrome, Prader-Willi syndrome, septo-optic dysplasia, or Klinefelter syndrome. It may also be a manifestation of partial androgen insensitivity syndrome or testosterone biosynthetic defects.

Evaluation

Penile length should be measured in a fully stretched state by grasping the glans between thumb and forefinger. A firm ruler or caliper should be pressed against the pubic ramus to depress the suprapubic fat pad. The measurement should be made along the dorsum to the tip of the glans penis excluding the length of foreskin. Penile size is often underestimated in boys with obesity (due to the suprapubic fat) and hypospadias (due to chordae). Investigations should include estimation of gonadotropins and testosterone levels, if the child has been evaluated during mini-puberty of infancy (between 3 weeks to 8 months of age) or puberty. Otherwise, between the age of 1 to 10 years, these levels are physiologically low, and will require stimulation testing for further interpretation. Low gonadotropins and testosterone levels indicate hypogonadotropic hypogonadism.

Management

All boys with micropenis are treated with a course of low dose testosterone (25 mg testosterone enanthate or cypionate monthly for three doses). The aim of this short course of testosterone treatment is to increase penile length and not to induce puberty. Boys with micropenis should be reared as males as normal sexual function is usually attainable with early intervention.

Suggested Reading

1. Ahmed SF, Achermann JC, Arlt W, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. Clin Endocrinol. 2011;75:12–26.
2. Penson D, Krishnaswami S, Jules A, McPheeters ML. Effectiveness of hormonal and surgical therapies for cryptorchidism; a systematic review. Pediatrics 2013;131:e1897–1907.
3. Rey RA, Grinspon RP. Normal male sexual differentiation and etiology of disorders of sex development. Best Pract Res Clin Endocrinol Metab 2011;25:221–38.

Competencies: **PE33.4; PE33.5**

DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and glycosuria. The factors that contribute to hyperglycemia include decreased insulin secretion and its action as well as increased glucose production. Hyperglycemia resulting from diabetes mellitus causes damage to several organs and body systems, including the kidneys, eyes and cardiovascular system. While type 1 diabetes caused by insulin deficiency remains the predominant form in children, type 2 diabetes has emerged as an important entity in adolescents with obesity.

Diagnostic Criteria

The definition of diabetes in children is similar to adults. Fasting blood glucose more than 126 mg/dL (7 mmol/L), postprandial blood glucose (two hours after an oral glucose load of 75 g) of more than 200 mg/dL (11.1 mmol/L) or random blood glucose greater than 200 mg/dL with classical symptoms is diagnostic of diabetes mellitus.

Glycated hemoglobin or hemoglobin A1c (HbA1c) is now accepted as a diagnostic criterion for diabetes in adults with levels greater than 6.5% indicating diabetes. The validity of HbA1c as the sole diagnostic criteria in children and adolescents is still disputed. Most children with type 1 diabetes have blood glucose level substantially higher than 200 mg/dL and do not need a glucose tolerance test (GTT). Tolerance testing is restricted to children with obesity and suspected type 2 diabetes. The test is performed after adequate carbohydrate intake for three days (150 g/m^2/day) and overnight fast. The child is given glucose (1.75 g/kg, maximum 75 g) as a chilled liquid with blood glucose measurements done at 0 and 120 minutes.

Classification

Most children with diabetes have type 1 diabetes caused by damage to beta cells of pancreas **(Table 18.30)**. Type 2 diabetes is an important cause in adolescents with obesity. Other forms of childhood diabetes include genetic forms of diabetes (monogenic diabetes of young, MODY) and neonatal diabetes.

In most situations, the type of diabetes is evident on clinical presentation and extensive diagnostic workup is not required. Investigations for classification of diabetes are reserved for children with onset after puberty (likely to be type 2 diabetes or MODY), no ketoacidosis at diagnosis (likely to be type 2 diabetes or MODY), those with obesity and acanthosis nigricans (likely to be type 2 diabetes) or in the presence of abdominal pain and steatorrhea (exocrine pancreatic disorder).

Investigations for classification for diabetes include ultrasound abdomen (for pancreatic calcification), levels

Table 18.30: Classification of diabetes mellitus (American Diabetes Association 2014)

Type 1 diabetes mellitus

Absolute insulin deficiency due to beta cell destruction: Up to 95% of all pediatric diabetes

1. IA (autoimmune)
2. IB (non-autoimmune)

Type 2 diabetes mellitus

Insulin resistance with relative insulin deficiency: 10–50% of diabetes in adolescents depending on ethnicity served

Other specific types of diabetes mellitus

- *Genetic defects of beta cell function:* Maturity onset diabetes of the young (MODY), neonatal diabetes, mitochondrial disorders, Wolfram syndrome
- *Genetic defects in insulin action:* Insulin receptor defects, lipodystrophy, type A insulin resistance, Rabson-Mendenhall syndrome
- *Diseases of exocrine pancreas:* Pancreatitis, trauma pancreatectomy, cystic fibrosis, fibrocalcific pancreatic disease, hemochromatosis
- *Endocrinopathies:* Growth hormone excess, Cushing syndrome, hyperthyroidism
- *Drug or chemical induced:* Steroids, L-asparaginase, cyclosporine, tacrolimus, interferon, pentamidine, thiazides, diazoxide, phenytoin
- *Infections:* Congenital rubella, cytomegalovirus
- *Uncommon forms:* Stiff-man syndrome, anti-insulin receptor antibodies

Gestational diabetes

Diabetes diagnosed in the second and third trimesters of pregnancy that is clearly not overt diabetes

of C-peptide (a marker of beta cell function), glutamic acid decarboxylase (GAD) and insulin autoantibodies (indicators of autoimmune nature of type 1 diabetes) and genetic analysis for MODY **(Table 18.31)**. The disease classification is often challenging as C-peptide levels may be low due to glucotoxicity in the initial stage of type 2 diabetes and autoantibodies are positive in only 60% of Indian children with type 1 diabetes.

