Endocrinology

12

Amr Morsi

GROWTH DISORDERS

Normal Growth Rate

- Birth length increases by 5% at 1 year (approximately 25 cm or 10 in./year)
- At 1–2 years of age, children grow 12.5 cm or 5 in./year (approximately half the growth rate of the 1st year of life)
- By 2 years of age, children are approximately half of their final adult height
- After 2–3 years of age, height increases by approximately 6.25 cm or 2.5 in./year
- Careful attention to growth rate (not only the height) facilitates early detection of a growth-slowing disorder

What is the relationship between the linear growth rate and weight gain?

- Poor nutrition and excess caloric intake can influence linear growth
- If a weight deceleration precedes and is greater than the height deficit, the child needs a gastrointestinal consultation (Fig. 12.1)
- Excess weight gain associated with a decline in growth rate is not nutritional and requires endocrine consultation

Family history of pubertal onset, age of adult height attainment, and bone age

- Height and pubertal onset in parents can be helpful in assessing the likelihood that similar growth pattern in the child represents a normal variation

Midparental target height (MPTH)

- Calculated as an average ± 2 SD (1 SD = 2 in.)

Midparental height (MPH) for boys

- Paternal height + (maternal height + 13 cm or 5 in.)/2

MPH height for girls

- Maternal height + (paternal height −13 cm or 5 in.)/2

Short Stature

Classification

Normal variant short stature

- Constitutional delay of growth and puberty (CDGP)
- Familial short stature
- Idiopathic short stature

Pathological short stature

- Chronic disease
- Chronic undernutrition
- Endocrine disorders (e.g., growth hormone deficiency [GHD], hypothyroidism, Cushing syndrome)
- Genetic syndromes (e.g., Turner, Noonan)
- Psychosocial

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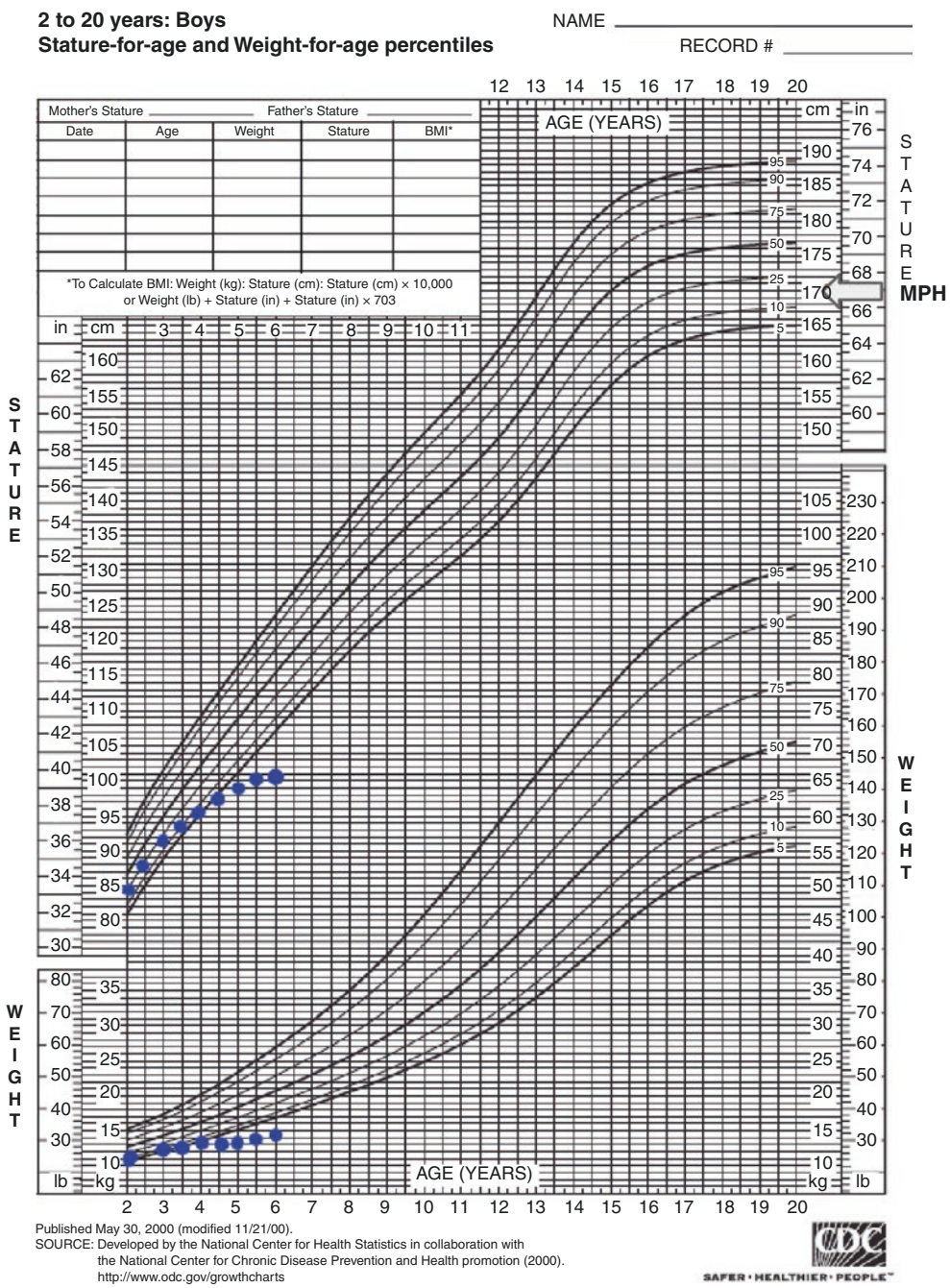

Fig. 12.1 Growth curve of a child with failure to thrive secondary to malabsorption. Weight is affected before height (http://www.cdc.gov/growthcharts)

Clinical Approach for Evaluating Short Stature and Poor Linear Growth

History

- Birth history (intrauterine growth retardation [IUGR], small for gestational age [SGA]), developmental history, and history of chronic illnesses
- Parental history of pubertal onset in males and menarche in females

Physical examination

- Anthropometric measurements to determine height and weight percentiles, as well as linear growth velocity and weight gain
- Detailed physical examination to look for signs of genetic syndromes, endocrinopathies, and signs of pubertal development
- Parental height for determining the mid-parental height (MPH) and MPTH height range

Laboratory evaluation

- Indications: Height ≤ 2 SD below the mean for age, sex, and population or poor linear growth (i.e., reduced growth velocity):
  - Complete blood count (CBC)
  - Electrolytes
  - Calcium, phosphate, and alkaline phosphatase (Ca, Phos, ALP)
  - Celiac disease screen: Total immunoglobulin A (IgA), tissue transglutaminase (tTG) IgA
  - Thyroid-stimulating hormone (TSH,) free thyroxine 4 (free T4)
  - Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
  - Insulin-like growth factor 1 (IGF-1), IGF binding protein 3 (IGFBP-3)
  - Bone age radiograph for skeletal maturation
  - Karyotype (for girls)

Imaging: Bone age radiograph to determine skeletal maturation

- Bone age will be similar to chronological age in familial short stature and genetic causes of short stature
- Bone age will be more delayed than the chronological age in CDGP and endocrinopathies
  - Bone age is usually mildly delayed in CDGP (usually > 2 SD below mean for age and sex)
  - The degree of bone age delay in endocrinopathy will depend on the duration of disease, e.g., in severe long-standing GHD, the bone age is usually > 3 SD below the mean for age and sex

Constitutional Delay of Growth and Puberty (CDGP)

Background

- The most common cause of short stature and pubertal delay
- Typically have retarded linear growth within the first 3 years of life
- Most children resume a normal growth velocity by the age of 2–3 years
- During childhood, these individuals grow along or parallel to the lower percentiles of the growth curve
- Children with CDGP are often referred to as "late bloomers" with onset of puberty also being later than peers

Diagnosis

- Family history of growth and pubertal delay is common (in 50% of cases)
- Delayed bone age
- Linear growth is 2 SD deviation below the mean for age in the first 3 years of life (Fig. 12.2)
- Pubertal growth spurt is delayed, and the growth rate continues to decline after those of their classmates have begun to accelerate
- IGF-1 tends to be low for chronological age but normal for bone age
- GH and thyroid studies are usually normal

Management

- Medical care in CDGP is aimed at obtaining several careful growth measurements at frequent intervals, often every 6 months
- These measurements are used to calculate linear height velocities and to establish a trajectory on the growth curve
- Medical treatment of this variation of normal growth is not necessary but may be initiated in adolescents experiencing psychosocial distress
- Boys with more than 2 years of pubertal delay may benefit from a short course of testosterone therapy after the age of 14 years

Familial Short Stature (FSS)

Background

- Height below the fifth percentile
- Growth velocity, i.e., parallel to but below the normal growth curve (Fig. 12.3)

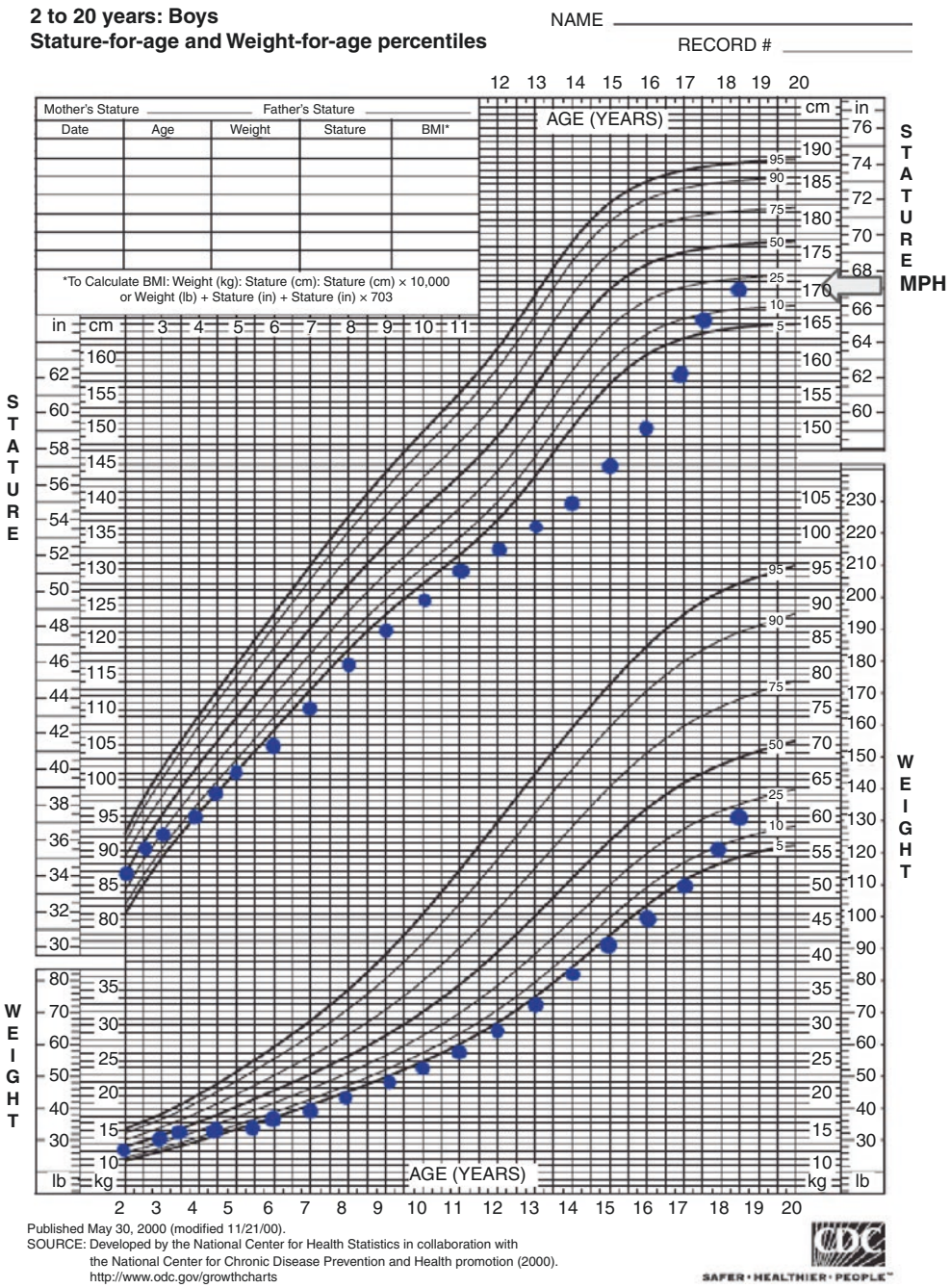

Fig. 12.2 Short stature secondary to constitutional delay. Growth is noted along or parallel to the lower percentiles of the growth curve and pubertal initiation is also delayed. Catch-up growth is noted from age of 16 to 17 years, and at 19 years of age, the boy reached his midpaternal target height ("late bloomer") (http://www.cdc.gov/growthcharts)

Diagnosis

- Bone age is congruent with child's chronological age
- The time of pubertal onset is normal
- Height percentile tracks that predicted by parental genetics

Idiopathic Short Stature (ISS)

- ISS is defined as a height ≤ 2 SD below the mean for age, sex, and population
- ISS is a diagnosis of exclusion. The diagnosis is given after a comprehensive workup fails to identify cause for the short stature
- ISS is differentiated from normal variant short stature (CDGP, FSS) by a predicted final adult height that is < –2 SD below the child's target height range
- GH therapy aiming to improve adult height is approved for ISS by the U.S. Food and Drug Administration (FDA)

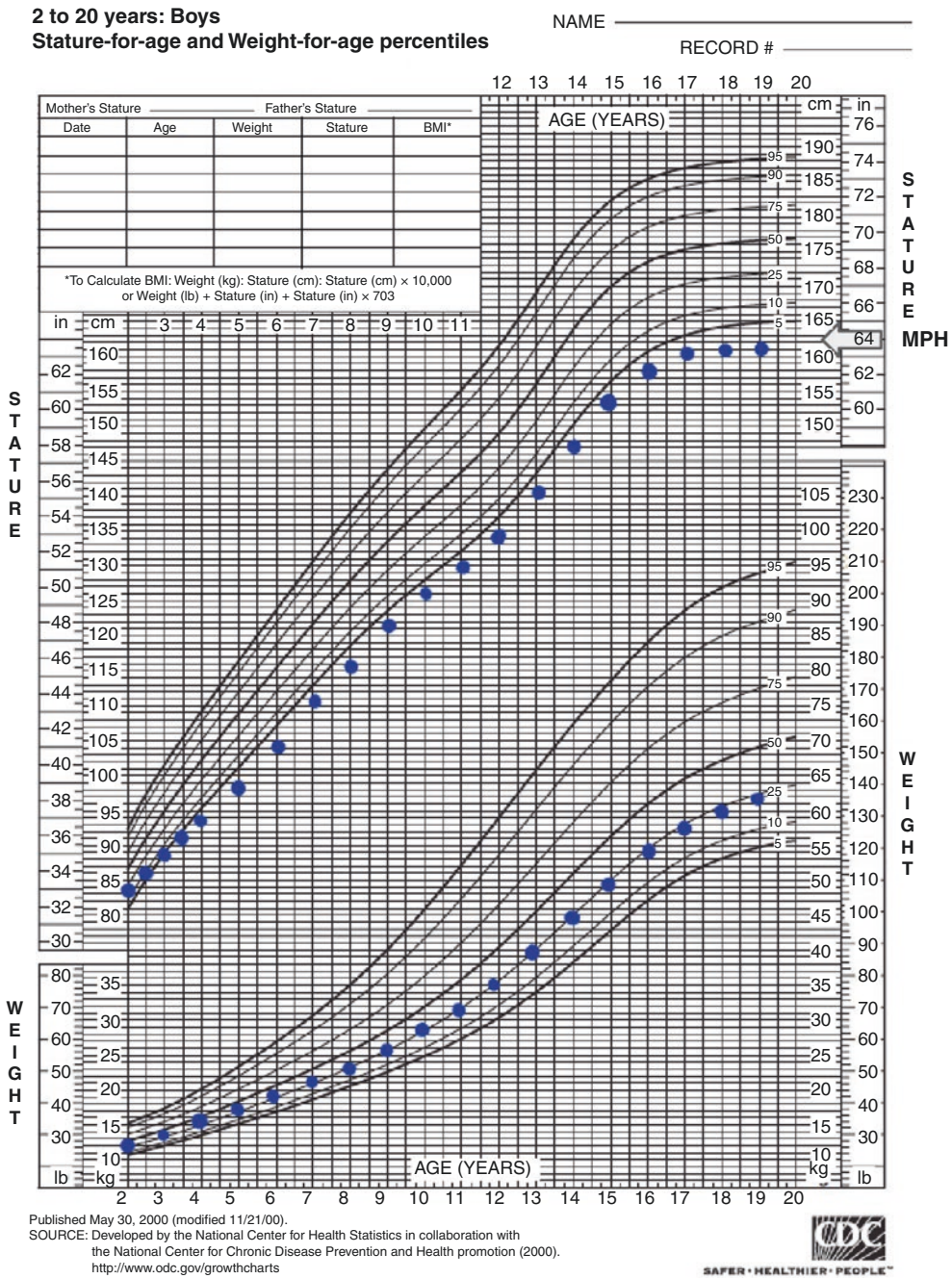

Fig. 12.3 Familial short stature. Growth rate is parallel to the lower percentiles of the growth curve and final adult height corresponds to midpaternal target height (http://www.cdc.gov/growthcharts)