Type 1 Diabetes Mellitus

Type 1 diabetes is the commonest form of childhood diabetes characterized by insulin deficiency due to damage to beta cells of pancreas. The disorder requires lifelong insulin replacement.

Epidemiology

There is a significant geographic variation in the incidence of type 1 diabetes. Scandinavia has the highest incidence, with Finland having the incidence of 35/100,000/year. Indian data suggest an incidence of 10.5/100,000/year. Type 1 diabetes can occur at any age but has two discernible age peaks of higher incidence. The first peak occurs around 5 to 7 years is related to exposure to viral infections, while the second peak around puberty is linked to increase in GH and sex steroids.

Pathogenesis

Children born to parents with type 1 diabetes have a higher risk of developing the disease. The risk is higher, if the affected parent is father (7% compared to 4%, if mother is affected). If a sibling is affected, the risk is 6% when the onset is before 10 years of age and 3% thereafter. The role of heredity is less significant in type 1 diabetes compared to type 2. In studies on identical twins, concordance rates of only 30–40% have been reported for type 1 diabetes suggesting that factors other than heredity play an important role in the pathogenesis.

The most important genetic focus for type 1 diabetes lies on chromosome 6 and is linked with expression of HLA antigens. HLA-DR3 and DR4 are important determinants of developing type 1 diabetes. The genes implicated in pathogenesis include insulin gene and cytotoxic T lymphocyte antigen 4 (*CTLA4*). Together these genes can explain around 60% heritability of type 1 diabetes. Protection against the disease is provided by the HLA-DR2 haplotype.

Infections predisposing to type 1 diabetes include mumps, coxsackievirus, cytomegalovirus and rubella (congenital rubella syndrome). There is increasing evidence

Table 18.31: Differentiating features of common causes of diabetes in children

Feature	*Type 1 diabetes mellitus*	*Type 2 diabetes mellitus*	*Maturity onset diabetes of the young (MODY)*
Age at onset	Any age; most common in children	Adults and adolescents	Adults and adolescents
Onset of disease	Acute	Insidious	Insidious
Diabetic ketoacidosis at onset	30–60%	5–25%	Less than 5%
Family history of diabetes	5–10%	75–90%	100%
Obesity	Around 20%	More than 90%	Unusual
Acanthosis nigricans	Absent	Usually present	Absent
Insulin requirement	Universal	Variable	Variable
C-peptide levels	Low	High or normal	Low-normal
Insulin sensitivity	Normal	Low	Normal
Islet cell antibodies	40–70%	Unusual	Negative
Management	Insulin	Diet, metformin	Diet, sulfonylurea

that early introduction of cow milk protein may be an important factor in the subsequent development of diabetes in genetically susceptible infants.

There is substantial evidence for autoimmunity in type 1 diabetes. Lymphocytic infiltration around the beta cells is found on autopsy of individuals of type 1 diabetes who die due to incidental causes. At diagnosis, 70–80% of children with type 1 diabetes have antibodies against one or more of the several islet cell antigens (ICA). These antibodies usually predate the clinical presentation of insulin-dependent diabetes mellitus by a few months or years. This suggests that they play a major role during the initial pathogenesis of the disease.

Clinical Features

Children and adolescents usually present with symptoms of diabetes that are ongoing for a month or two prior to seeking physician's contact, with an acute increase in symptoms over the previous week. Symptoms of type 1 diabetes include polyuria, nocturia, enuresis, polydipsia, recent weight loss, polyphagia and fatigue. Recent acute infection is often noted at presentation. Unfortunately, these symptoms are often ignored resulting in delayed diagnosis.

Course of Illness

Insulin is the mainstay of therapy. Once insulin is initiated, blood glucose levels gradually decline. Often, after few weeks of insulin therapy, the need for exogenous insulin declines, due to a transient recovery of insulin secretion. This phase is called the "honeymoon phase of diabetes". Some children may be completely insulin-free during this time. This phase lasts from a few weeks to months, and rarely to one year, after which the need for insulin gradually increases.

Ambulatory Care

Day-to-day management of type 1 diabetes involves management of glycemic control, and avoidance of acute complications and prevention of chronic complications on one hand and achieving social, scholastic and psychological goals of the child on the other. Comprehensive education and ongoing involvement with the family is mandatory. Teamwork approach with pediatrician/endocrinologists, diabetic nurse educator, social worker and nutritionist is essential.

Insulin

Insulin is the cornerstone of type 1 diabetes management. The body secretes insulin at a basal rate with intermittent secretion with meals. The aim of management is to mimic this pattern as best as possible.