Psychosocial Dwarfism

Background

- Emotional deprivation can cause short stature and growth failure
- A good history may reveal a disturbed child–family relationship

Diagnosis

- Diagnosis of exclusion

Common causes of short stature (Table 12.1)

DISORDERS OF PITUITARY GLAND

Introduction

- The pituitary gland, located at the base of the brain, is composed of anterior (i.e., adenohypophysis) and posterior (i.e., neurohypophysis) regions
- Origin of the adenohypophysis is from the Rathke pouch as an invagination of the oral ectoderm

Table 12.1 Common causes of short stature: differences between constitutional delay, familial short stature, and growth hormone deficiency

	Constitutional delay	Familial short stature	Growth hormone deficiency
Growth curve	Growth velocity along or parallel to the lower percentiles of the growth curve	Growth velocity is parallel to but below the normal growth curve	Height or length > 3 SD below the mean
Family history	Positive late bloomers	One or two parents are short	Depends on the cause
Bone age	Mildly delayed	Equal to chronological age	Delayed
Hormonal studies	Normal	Normal	Low IGF-1 and low IGFBP-3
Treatment	Reassurance Some may benefit from testosterone short course if puberty is delayed	Reassurance and monitoring	Growth hormone

IGF-1 insulin-like growth factor 1, *IGFBP-3* IGF binding protein 3

The major biologically active hormones released into systemic circulation include the following

- Growth hormone (GH)
- Adrenocorticotropic hormone (ACTH)
- TSH
- Luteinizing hormone (LH)
- Follicle-stimulating hormone (FSH)
- Prolactin (PRL)
- Antidiuretic hormone (ADH)

Growth hormone (GH)

- GH is 191-amino acid (191-AA) single-chain polypeptide. The GH gene is called *GH1* and is located on chromosome 17

Biologic effect of GH

- Linear growth
- Bone thickness growth
- Soft tissue growth
- Protein synthesis
- Fatty acid release from adipose tissue
- Insulin resistance

IGF-1

- IGF-1 *is both* synthesized in the liver and formed locally in bones and muscles of children
- Gene located on chromosome 12
- Circulating IGF-1 is directly related to GH activity and nutritional status

GH therapy (Fig. 12.4)

- In children with classic GHD, treatment should be started as soon as possible to ensure the greatest effect on final adult height
- Higher doses during puberty can be considered
- Maximal response is usually during the 1st year

Criteria for discontinuing GH treatment

- Decision by the patient/parent to discontinue
- Growth rate less than 2 cm/year
- Bone age of 14 years in girls and 16 years in boys

Adverse effects of GH

- Pseudotumor cerebri (headaches and papilledema)
- Slipped capital femoral epiphysis (limping, and hip or knee pain)
- Gynecomastia
- Worsening scoliosis (needs to be monitored)
- Insulin resistance

Other indications for GH therapy

1. Turner syndrome
2. Noonan syndrome
3. *SHOX*-gene mutation
4. Prader–Willi syndrome
5. Idiopathic short stature
6. Small for gestational age

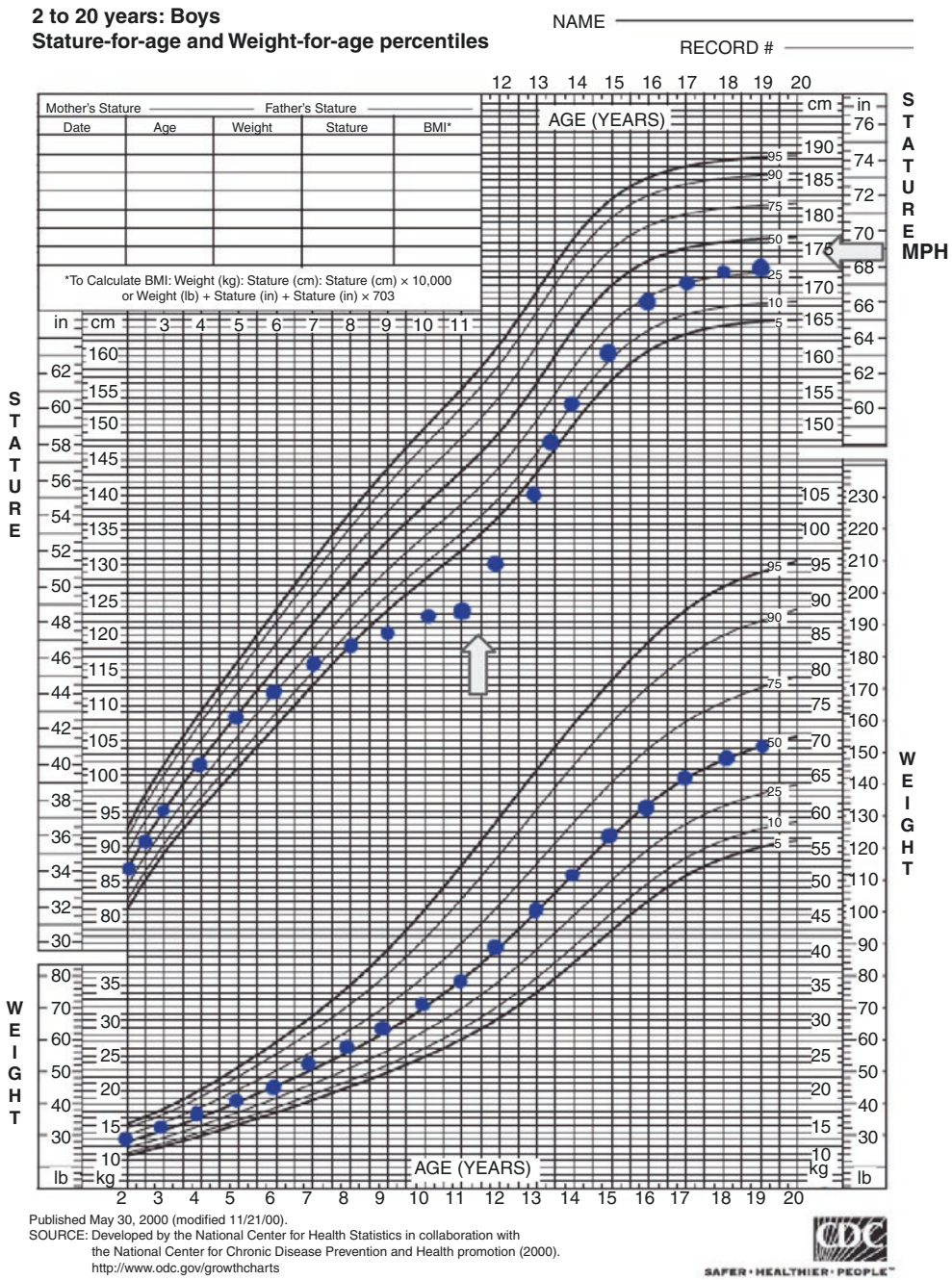

Fig. 12.4 Short stature secondary to growth hormone (GH) deficiency. Height deceleration is noted after 3 years of age and weight is not very much affected. GH therapy initiated at 11 years of age with marked improvement in auxology (http://www.cdc.gov/growthcharts)

Congenital Hypopituitarism

Background

- Involves one or more of the six hormones secreted by the pituitary gland
- Could be isolated GHD (IGHD) or combined pituitary hormone deficiency (CPHD). Some patients start as having IGHD then progress to having CPHD

Conditions associated with GHD

Hall–Pallister syndrome

- Absence of pituitary gland
- Hypothalamic hamartoblastoma
- Postaxial polydactyly
- Nail dysplasia
- Bifid epiglottis
- Imperforate anus
- Anomalies of the heart, lungs, and kidneys

Septo-optic dysplasia

- Absence of optic chiasm, optic nerve hypoplasia, or both
- Agenesis of the septum pellucidum, and schizencephaly
- Midfacial anomalies, e.g., solitary maxillary central incisors, cleft lip/palate
- Micropenis/microphallus

Clinical presentation

- Neonate
  - Hypoglycemia usually severe and persistent, with or without seizure
  - Micropenis/microphallus (diagnostic clue in boys; < 2.5 cm stretched in term infants)
  - Apnea
  - Cyanosis
  - Prolonged neonatal jaundice
  - Most neonates with hypopituitarism have normal length and weight at birth
- Older infants and children
  - Growth failure is the most common presentation
  - Delayed tooth eruption
  - Central diabetes insipidus may develop or become clinically obvious as they become older

Diagnosis

- Height or length > 3 SD below the mean, failure to thrive
- Slow growth velocity (< 5 cm/year)
- Delayed skeletal age
- Low IGF-1 and low IGFBP-3
- Provocative tests: Administration of insulin, arginine, clonidine, or glucagon rapidly increases the level of GH in normal children
  - GH < 10 ng/ml in two provocative tests with different agents is the usual diagnostic criteria
- Other pituitary hormones must be tested, e.g., TSH, ACTH, gonadotropins (age-dependent)
- Clinical history (polydipsia, cold water craving)

Treatment

- Appropriate hormone replacement

Neonatal Hypoglycemia

Background

- Hypoglycemia is the most common metabolic problem in neonates
- Plasma glucose less than 30 mg/dL in the first 24 h and less than 70 mg/dL thereafter in newborns. (Point-of-care glucose measurements not diagnostic, needs confirmation with serum level)
- Plasma glucose value of less than 50 mg/dL in children

Causes

- Transient hypoglycemia
  - Prematurity (low glycogen stores), infant of diabetic mother, SGA, perinatal stress, and sepsis
- Inborn errors of metabolism, e.g., carnitine–acylcarnitine translocase deficiency
- Glycogen storage disorders
- Gluconeogenesis disorders
- Fatty acid oxidation disorders
- Disorders of hormonal regulation of glucose metabolism:
  - GHD or hypopituitarism
  - Isolated cortisol deficiency (congenital adrenal hyperplasia [CAH)]
  - Congenital hyperinsulinism (genetic defect) is the most common permanent cause in the first 3 months of life
- Genetic diseases, e.g., Beckwith–Wiedemann syndrome

Diagnosis

- Micropenis is a red flag for possible GHD
- Critical sample should be taken during hypoglycemia (usually if the cause is unknown and in persistent cases):
  - Glucose

  - CO2 (chemistry panel)
  - Insulin, C-peptide
  - Ammonia, lactate
  - GH
  - Cortisol
  - Free fatty acids
  - Beta-hydroxybutyrate and acetoacetate (serum ketones)
  - Acylcarnitine profile, total and free carnitine
  - Save serum tube
  - Urine ketones, urine organic acids
- Hypopituitarism or adrenal failure
  - Ketonemia and ketonuria
  - Low GH or low cortisol
  - Appropriately suppressed insulin
- Glycogen storage disease
  - Ketonemia and ketonuria
  - Normal response of GH and cortisol to hypoglycemia
  - Appropriately suppressed insulin
- Fatty acid oxidation defect or carnitine deficiency
  - No ketonemia and no ketonuria
  - No acidosis
  - Appropriately suppressed insulin
- Hyperinsulinism or insulinoma in older children
  - No ketonemia, no ketonuria
  - Usually induced by fasting
  - Inappropriately elevated insulin concentration (in the presence of hypoglycemia)
  - May respond to diazoxide
  - Consider multiple endocrine neoplasia type 1 (MEN-1) syndrome
- Ketotic hypoglycemia in older children
  - The most common cause of childhood hypoglycemia and is a diagnosis of exclusion
  - Typical age is 18 months to 5 years with resolution by age 7 years
  - Normal physiologic response to hypoglycemia with elevated serum and urine ketone levels
  - Cortisol and growth hormone are counter-regulatory hormones and are normally elevated in response to hypoglycemia
  - Appropriately suppressed insulin (undetectable)
  - Acute treatment is IV dextrose
  - Long-term management consists of avoidance of fasting and ensuring adequate sugar-containing fluids when ill

Craniopharyngioma

Background

- Most common pituitary tumor: Benign histology and malignant behavior
- Persistence of remnants of the original connection between the Rathke pouch and the oral cavity
- Peak incidence in children aged 5–10 years
- More common in males

Clinical presentation

- Headache
  - Most common presentation (55–86%)
  - Hydrocephalus
- Visual disturbance (37–68%)
  - Decline of visual acuity
  - Constriction of visual fields, bitemporal hemianopsia
  - Papilledema
  - Horizontal double vision
- Endocrine dysfunction (66–90%), e.g.,
  - Hypothyroidism (e.g., weight gain, fatigue, cold intolerance, and constipation)
  - Diabetes insipidus
  - Growth failure and delayed puberty

Diagnosis

- Contrast magnetic resonance imaging (MRI)
- Magnetic resonance angiography (MRA)
- Complete endocrinologic and neuro-ophthalmologic evaluation with formal visual field documentation

- Neuropsychological assessment

Management

- Surgical removal
- Postsurgical follow-up should be planned in 1–2 weeks for all patients
- Appropriate hormone replacement

Diabetes Insipidus (DI)

Background

- DI is defined as the passage of large volumes of dilute urine (< 300 mOsm/kg)
- **Central DI,** (neurogenic, pituitary, or neurohypophyseal) characterized by decreased secretion of antidiuretic hormone (ADH; also referred to as arginine vasopressin [AVP])
- **Nephrogenic DI,** characterized by decreased ability to concentrate urine because of resistance to ADH action in the kidney

Cause of central DI

- Trauma or surgery to the region of the pituitary and hypothalamus are common causes
- Neoplasm
- Infiltration (histiocytosis X)
- Infection
- Autoimmune
- Congenital

Cause of nephrogenic DI

- Congenital X-linked or autosomal dominant
- Electrolyte disturbances (hypercalcemia, hypomagnesemia, and hypokalemia)
- Drugs (lithium, demeclocycline, cisplatin, amphotericin B, loop diuretics)
- Ureteral obstruction, chronic renal failure, polycystic kidney disease, Sjogren syndrome, and sickle cell anemia
- Psychogenic

Clinical presentation

- Polyuria
- Irritability
- Failure to thrive
- Intermittent fever

Diagnosis

- Serum osmolality > 300 mOsm/kg
- Urine osmolality < 300 mOsm/kg
- Hypernatremia
- Urine specific gravity of 1.005 or less and a urinary osmolality less than 200 mOsm/kg are the hallmarks of DI
- Polyuria and elevated plasma osmolality despite a relatively high basal level of ADH suggests nephrogenic DI
- Water deprivation test and response to desmopressin can differentiate between central and nephrogenic DI
- If serum osmolality < 270 mOsm/kg and urine osmolality > 600 mOsm/kg, this will rule out DI
- Suspect primary polydipsia when large volumes of very dilute urine occur with plasma osmolality in the low–normal range

Treatment of central DI

- Desmopressin
- Complication is water intoxication; patient should have water breakthrough every day to prevent water intoxication
- Under most circumstances, water intake should be limited to 1 L/m^2/24 h during antidiuresis
- **Important:** Water should always be made available to the child with DI and intact thirst mechanism
- **Important:** Some patients may *not* have intact thirst mechanism. They need to be put on a daily fluid (free water) goal
- *Infants can also be treated with thiazides and low solute formulas*

Treatment of nephrogenic DI

- Thiazide diuretics
- May be combined with amiloride and indomethacin

Syndrome of Inappropriate ADH Secretion (SIADH)

Background

- Hyponatremia and hypo-osmolality resulting from inappropriate, continued secretion or action of the hormone despite normal or increased plasma volume, which results in impaired water excretion

Causes

- Central nervous system (CNS) pathology
  - Infection, e.g., tumor, thrombosis, neurosurgery, hydrocephalus, meningitis, pneumonia, hypoxia, and brain abscess
  - Head trauma
- Pulmonary disease
  - Pneumonia, asthma, positive pressure ventilation, tuberculosis, cystic fibrosis
- Neoplastic, e.g., lymphoma and leukemia
- Hypothyroidism
- Excessive treatment of central DI
- Carbamazepine/oxcarbazepine, cyclophosphamide, phenothiazines, fluoxetine, vincristine, and cisplatin—important drugs that cause SIADH
- Anorexia
- Schizophrenia