Dose: Insulin dose is guided by pubertal status with lower dose for prepubertal children (0.6 unit/kg/day) compared to pubertal (1.0–1.2 unit/kg/day) and post-pubertal children (1.0 unit/kg/day). In the post-ketoacidosis phase, the dose may be as high as 2–2.5 unit/kg/day.

Preparations: Chemical modifications of insulin alter their action profile providing flexibility in tailor made insulin regimen. Currently all available forms of insulin are derived by recombinant DNA technology **(Table 18.32)**.

Short-acting (regular) insulin: Regular insulin that is structurally the same as natural insulin, is the agent of choice for IV infusion while managing diabetic ketoacidosis (DKA). On subcutaneous administration, the medication forms hexamers in the skin, delaying onset of action by 30–60 minutes. Regular insulin should hence be given 30 minutes before a meal, which may be a problem in young children and toddlers with unpredictable eating patterns. The longer duration of action is helpful, if there is a substantial gap between meals especially in school-going children who have early breakfast and late lunch.

Rapid-acting insulins (lispro, aspart, glulisine, and fast-acting aspart): These insulins do not form hexamers after injection and have immediate onset of action. They are ideal for toddlers with irregular eating patterns and can be given even after a meal. They provide better post-meal glycemic control compared to regular insulin and reduce the risk of hypoglycemia.

Intermediate-acting insulin (NPH): NPH is a chemically modified insulin (protamine) with prolonged duration of action of 12–18 hours. It is traditionally used with short-acting insulin for split-mix regime, but has significant intra-individual variability in absorption resulting in fluctuating glycemic control.

Long-acting insulin (glargine, detemir and degludec): These long-acting forms provide peakless cover for 18–36 hours. They are useful as basal insulin in basal-bolus regimen.

Table 18.32: Pharmacokinetic profile of insulin preparations

Preparation	*Onset*	*Peak*	*Duration*	*Indications*
Rapid-acting Lispro, Aspart, Glulisine	5–10 min	1–3 hr	3–4 hr	For use with insulin pump, as the bolus insulin in multiple daily injections (MDI) regimes
Short-acting Regular	30–60 min	2–4 hr	5–8 hr	Diabetic ketoacidosis (DKA), mix-split regimen
Intermediate-acting NPH	1–2 hr	2–8 hr	16–24 hr	Mix-split regimen, basal bolus regimen
Long-acting Glargine Detemir Degludec	 2–4 hr 1–2 hr 0.5–1 hr	 Peakless 6–12 hr Peakless	 20–24 hr 20–24 hr >24 hr	 Basal insulin Basal insulin, mix-split regimen Basal insulin

Insulin Regimen

The decision about the choice of insulin regimen is dependent on age, socioeconomic status and level of glucose control of a child. A physiological regimen with multiple daily injections is preferred in most children with the exception in a resource-poor setting where a conventional regimen is more practical.

Basal-bolus regimen: Basal-bolus regimen tries to mimic physiological insulin secretion with the use of a long-acting basal insulin (detemir or glargine, 40–50% of total daily dose in older children, and 25–30% in children below 5–6 years of age) and mealtime rapid-acting analog (aspart, glulisine or lispro, remaining total daily dose, **Fig. 18.18**). The mealtime dose is distributed over 3–5 times a day depending on the diet pattern of the child. This regimen offers flexibility, as changes in mealtimes do not cause significant fluctuations in glycemic control. The risk of hypoglycemia is also lower compared to split-mix regimen.

Mix-split regimen (two or three injections per day, Fig. 18.19): This involves the combination of short- and intermediate-acting insulins mixed at the time of injection. The injections are given 30 minutes before breakfast (two-thirds of daily dose) and 30 minutes before dinner (one-third of daily dose). The ratio of short- to intermediate-acting insulin is 1 to 2. This regimen has the advantage of less frequent injections and lower cost. The regimen requires rigid dietary control and strict lifestyle with regular mealtimes and snacks. In a variation of the regimen, another dose of regular injection is given before lunch. In yet another variation, the intermediate-acting insulin is shifted to bedtime to prevent nocturnal hypoglycemia and morning hyperglycemia **(Fig. 18.20)**.

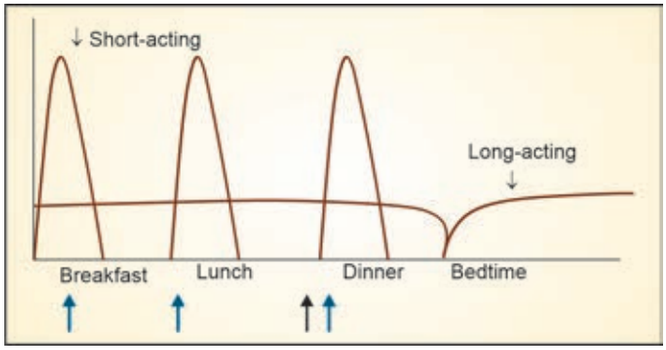

Fig. 18.18: Basal-bolus regimen. Intermediate- (NPH) or long-acting insulin (glargine or detemir) is given before dinner or at bedtime (40–50% of total daily dose; black arrow). Rapid- or short-acting insulin (aspart or lispro) is given before each meal (50–60% of total daily dose; blue arrows)