Clinical presentation

- Hypervolemic state
- Depending on the magnitude and rate of development, hyponatremia may or may not cause symptoms
- Anorexia, nausea, and malaise are early symptoms when the serum Na^+ level is less than 125 mEq/L
- Headache, muscle cramps, irritability, drowsiness, confusion, weakness, seizures, and coma can occur with further decrease in the serum Na

Diagnosis

- Hyponatremia (i.e., serum $Na^+ < 135$ mmol/L) with concomitant hypo-osmolality (serum osmolality < 280 mOsm/kg) and high urine osmolality is the hallmark of SIADH

Management

- Depends on the severity of hyponatremia and chronicity of condition
- Correcting hyponatremia too rapidly may result in central pontine myelinolysis with permanent neurologic deficits
- Fluid restriction in mild cases
- Administration of 3% hypertonic saline should be used only in severe and emergent cases
- The objective is to raise serum Na^+ levels by 0.5–1 mEq/h and not more than 10–12 mEq in the first 24 h, to bring the Na^+ value to a maximum level of 125–130 mEq/L

Cerebral Salt Wasting

Background

- Hypersecretion of atrial natriuretic peptides

Causes

- Head trauma, hydrocephalus, neurosurgery, cranial irradiation, hypothalamic/pituitary neoplasms, cerebral vascular accident, and brain death

Presentation (Table 12.2)

- Excessive salt wasting
- Very high urinary Na^+
- Hyponatremia

Diagnosis

- Hypovolemic state (SIADH is euvolemic/hypervolemic)
- High urine output (SIADH is the opposite)
- Normal or high uric acid
- High atrial natriuretic peptide

Treatment

- Hydration
- Treatment of underlying cause

Table 12.2 Difference between diabetes insipidus, SIADH, and cerebral salt wasting

	Diabetes insipidus	SIADH	Cerebral salt wasting
Cause	Low or resistance to ADH	High ADH	Unclear pathophysiology; however, may be associated with increased natriuretic peptides
Na^+ level	High	Normal or low	Low
Serum osmolality	High	Low	Low
Urine osmolality	Low	High	Relatively dilute because of high urine output
Intravascular volume	Hypovolemia	Euvolemia or hypervolemia	Hypovolemia
Urine output	High	Low	High
Urine Na^+	Low	High or match Na intake	Very high, more than Na^+ intake, > 40 mEq/L
Management	Allow access to free water all the time + desmopressin or treat for nephrogenic DI	Fluids restrictions	IV fluids, NS, or even 3% NS May need salt supplement

SIADH syndrome of inappropriate ADH secretion, *ADH* antidiuretic hormone, *Na^+* sodium, *IV* intravenous, *NS* normal saline, *DI* diabetes insipidus

- If hyponatremia occurred in < 12 h, rapid correction is required if serum Na^+ < 120 mEq/L
- Serum Na^+ should be raised only enough to make patient stable, 0.5 mEq/h (12 mEq/L/24 h)

Hyperpituitarism

Gigantism and acromegaly

- Hypersecretion of GH before ossification of the epiphysis causes gigantism and after epiphyseal closure causes acromegaly

Prolactinoma

Background

- Prolactin-secreting tumor is the most common cause in adolescents
- Based on its size, a prolactinoma can be classified as a microprolactinoma (< 10 mm diameter) or a macroprolactinoma (> 10 mm diameter)

Clinical presentation

- Headache
- Amenorrhea
- Galactorrhea
- Visual disturbance if tumor affects the optic chiasm, e.g., bitemporal hemianopsia or total vision loss in severe cases

Diagnosis

- Elevated serum PRL
- TSH and pregnancy test must be performed
- MRI: A serum PRL value of 200 ng/mL or greater in the presence of a macroadenoma (> 10 mm) is virtually diagnostic of prolactinoma

Treatment

- Bromocriptine
- Cabergoline (better tolerated than bromocriptine)

THYROID DISORDERS

Introduction

Location

- The thyroid gland is found in the neck, below the thyroid cartilage (which forms the laryngeal prominence or "Adam's apple")

Function

- It produces thyroid hormones, the principal ones being triiodothyronine (T3) and thyroxine, sometimes referred to as tetraiodothyronine (T4)
- These hormones regulate the growth and rate of function of many other systems in the body
- T3 and T4 are synthesized from iodine and tyrosine. The thyroid also produces calcitonin, which plays a role in calcium homeostasis
- Hormonal output from the thyroid is regulated by TSH produced by the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus

Congenital Hypothyroidism

Background

- Thyroid dysgenesis (aplasia, hypoplasia, or an ectopic) is the most common cause of congenital hypothyroidism
- Most common form of thyroid dysgenesis is ectopic thyroid
- Occasionally associated with thyroglossal cyst

Clinical presentation

- Most infants are asymptomatic at birth because of transplacental passage of maternal T4
- Length and weight are normal at birth, but head may be larger at birth
- Prolongation of physiologic jaundice
- Poor feeding, especially sluggishness
- Somnolence and choking spells during feeding may be the first sign in the 1st month
- Respiratory difficulties due to large protruded tongue, apneic episodes, noisy breathing, nasal obstruction
- Cold, mottled, and dry skin
- Constipation that usually does not respond to treatment
- Umbilical hernia
- Large anterior fontanelle
- Associated congenital anomalies; cardiac is the most common
- Hypotonia

Laboratory

- High TSH and low T4
- Low to normal total T4 and TSH within reference range indicates thyroid-binding globulin (TBG) deficiency (normal free T4)
- If maternal antibody-mediated hypothyroidism is suspected, maternal and neonatal antithyroid antibodies may confirm the diagnosis
- Thyroid ultrasound
- Thyroid scanning (many clinicians treat without imaging studies)

Treatment

- Levothyroxine given orally is the treatment of choice
- 10 to 15 μg/kg/day initial dose
- No liquid preparations of levothyroxine should be given to neonates or infants. These preparations are very difficult to keep in suspension, and the delivery of drug is inconsistent
- **If the newborn screen is positive for hypothyroidism, order TSH and free T4 to confirm, then start the treatment immediately, before the results of the confirmatory tests are available**
- No treatment is required for TBG deficiency

Prognosis

- Early diagnosis and treatment of congenital hypothyroidism prevents severe intellectual disability and other neurologic complications

Thyroid-Binding Globulin Deficiency

- X-linked condition
- Could be partial (1 in 4000) or complete (1 in 15,000)
- Heterozygous males are more frequently detected

- Depending on X inactivation, females may have normal, partial, or complete deficiency
- T4 and T3 levels are low, TSH is normal, free T4 and free T3 are normal, high T3 uptake (T3U)
- Prognosis: Benign condition → no treatment needed

Hashimoto, Lymphocytic Thyroiditis (Autoimmune Thyroiditis)

Background

- Hashimoto thyroiditis is part of the spectrum of autoimmune thyroid diseases and is characterized by the destruction of thyroid cells by various cell- and antibody-mediated immune processes
- The most common cause of hypothyroidism in the United States in individuals older than 6 years
- Girls 2 to 3 times > boys
- Familial clusters of lymphocytic thyroiditis are common

Clinical presentation

- Goiter and growth retardation (most common)
- Fatigue
- Constipation
- Dry skin
- Cold intolerance
- Hair loss
- Weight gain
- Depression, dementia, and other psychiatric disturbances
- Decreased school performance
- Menstrual irregularities
- Galactorrhea
- Other manifestations, depending on the severity of hypothyroidism and other factors, e.g., age (myxedema)
  - Puffy face and periorbital edema typical of hypothyroid facies
  - Cold, dry skin, which may be rough and scaly
  - Peripheral edema of hands and feet, typically non-pitting
  - Thickened and brittle nails (may appear ridged)
  - Bradycardia
  - Elevated blood pressure (typically diastolic hypertension)
  - Diminished deep tendon reflexes and the classic prolonged relaxation phase
  - Macroglossia
  - Slow speech
  - Ataxia
- In most cases, the thyroid is diffusely large, firm, and nontender (Fig. 12.5)
- In 30%, the gland is lobular and may seem to be nodular

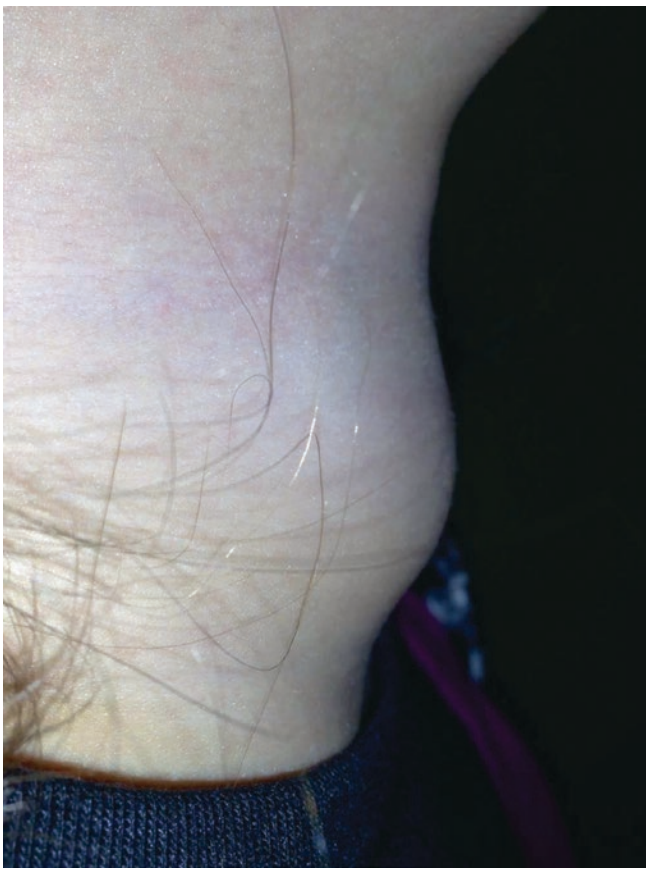

Fig. 12.5 A 4-year-old female with thyroid enlargement, fatigue, and daytime somnolence. Thyroid-stimulating hormone > 150 mIU/L and free thyroxine 4 < 0.4 ng/dL. Antithyroid peroxidase antibodies were very high

Diagnosis

- Thyroid function tests are usually normal
- Elevated TSH and presence of thyroid autoantibodies, antithyroid peroxidase (TPO) and antithyroglobulin (TG) antibodies, are the best markers of progression to overt hypothyroidism; however, degree of elevation does not predict severity of disease

Management

- If there is evidence of hypothyroidism, levothyroxine can be given
- Fine-needle aspiration/biopsy (FNAB) of any dominant or suspicious thyroid nodules to exclude malignancy or the presence of thyroid lymphoma in fast-growing goiters

Subacute (de Quervain) Thyroiditis

Background

- Subacute thyroiditis is a self-limited disease of thyroid gland
- Usually occurs after an upper respiratory tract infection

Clinical presentation

- Fever
- Thyroid gland tenderness and pain

Laboratory

- Initially hyperthyroidism (elevated T4 and T3)
- Followed by more prolonged period of hypothyroidism

Management

- Nonsteroidal anti-inflammatory drugs (NSAIDs) for pain
- Prednisone in severe cases

Prognosis

- Almost all patients recover with no thyroid problems

Stepwise approach to a child presenting with elevated TSH

- It is important to note that children have higher thyroid hormone and TSH level values than adults. Hence, it is important to use pediatric reference ranges while interpreting laboratory data
- TSH has a diurnal variation, with an 8:00 AM measurement being more sensitive in detecting primary hypothyroidism
- TSH is obtained to screen for primary hypothyroidism usually only after a thorough history and physical examination
- If TSH is elevated: Thyroid hormone levels including total T4 and free T4 levels need to be obtained
- If TSH is elevated with low free T4 level: An arbitrary cutoff of 10 uIU/ml or above is generally used to start therapy with levothyroxine. Levels between 5 and 10 uIU/ml are considered mild elevations and repeat testing is indicated
- If TSH is elevated with normal free T4 level (subclinical hypothyroidism), monitoring is warranted with repeat thyroid function every 6 months to 1 year. This scenario is common in obese children who tend to have mild elevations in TSH

Graves Disease

Background

- Graves disease is the most common cause of hyperthyroidism in pediatric patients
- An immune-mediated disorder that results from the production of thyroid-stimulating immunoglobulins by stimulated B lymphocytes
- These immunoglobulins bind to the TSH receptor to mimic the action of TSH and stimulate thyroid growth and thyroid hormone overproduction

Clinical presentation

- Weakness

- Weight loss or muscle wasting
- Diarrhea
- Heat intolerance
- Pruritus
- Palpitations
- Sleeplessness
- Behavioral changes
- Enlarged thyroid, which may cause dysphagia if very large
- Exophthalmos usually mild and more common in adults
- Upper eyelid retraction
- Infrequent blinking (Stellwag sign)

Laboratory

- Elevated free T4 and T3
- Suppressed TSH
- Sometimes free T3 is more elevated than T4
- Antithyroid antibodies (TPO) are often present
- Thyrotropin receptor-stimulating immunoglobulin (TSI) confirms the diagnosis, and its absence means remission
- To differentiate between Graves disease and exogenous thyroid hormone administration, all labs are the same, except thyroglobulin will be low in exogenous thyroid hormone and high in Graves disease

Treatment

- Methimazole is the most common antithyroid drug used in the United States
- Propylthiouracil (PTU) is the drug of choice in pregnant women with Graves disease
  - Sides effects of antithyroid hormone
    - Transient urticarial rash (the most common side effect)
    - Agranulocytosis (more common in elderly)
    - PTU associated with more cases of liver injuries
- Radioactive iodine
  - Permanent hypothyroidism almost inevitable
  - Might worsen ophthalmopathy
  - May carry a small risk of malignancy in children
  - Pregnancy must be deferred 6–12 months and mother cannot breastfeed
- Beta-blockers to blunt the toxic effect of the circulating T4 and T3

Treatment follow-up

- Monitor the patient at 6-week to 3-month intervals with thyroid function tests (TSH, total T4/free T4 levels), liver function tests, and CBC
- Assess other potential adverse effects of the agent by history

Neonatal Thyrotoxicosis

Background

- Due to transplacental transmission of TSH receptor immunoglobulin from the mother to the fetus

Clinical presentation

- Irritability
- Flushing
- Tachycardia
- Hypertension
- Thyroid enlargement
- Exophthalmos

Diagnosis

- High T4 and T3
- Low TSH
- Positive TSI

Treatment

- Mild cases: Symptomatic treatment with a beta-blocker (e.g., propranolol)
- More severe cases: Antithyroid medications are necessary
- In very severe cases: Iodides in the form of Lugol iodine solution or saturated solution of potassium iodide (SSKI) are used

Prognosis
- Usually resolve in 3–12 weeks

Solitary Thyroid Nodules

Background
- Thyroid nodules are much more likely to be malignant in children than they are in adults

Diagnosis
- Child's history, including familial history and radiation exposure
- Thyroid function is usually normal
- Ultrasonography to determine whether the nodule is cystic, solid, or mixed
- FNAB is used for definitive diagnosis (study of choice)
- FNAB is not necessary or recommended in the case of toxic nodules

Management
- All solitary nodules including cold or non-toxic nodules must be biopsied
- After initial diagnosis and investigation of the thyroid nodule, medical and/or surgical therapy is decided
- Presumed benign nodule, especially in an adolescent, may simply be observed
- Close observation and follow-up care are essential

Important to know
- Palpable thyroid nodule, more than or equal 1 cm on imaging, next step:
  - Thyroid ultrasound-guided FNAB

Thyroid Cancer

Background
- Prior radiation therapy to the neck increases the risk of thyroid cancer
- More than 95% of thyroid cancers are of thyroid-cell (well-differentiated) origin
- Papillary (subtype) carcinoma is the most common
- High rate of regional and distant metastasis
- MEN type 2 is autosomal dominant

Types of thyroid cancers
- Follicular cell origin
  - Papillary cell carcinoma
  - Follicular cell carcinoma
- Medullary thyroid cancer
  - MEN type 2
    - MEN-2A (medullary thyroid cancer, hyperparathyroidism, and pheochromocytoma)
    - MEN-2B (medullary thyroid cancer, pheochromocytoma, and mucosal neuroma)

Clinical presentation
- Most childhood thyroid nodules are asymptomatic and are detected as a neck mass by parents or by physicians during routine examination

Diagnosis
- Thyroid ultrasound to confirm the presence of a nodule
- FNAB is indicated if nodule is suspicious-looking or is 1 cm or more in diameter
- Calcitonin level is elevated in medullary thyroid cancer
- Abnormal biochemical labs, e.g., elevated calcium level (hyperparathyroidism) due to associated conditions in medullary thyroid cancers (MEN type 2)

Management
- TSH suppressive therapy in children with papillary or follicular-type thyroid cancer
- Surgery
- Radiotherapy
- Surveillance