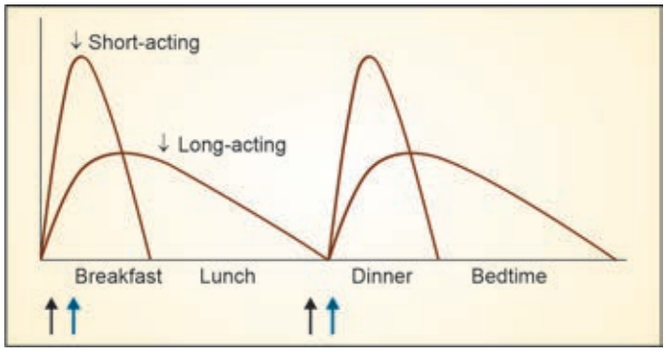

Fig. 18.19: Split-mix regimen. Insulin is given before breakfast (two-thirds of daily dose) and dinner (one-third of daily dose). Each injection is a combination of intermediate- or long-acting (NPH or detemir; two-thirds of the total dose; black arrows) and short- (regular) or rapid-acting insulin (lispro or aspart, one-third of the total dose; blue arrows). Regular meal pattern is required to prevent hypoglycemia

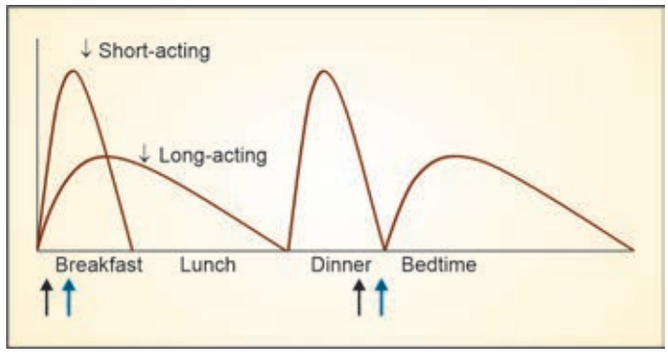

Fig. 18.20: Modified mix-split regimen. The night-time intermediate-acting insulin has been shifted from before dinner to bedtime. This is indicated in the presence of nocturnal hypoglycemia and high pre-breakfast blood glucose levels. Delayed administration and thereby peak of intermediate-acting insulin reduces the risk of nocturnal hypoglycemia on one hand while providing reasonable cover for morning hyperglycemia

Continuous subcutaneous insulin infusion (CSSI) or insulin pump: Insulin pump is an external device that infuses insulin at a predetermined rate with additional boluses given at mealtime. The basal dose can be adjusted for different times of the day and boluses tailored to different amount and types of meals to provide good glycemic control with limited glycemic variability. Insulin pump is superior to basal-bolus regimen in terms of insulin requirement, glycemic variability and weight gain. Closed loop systems and insulin pumps with capability to detect blood glucose levels and infusing desired amount of insulin have also been introduced, and provide a more physiological glycemic control.

Diabetes Education

Structured diabetes education is mandatory for the management of diabetes in children. Key areas to be covered in the program include pathophysiology of diabetes, insulin use, sick day management, hypoglycemia, nutrition, physical activity and social issues **(Table 18.33)**.

Nutritional Management

The key to successful nutritional management in type 1 diabetes is flexibility. Overzealous control is associated with rebellious behavior and dietary indiscretion. There is no 'diabetic diet' for children and they should be encouraged to have a normal healthy diet. Importance should be given to consistency of meal timings. Dietary exchanges and a 'nutritional pyramid approach' are useful in providing variety for children. Occasional treats during

Table 18.33: Diabetes education in children with type 1 disease

Category	*Should know*	*May know*	*Optional*
Disease	Diabetes is a lifelong disease	Role of insulin as life-saving therapy	Glucose homeostasis
	Normal outcome is possible with appropriate therapy	Differences of type 1 vs. 2 diabetes	Disease classification
		Pathophysiology of diabetes	Role of autoimmunity
		Complications	Disease associations
Treatment	Insulin is the only mode of treatment	Insulin preparations	Insulin regimens
	Daily injections are a must	Time course of injections	Insulin pumps
	Physical activities	Injection devices	Newer insulins
	No alternative medicine	Exercise and sports	Competitive sports
Skills	Insulin storage	Glycemic targets	Ketone monitoring
	Drawing up and mixing of insulin	Insulin changes	Glucagon injection
	Insulin injection techniques	Ketone monitoring	
	Self-monitoring of blood glucose		
	Diabetes diary and log		
Nutrition	Healthy eating	RDA for age	Carbohydrate counting
	Avoid simple sugars	Food exchanges	Insulin to carb ratio
	Mid-meal snacks	High fiber intake	Glycemic index
Follow-up	Honeymoon phase	Role of HbA1c	CBGM
	Hypoglycemia	Complications; DKA prevention	Transplantation
	Sick day guidelines	Physical activity	Career counseling

CBGM continuous blood glucose monitoring; DKA diabetic ketoacidosis; RDA recommended dietary allowances

Table 18.34: Nutritional guidelines for type 1 diabetes

Component	*Recommendation*	*Implication*
Energy	100% of RDA	No restriction
Carbohydrate	50–55% of calories Low GI carbohydrate	No restriction Reduced sugar intake
Fat • Saturated • Polyunsaturated • Monounsaturated • Cholesterol	25–40% of energy <10% of total energy <10% of total energy >10% of total energy <300 mg/day	Less saturated fat Less red meat, whole milk
Protein	10–15% of calories	No restriction
Fiber	More than 10 g/day	More fruits, vegetables

GI glycemic index; RDA recommended daily allowance

special occasions and eating out are allowed, if covered appropriately with insulin **(Table 18.34)**.