Thyroid Storm

Background

- Thyrotoxic crisis is an acute, life-threatening, hypermetabolic state induced by excessive release of thyroid hormones in individuals with thyrotoxicosis

Clinical presentation

- Fever (may be the only presenting symptom)
- Profuse sweating
- Poor feeding and weight loss
- Respiratory distress
- Fatigue (more common in older adolescents)
- Nausea and vomiting
- Diarrhea
- Abdominal pain
- Jaundice
- Anxiety (more common in older adolescents)
- Altered behavior
- Seizures
- Coma

Diagnosis

- Elevated triiodothyronine (T3), thyroxine (T4) levels
- Suppressed TSH levels

Management

- Patients with thyroid storm should be treated in an ICU setting
- Correct electrolyte abnormalities
- Propranolol to minimize sympathomimetic symptoms
- Treat cardiac arrhythmia, if necessary
- Aggressively control hyperthermia by applying ice packs and cooling blankets and by administering acetaminophen
- Consider methimazole and consult pediatric endocrinologist
- Consider iodine compounds (Lugol iodine or potassium iodide) orally or via nasogastric tube to block the release of thyroid hormone (at least 1 h after starting antithyroid drug therapy)
- Consider glucocorticoids to decrease peripheral conversion of T4–T3

BONE AND MINERAL DISORDERS

Hypocalcemia

Background

- Hypocalcemia is defined as a total serum calcium concentration of less than 8.5 mg/dL in children, less than 8 mg/dL in term neonates, and less than 7 mg/dL in preterm neonates

Causes

- Early neonatal hypocalcemia (48–72 h of birth)
  - Prematurity
  - Birth asphyxia
  - Diabetes mellitus (DM) in the mother (magnesium depletion in mothers with DM)
  - IUGR
- Late neonatal hypocalcemia (3–7 days after birth)
  - Exogenous phosphate load; this is most commonly seen in developing countries (phosphate-rich formula or cow's milk)
  - Gentamicin use
  - Magnesium deficiency
  - Transient hypoparathyroidism of newborn
  - Hypoparathyroidism due to other causes
- Infants and children
  - Hypoparathyroidism
  - Vitamin D deficiency
  - Acquired or inherited disorders of vitamin D metabolism
  - Resistance to the action of vitamin D
  - Liver diseases
  - Renal failure

  - Malabsorption
  - Pseudohypocalcemia due to hypoalbuminemia

Clinical presentation

- Newborn period
  - Possibly no symptoms
  - Lethargy
  - Poor feeding
  - Vomiting
  - Abdominal distension
- Children, possible presentation
  - Seizures
  - Twitching
  - Cramping
  - Laryngospasm, a rare initial manifestation
  - Tetany and signs of nerve irritability, such as the Chvostek sign, carpopedal spasm, the Trousseau sign, and stridor

Diagnosis

- Total and ionized serum calcium levels
  - A decrease in total calcium can be associated with low serum albumin concentration and abnormal pH
- Serum magnesium levels
  - Serum magnesium levels may be low in patients with hypocalcemia, which may not respond to calcium therapy if hypomagnesemia is not corrected
- Severe hypomagnesemia causes hypocalcemia by impairing the secretion of and inducing resistance to parathyroid hormone
- Serum electrolyte and glucose levels
  - Low bicarbonate levels and acidosis may be associated with Fanconi syndrome and renal tubular acidosis
- Phosphorus levels
  - Phosphate levels are increased in cases of exogenous intake
  - High phosphate may indicate
    - Endogenous phosphate loading
    - Renal failure
    - Hypoparathyroidism
  - Low phosphate may indicate
    - Vitamin D abnormalities and rickets
- PTH levels
  - Hormone studies are indicated if hypocalcemia persists in the presence of normal magnesium and normal or elevated phosphate levels
  - Low PTH (or inappropriately normal) levels suggest
    - Hypoparathyroidism; serum calcium rises in response to PTH challenge
  - High PTH levels suggest
    - Vitamin D abnormalities
    - Pseudohypoparathyroidism (PHP)
    - Calcium levels do not rise in response to PTH challenge
- 25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D
- Urine calcium, magnesium, phosphorus, and creatinine levels
  - These values should be assessed in patients with suspected renal tubular defects and renal failure. Urine should also be evaluated for pH, glucose, and protein
- Urine calcium-to-creatinine ratio of more than 0.3 on a spot sample in the presence of hypocalcemia suggests inappropriate excretion
- Serum alkaline phosphatase (ALP) levels (generally elevated in patients with rickets)

Management

- Treatment of the underlying cause
- Treatment of asymptomatic patients with hypocalcemia remains controversial
- Hypocalcemia should be treated promptly in any symptomatic neonate or older child because of the condition's serious implications for neuronal and cardiac function

- Intravenous (IV) infusion with calcium-containing solutions can cause severe tissue necrosis

Hypoparathyroidism

Background

- Hypoparathyroidism is a condition of PTH deficiency

Causes

- Iatrogenic (most common cause), e.g., secondary thyroidectomy with accidental removal of parathyroid glands
- Congenital causes, e.g., DiGeorge syndrome
- Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) (aka autoimmune polyendocrinopathy syndrome type 1 [APS 1])
- Metal overload, e.g., Wilson disease or hemochromatosis
- Maternal hypercalcemia in unborn infant may cause suppression of PTH in neonate

Clinical presentation

- Paresthesias (involving fingertips, toes, perioral area)
- Hyperirritability
- Fatigue
- Anxiety
- Mood swings and/or personality disturbances
- Seizures (especially in patients with epilepsy)
- Hoarseness (due to laryngospasm)
- Wheezing and dyspnea (due to bronchospasm)
- Muscle cramps, diaphoresis, and biliary colic
- Hypomagnesemia, hypokalemia, and alkalosis (e.g., hyperventilation), which worsen signs and symptoms of hypocalcemia
- Hypocalcemia may be demonstrated at the bedside by eliciting the following signs:
  - Chvostek sign: Facial twitching, especially around the mouth, is induced by gently tapping the ipsilateral facial nerve as it courses just anterior to the ear
  - Trousseau sign: Carpal spasm is induced by inflating a blood pressure cuff around the arm to a pressure 20 mmHg above obliteration of the radial pulse for 3–5 min

Diagnosis

- Primary hypoparathyroidism
  - Low (or inappropriately normal) PTH and low calcium level
- Pseudohypoparathyroidism
  - High PTH (due to resistance and PTH receptor mutation) and low calcium
- Secondary hypoparathyroidism
  - Low PTH and high calcium level
- Calcium
  - Hypoalbuminemia causes a drop in total calcium concentration, but the ionized fraction may be within the reference range
  - Alkalosis may trigger symptoms of hypocalcemia
- Serum magnesium
  - Hypomagnesemia may cause PTH deficiency and subsequent hypocalcemia
  - Exclude it in any patient with primary hypoparathyroidism
- Serum phosphorus
  - PTH is a phosphaturic hormone. In its absence, phosphorus levels in the blood rise
- 25(OH)D to exclude vitamin D deficiency as a cause of hypocalcemia

Management

- Correct the hypocalcemia by administering calcium and vitamin D (calcitriol)

Pseudohypoparathyroidism (PHP); Albright Hereditary Osteodystrophy (AHO)

Background

- PHP is a heterogeneous group of disorders characterized by hypocalcemia, hyperphos-

phatemia, increased serum concentration of PTH, and insensitivity to the biological activity of PTH

Genetic defect
- PHP IA
  - Account for majority of patients
  - It is a resistance to PTH
  - Genetic defect of the alpha subunit of stimulatory guanine nucleotide-binding protein. This factor is required for PTH bound to cell surface receptors to activate cyclic adenosine monophosphate (cAMP)
  - It is inherited as autosomal dominant trait
- PHP IB
  - Affected patients have normal level of G protein activity and a normal phenotype appearance
  - These patients have tissue-specific resistance to PTH but not to other hormones
- PHP II
  - Rare
  - Normal phenotype appearance (no AHO)

Clinical presentation
- Hypocalcemia can present in infancy
- Tetany
- Albright hereditary osteodystrophy (AHO; PHP type 1A) characterized by:
  - Short stature
  - Stocky habitus
  - Round face
  - Brachymetacarpals (particularly the fourth and fifth digits)
  - Dimpling over the knuckles of a clenched fist due to short metacarpals
  - Brachymetatarsals
  - Intellectual disability
  - Subcutaneous calcifications

Diagnosis
- High serum PTH/low serum Ca/high phosphate/skeletal defect is a classic finding in Albright hereditary osteodystrophy
- High serum PTH/low serum Ca is either PHP or secondary hyperparathyroidism
- Skeletal defect/normal PTH/normal Ca/normal phosphate is pseudopseudohypoparathyroidism