Monitoring

Self-monitoring of blood glucose (SMBG): SMBG is critical for management of type 1 diabetes. It should ideally be done before each meal and at bedtime. Post-meal and midnight blood glucose levels are measured as required, adjusted according to the patient age **(Table 18.35)**. In children with significant glycemic variability, continuous glucose monitoring system (CGMS) provides information about glycemic control every 5 minutes over a 72-hour period to help decide about insulin adjustment.

Table 18.35: Age-related glycemic targets for self-monitoring of blood glucose

Target	*<6 years*	*6–12 years*	*>12 years*
Blood glucose Premeal Bedtime	 100–180 mg/dL 110–200 mg/dL	 70–180 mg/dL 100–180 mg/dL	 70–130 mg/dL 90–140 mg/dL
HbA1c	Less than 8%	Less than 7.5%	Less than 7%

Hemoglobin A1c: HbA1c is a marker of glycemic control over previous 3 months and is the best predictor of long-term complications. Target levels for HbA1c are less than 7% in children and adolescents. These levels may be falsely low in children with sickle cell disease and increased red cell turnover as in hemolytic anemia. Falsely elevated HbA1c levels are seen with uremia and high dose aspirin treatment.

Follow-Up

Children with diabetes should be followed every three months or more frequently as needed. Clinical assessment should include assessment of growth, puberty, blood glucose levels, and examination of injection sites and care of feet. Children with unexplained hypoglycemia should be evaluated for adrenal insufficiency, hypothyroidism and celiac disease. Puberty is associated with an increase in insulin requirement. The requirement further increases in adolescents with obesity.

Sick Day Care

Key aspects of sick day management include frequent self-monitoring of glucose, regular fluid intake and treatment of the intercurrent illnesses. Insulin requirement usually increases during a febrile illness but may decrease with vomiting and diarrhea. Basal insulin should never be omitted in sick children with type 1 diabetes. In children with blood glucose less than 80 mg/dL, rapid-acting insulin should be withheld and the dose of intermediate-acting insulin is reduced by 20–30%. No extra insulin is required in children with febrile illness and blood glucose between 80 and 270 mg/dL. Blood or urine ketones should be measured, if blood glucose is more than 270 mg/dL. Children with moderate ketosis (blood ketones between 1 and 1.5 mmol/L) should be given extra regular insulin (10% of total daily dose). Impending DKA (blood ketone >1.5 mmol/L) is managed with extra doses of regular insulin (15–20% of total daily) and hourly blood glucose monitoring **(Fig. 18.21)**. The child should be hospitalized, if recurrent vomiting, poor oral intake and persistent hyper- or hypoglycemia are present.

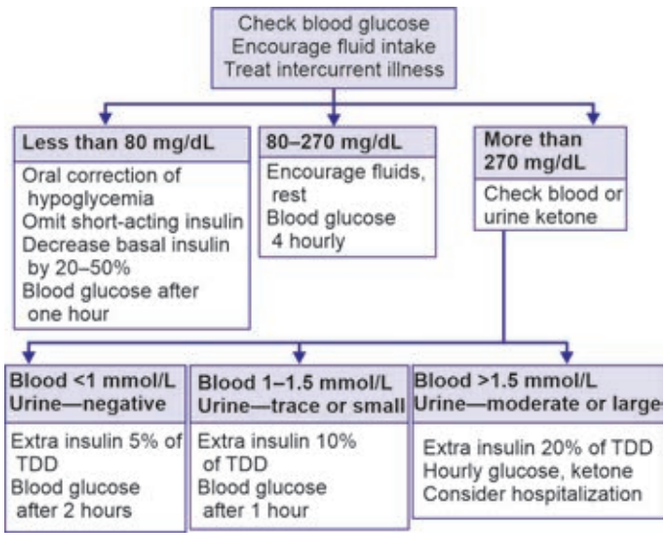

Fig. 18.21: Guidelines for sick day management in children with type 1 diabetes mellitus. TDD total daily dose

Acute Complications of Type 1 Diabetes

Hypoglycemia

In patients with diabetes, hypoglycemia is defined as blood glucose <70 mg/dL. It is quite common in children and is an impediment to optimal glycemic control. It should be considered in the presence of autonomic (e.g. sweating, palpitations, tremor, and hunger) or neuroglycopenic symptoms (e.g. headache, confusion, drowsiness and seizures). Children with hypoglycemia should immediately receive 0.3 g/kg rapidly absorbed glucose (upto 15 g), followed by long-acting carbohydrate. Severe hypoglycemia is a medical emergency and should be treated with injectable glucagon (0.5 mg for weight <25 kg; 1 mg for weight >5 kg) or intravenous dextrose.

Diabetic Ketoacidosis (DKA)

DKA is the most severe acute complication of diabetes mellitus. Previously believed to be limited to subjects with type 1 diabetes, DKA is increasingly observed in type 2 diabetes and MODY. Early identification and management are essential to limit the extent of mortality and morbidity associated with DKA. Thirty to forty percent of newly diagnosed children with type 1 diabetes present with DKA. Although epidemiological data from India is lacking, the figure is higher than the developed countries.

Pathophysiology: DKA is the end result of absolute or relative insulin deficiency combined with excess of counter-regulatory hormones such as glucagon, catecholamines, cortisol and GH. DKA is usually precipitated by infection, stress and trauma, and conditions associated with increased insulin requirement and higher level of counter-regulatory hormones. These hormonal alterations result in hyperglycemia and lipolysis resulting in increased free fatty acid production. Oxidation of fatty acids in liver generates β-hydroxybutyrate and acetoacetic acid (ketones). Accumulation of ketoacids produces acidosis resulting in Kussmaul breathing (acidosis), abdominal pain (acidosis) and fruity odor of breath (acetone). Hyperglycemia results in increased urinary water losses due to osmotic diuresis and dehydration. Acidosis causes shift of intracellular ions, most importantly potassium and phosphate, to the extracellular compartment. However, serum levels of potassium are variable, depending on the stage of DKA. Initially, serum potassium levels are high; as therapy with insulin is initiated, the patient becomes hypokalemic. Hyperglycemia also falsely lowers serum sodium resulting in pseudohyponatremia; each 100 mg/dL elevation in blood glucose lowers sodium by 1.6 mEq/dL.

When to suspect: There is need for high index of suspicion for DKA and it should be considered in the differential diagnosis of the following:

- *Encephalopathy:* CNS infections, severe malaria, poisoning
- *Acute abdomen:* Pancreatitis, appendicitis
- *Dehydration:* Gastroenteritis
- *Tachypnea:* Bronchial asthma, pneumonia

- *Hyperglycemia with acidosis without ketosis:* Renal failure, septicemia
- *Ketoacidosis without hyperglycemia:* Starvation, salicylate poisoning, organic acidemia

Criteria for diagnosis: DKA should be diagnosed in presence of all of the following:

i. Hyperglycemia (blood glucose >200 mg/dL);
ii. Metabolic acidosis (pH <7.3, bicarbonate <15 mEq/L); and
iii. Ketosis (blood ketone >1.5 mmol/L, or urine ketone >2+).

Management: DKA is a life-threatening condition and should be managed in a hospital equipped with facilities for intravenous infusion and measurement of blood gas and electrolytes. Children younger than 2 years of age and those with severe DKA should be managed in an ICU.

Evaluation

Clinical: Initial evaluation should be guided towards assessment of adequacy of airway, breathing and circulation. Level of dehydration is ascertained along with hemodynamic status. Careful neurological evaluation including assessment of level of consciousness, pupils (dilated fixed in presence of cerebral herniation), cranial nerves (sixth nerve palsy suggests cerebral edema) and deep tendon reflexes (brisk if raised intracranial tension) is mandatory.

Investigations

Serum sodium: There is usually a significant sodium deficit (4–6 mEq/kg). The sodium levels are falsely reduced in hyperglycemia mandating the need to use corrected sodium. Rapid decline in serum sodium is a risk factor for cerebral edema.

Serum potassium: There is substantial intracellular potassium deficit (3–6 mEq/kg). Serum levels are, however, normal or high due to extrusion of intracellular potassium due to acidosis and insulin deficiency. Treatment of DKA is associated with the risk of hypokalemia due to its intracellular shift following reversal of metabolic acidosis and correction of insulin deficiency.

Serum phosphate: Usually there is significant phosphate deficit. Treatment is required, if phosphorus level is below 1 mg/dL.

Infection screening: Transient leukocytosis is common; infection should be considered in the presence of persistent leukocytosis and fever.

Renal function tests: High blood urea usually indicates severe DKA.

Electrocardiography: This is often done to screen for hypo- or hyperkalemia.

Management

Initial stabilization: The child should be assessed for adequacy of airway, breathing and circulation. Initial fluid bolus of 10 mL/kg normal saline over 1-hour should be given in children with dehydration. Oxygen and respiratory support should be provided, if required. The child should be kept nil by mouth with insertion of nasogastric tube and urinary catheter, if unconscious. Intubation should be deferred as it may worsen CNS acidosis.

Fluid therapy: Fluid therapy is the mainstay of treatment for DKA. However, rapid and excessive fluid intake is a risk factor for developing cerebral edema. The aim is to provide maintenance requirement and deficit evenly over 48 hours (72 hours for children with high plasma osmolality). In most children, the fluid deficit is 5–10%. Fluid requirement is usually around 3–3.5 L/m^2/day. Care is taken to avoid fluid administration of more than 4 L/m^2/day due to risk of cerebral edema. The amount of fluids given at other centers prior to referral should also be considered while calculating fluid requirements.

Insulin: Insulin should be administered after initial hydration as blood glucose levels fall rapidly even without insulin. Early insulin treatment is associated with drastic fall in plasma osmolality, hypokalemia and increased risk of cerebral edema.

Continuous intravenous infusion is the preferred route. The intravenous tubing should be flushed with insulin as insulin binds to plastic tube. There is no role of initial insulin bolus. In infants and mild DKA, the insulin infusion rate should be kept at 0.05 unit/kg/hr. The dose should be increased, if the fall in glucose is less than 50 mg/dL/hr, or if the acidosis is not resolving satisfactorily. The dose is increased in quantum of 0.02 unit/kg/hr. The insulin infusion rate should be reduced only after resolution of acidosis.

If facility for intravenous insulin is not available, intramuscular regular insulin may be used. The first dose is 0.3 unit/kg followed by 0.1 unit/kg hourly. Recurrent intravenous boluses of insulin should be avoided due to the risk for cerebral edema. Subcutaneous insulin is not recommended due to decreased absorption in the setting of poor perfusion.

Serum sodium: Most patients have significant sodium deficits (4–6 mEq/kg). Slow rise in sodium in patients with rapid fall in glucose is a risk factor for cerebral edema. Normal saline (154 mEq/L) should be used in the first 6 hours of therapy; thereafter the sodium content should be between 77 and 154 mEq/L.

Serum potassium: Although there is deficit in total body potassium, extracellular potassium levels may initially be high due to acidosis and insulin deficiency. There is a risk of life-threatening hypokalemia following correction of insulin deficiency and resolution of metabolic acidosis. In patients with initial potassium levels less than 3.5 mEq/ L, potassium replacement should precede administration of insulin. In other situations, potassium replacement is begun, at a concentration of 40 mEq/L, after initial hydration at the time of initiation of insulin infusion. Potassium should not be administered, if the level is >6 mEq/L, the patient is anuric or ECG changes of hyperkalemia are present.

Dextrose: Hyperglycemia resolves prior to correction of acidosis. Decreasing insulin infusion rate with lowering of blood glucose is not recommended since that would prolong the duration of acidosis. Dextrose (5%) is, therefore, added

to intravenous fluids once blood glucose levels fall below <270 mg/dL.

Acid–base management: Alkali treatment should be avoided as it poses risks for cerebral edema, lactic acidosis and hypokalemia. It is considered only if pH is less than 6.9 with hemodynamic compromise or if there is severe hyperkalemia (serum potassium >6.5 mEq/L with ECG changes).

Monitoring: Careful clinical and laboratory monitoring is necessary. This should include hourly monitoring of neurological status, heart rate, blood pressure and fluid input/output. Laboratory monitoring includes hourly blood glucose and four-hourly blood ketone, pH, bicarbonate and electrolytes **(Table 18.36)**.

Discontinuation of acute treatment: Subcutaneous insulin should be considered once the patient is conscious, ready to accept feeds orally and has resolution of acidosis. Regular or rapid-acting insulin (0.25 unit/kg) should be given 30 minutes before eating. Alternatively, the child may be started on a basal-bolus or mix-split regime. Insulin infusion should be stopped only 30 minutes after insulin to provide overlap, and avoid recurrence of hyperglycemia.

Complications of DKA: DKA is a life-threatening condition with potential for significant long-term morbidity. Timely identification and treatment of these complications are essential.

Cerebral edema: Cerebral edema is the most serious complication of DKA and the most common cause of death. Risk factors include age less than 5 years, severe acidosis, insulin bolus, excessive hydration, CO_2 levels less than 10 mmol/L, and alkali treatment. Cerebral edema usually presents at 4–12 hours following treatment, but may be present at diagnosis. The condition is suspected in the presence of persistent hemodynamic instability or worsening in clinical condition after initial improvement. Early pointers include headache, vomiting, drowsiness, irritability, and hypertension with bradycardia. Severe cerebral edema is indicated by unconsciousness, focal neurological deficits, papilledema and fixed dilated pupils. The diagnosis is clinical. Children with suspected cerebral edema should be immediately treated with intravenous mannitol (5 mL/kg) followed by fluid restriction and head end elevation.

Infections: Bacterial and fungal infections are common. Indicators include persistent fever, leukocytosis, black nasal discharge (rhinocerebral mucormycosis) and hemoptysis (pulmonary aspergillosis).

Long-term Complications of Type 1 Diabetes

Regular screening for long-term complications is essential for their early identification, prevention and appropriate treatment **(Table 18.37)**. Screening for complications should

Table 18.36: Laboratory parameters and response to treatment in DKA

Parameter	*Expected*	*Concern*	*Action*
Blood glucose	Decrease by 50–100 mg/dL/hour	Decline >100 mg/dL/hour Decline <50 mg/dL/hour	Add dextrose to IV hydration fluid Prepare fresh infusion, flush tubing with insulin
Blood pH	Resolution by 12 hours	Persistent at 12 hours	Exclude infection, shock, lactic acidosis
Serum sodium	Increase	Increase <2 mmol/L/hour	Increase sodium concentration in IV fluid
Serum potassium	Gradual decrease	Hypokalemia	Increase potassium concentration in IV fluid
Anion gap	Resolution by 12 hours	Elevated at 12 hours	Exclude lactic acidosis, consider infection
Plasma osmolality	Stable	Decrease by >2 mOsm/kg/hour	Increase sodium concentration, decrease fluid rate
Blood urea	Decrease	Persistently elevated	Exclude renal failure

Table 18.37: Screening for complications in children with type 1 diabetes mellitus

Complications	*Indications*	*Procedures*	*Management*
Retinopathy Prepubertal Pubertal	First eye examination after 3 months of diagnosis; screening after 11 years Duration of diabetes >5 years from onset Duration of diabetes >2 years from diagnosis	Initial examination of dilated fundus	Improvement in diabetes control Laser treatment for visual loss
Nephropathy Prepubertal Pubertal	Annual screening after 11 years Duration of diabetes >5 years from onset Duration of diabetes >2 years from diagnosis	Annual screening for micro-albuminuria: Albumin excretion rate (AER) 20–200 µg/min or AER 30–300 mg/day	Improvement in diabetes control Control of blood pressure ACE inhibitors to reduce proteinuria
Hypothyroidism	At diagnosis; thereafter every 2 years	Serum TSH and FT_4 estimation Thyroid autoantibodies	Thyroxine therapy
Hyperlipidemia Prepubertal Pubertal	Annual screening after 12 years At diagnosis; thereafter every 5 years At diagnosis; thereafter every 2 years	Serum lipid profile	Strict diet control Statins

be started after 5 years of diagnosis, if the onset of diabetes is before puberty, and 2 years, if diagnosed in puberty.

Lipodystrophy manifests as fat atrophy or hypertrophy at the injection sites. This can be prevented by rotation of injection sites. Limited joint mobility is due to flexion contractures of metacarpophalangeal and proximal interphalangeal joints, typically noted in the hands.

Growth failure occurs in children whose diabetes is not well controlled. Mauriac syndrome occurs with poor control of diabetes and is characterized by hepatomegaly, pale skin and extreme short stature. Delayed puberty is associated with inadequate control of diabetes and delayed bone age.

Hypoglycemic unawareness is caused by frequent hypoglycemia associated with tight metabolic control of diabetes. It is due to impaired counter-regulatory hormone response to hypoglycemia. Raising blood glucose targets and prevention of hypoglycemia usually causes reversal of hypoglycemic unawareness.

Retinopathy is characterized by microaneurysms and proliferative disease. Ophthalmologic examination should be conducted when the child is more than 10-year-old and has had diabetes for 3–5 years. Annual follow-up is suggested.

Peripheral neuropathy is unusual in children and adolescents. This results in decreased nerve conduction velocity and sensory changes. An abnormality in vibration perception may be the first clinical finding.

Nephropathy is defined by presence of albumin in the urine. Annual screening for microalbuminuria is initiated when the child is 10 years of age or has had diabetes for 5 years. Patients with significant microalbuminuria should receive ACE inhibitors to delay the progression of nephropathy.

Dyslipidemia: Fasting lipid profile is performed on all children more than 2 years of age at the time of diagnosis (after glucose control is achieved), or if there is family history of high cholesterol (>240 mg/dL) and/or a cardiovascular event before the 55 years. If there are no concerns of hyperlipidemia in the family, screening is performed after onset of puberty (>12 years). For pubertal children (>12-year- old), a fasting lipid profile is performed at diagnosis after glucose control is achieved. If LDL is <100 mg/dL, lipid profile is repeated every 5 years. Intervention is needed, if fasting LDL >100 mg/dL, initially by dietary modification with decrease in saturated fat in diet. A pharmacologic agent is added for LDL >160 mg/ dL, and in patients at risk of cardiovascular disease and LDL values 130–159 mg/dL after initiation of dietary changes and lifestyle intervention. The goal of therapy is LDL level <100 mg/dL.

Type 2 Diabetes Mellitus

Type 2 diabetes in children and adolescents is increasing rapidly with the advent of childhood obesity epidemic. The disorder presents with milder symptoms than type 1 diabetes though DKA can develop occasionally. Diagnosis is established based on the presence of obesity, acanthosis nigricans, elevated insulin levels, normal C-peptide, and lack of GAD antibodies. Lifestyle measures and metformin are the mainstay of treatment. Adolescent type 2 diabetes, however, has an aggressive course compared to adult type 2 diabetes, with faster loss of cell function. Children who present with ketosis are treated with insulin initially and transitioned to metformin when endogenous glucose secretion recovers. GLP1 receptor analog, liraglutide has recently been approved in adolescents with type 2 diabetes. These children and adolescents should be evaluated for hyperlipidemia, diabetic retinopathy and nephropathy at diagnosis. It is recommended that children at risk of type 2 diabetes be regularly screened for diabetes.

Maturity Onset Diabetes of Young (MODY)

MODY represents a group of inherited conditions due to monogenic defects (single gene mutations) characterized by impaired glucose sensing (glucokinase, *GCK*) or insulin secreting capacity of beta cells (*HNF1A* and *HNF4A* and *HNF*1B). The disorder presents with relatively mild, non-ketotic diabetes in a lean individual with strong family history of diabetes affecting three generations. The condition responds to lifestyle measures and low doses of sulfonylurea.

Neonatal Diabetes Mellitus

Onset of diabetes before 6 months of age suggests neonatal diabetes due to inherited monogenic causes. The disease represents transient cell dysfunction (transient neonatal diabetes), permanent insulin secretion defect (permanent neonatal diabetes) or congenital insulin resistance syndrome. The most common cause of permanent neonatal diabetes is activating mutation in *ABCC8* or *KCNJ11* genes, that encode for one of the two sub-units of KATP channel, the on-off button for insulin secretion. These disorders are amenable to treatment with sulfonylureas.

Suggested Reading

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