Management
- All patients with severe symptomatic hypocalcemia should be initially treated with IV calcium
- Administration of oral calcium and 1 alpha hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment

Familial Hypocalciuric Hypercalcemia (Familial Benign Hypercalcemia)

Background
- Autosomal dominant condition of benign hypercalcemia
- Asymptomatic
- Usually discovered incidentally on routine labs

Diagnosis
- Hypercalcemia with calcium level > 10.2 mg/dL
- Urine calcium to creatinine ratio < 0.01 and urine calcium < 200 mg/day
- Normal PTH and normal phosphate

Treatment
- None

Hyperparathyroidism

Background
- Hyperparathyroidism is rare in children
- Primary hyperparathyroidism is caused by a single adenoma and is the most common cause
- Familial cases can occur as part of the MEN syndromes (MEN-1 or MEN-2A)
- Secondary hyperparathyroidism can occur with chronic renal failure, cholestatic liver disease, or as an iatrogenic effect, e.g., lithium

Clinical presentation

- Commonly presents without symptoms
- Hypercalcemia
- Muscular weakness
- Bone pain
- Abdominal pain
- Acute pancreatitis
- Nephrolithiasis

Diagnosis

- Serum calcium usually > 12 mg/dL
- Low serum phosphorus < 3 mg/dL
- High PTH
- Normal calcitonin level

Management

- For primary hyperparathyroidism, subtotal or total parathyroidectomy is the most common choice for adults or children
- Calcitriol may help in cases with chronic renal failure
- Treatment of acute severe hypercalcemia: Ca > 14 mg/dL
  - IV hydration
  - Loop diuretics (e.g., furosemide) after hydration
  - Hemodialysis in severe cases

RICKETS

Vitamin D Deficiency Rickets

Background

- Disease of growing bone that is unique to children and adolescents
- Caused by a failure of osteoid to calcify in a growing person. Failure of osteoid to calcify in adults is called osteomalacia
- Vitamin D deficiency rickets occurs when the metabolites of vitamin D are deficient
- Less commonly, a dietary deficiency of calcium or phosphorus may also produce rickets

Vitamin D metabolism

- Cholecalciferol (i.e., vitamin D-3) is formed in the skin from 5-dihydrotachysterol
- First hydroxylation step occurs in the liver (position 25)
- Produces calcidiol (aka 25-hydroxycholecalciferol or 25-hydroxyvitaminD) or 25(OH)D
  - 25(OH)D is the best indicator of overall vitamin D status and commonly tested
- Second hydroxylation step occurs in the kidney (position 1)
  - Calcitriol (1,25-dihydroxycholecalciferol) is active metabolite
  - Calcitriol acts at three known sites to tightly regulate calcium metabolism:
    - Promotes absorption of calcium and phosphorus from the intestine
    - Increases reabsorption of phosphate in the kidney
    - Acts on bone to release calcium and phosphate
- Calcitriol
  - Increases calcium and phosphorus in extracellular fluid
  - Increases calcification of osteoid, primarily at the metaphyseal growing ends of bones
- Parathyroid hormone (PTH)
  - PTH facilitates the 1-hydroxylation step in vitamin D metabolism in the kidney
  - In the vitamin D deficiency state, hypocalcemia develops, which stimulates excess secretion of PTH
  - In turn, renal phosphorus loss is enhanced, further reducing deposition of calcium in the bone
  - Excess PTH also produces changes in the bone similar to those occurring in hyperparathyroidism
  - Early in the course of rickets, the calcium concentration in the serum decreases. After the parathyroid response, the calcium concentration usually returns to the reference range, though phosphorus levels remain low

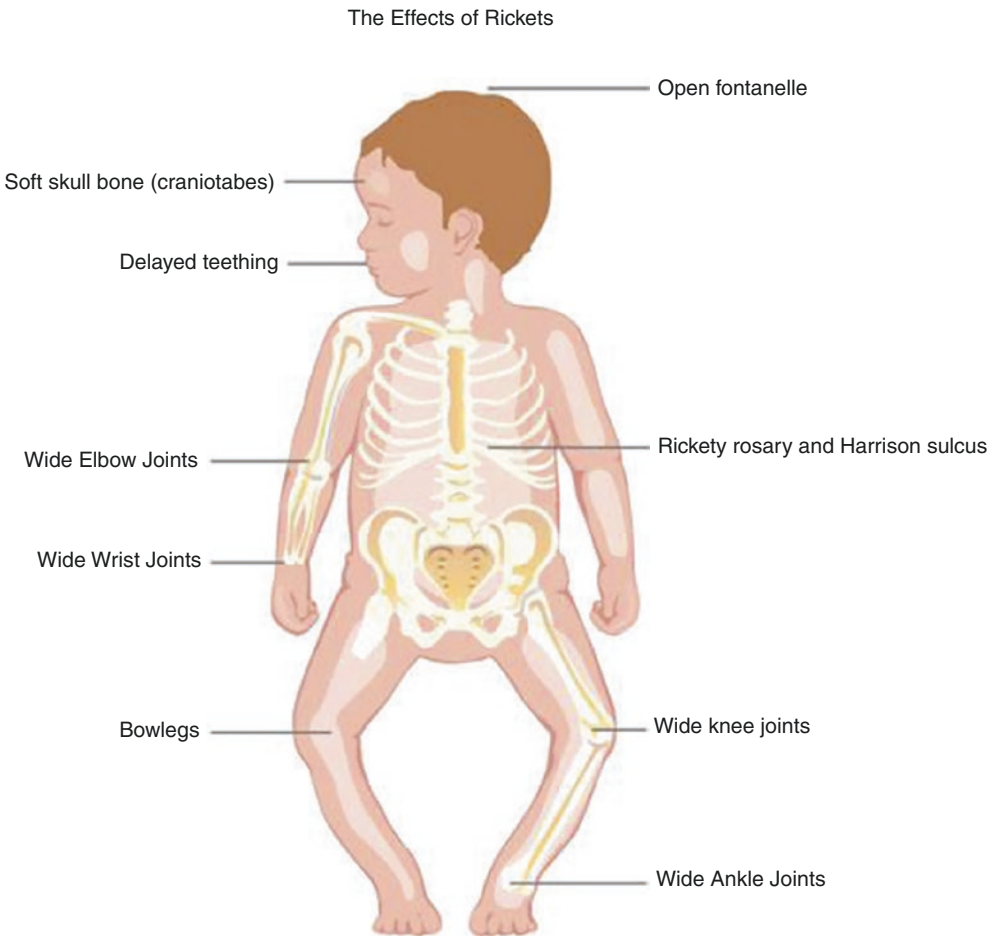

Fig. 12.6 Skeletal manifestations of rickets

- Alkaline phosphatase
  - Produced by overactive osteoblast cells
  - Usually very high levels in growing children

Causes of rickets

- Nutritional deficiency still the most common cause of rickets worldwide
- Prolonged and exclusive breastfeeding without vitamin D supplementation with minimal sunlight exposure
- Intestinal malabsorption of fat
- Liver or kidney disease
- Anticonvulsant drugs (e.g., phenobarbital, phenytoin)
- Accelerate metabolism of 25(OH)D
- Vegan diets, especially lacto-vegans
- Genetic defects

Clinical presentation (Fig. 12.6)

- At very young ages, vitamin D deficiency is more likely to present as hypocalcemia than as rickets
- Muscular hypotonia
- Craniotabes (areas of thinning and softening of the bones of the skull)
- Frontal bossing and delays the closure of the anterior fontanelle
- Bowlegs and knock knees on weight limbs
- Rachitic rosary along the costochondral junctions
- Harrison groove due to weakened ribs pulled by muscles also produces flaring over the diaphragm
- Kyphoscoliosis in older children

- Knobby deformity of long bone, which is visualized on radiography as cupping and flaring of the metaphyses
- Marfan sign; palpation of the tibial malleolus gives the impression of a double epiphysis
- Greenstick fracture

Diagnosis (Table 12.3)

- Low to normal calcium
- Low phosphorus
- High alkaline phosphatase
- High PTH
- Low 25(OH)D
- Low to high 1,25-dihydroxyvitamin D
- Normal HCO3

Radiography (Fig. 12.7)

- Anterior view of the knee is the best site to study, also the wrist and ankle
- Widening and cupping of the metaphysis
- Fraying of metaphysis
- Epiphyseal plate is widened and irregular
- Osteopenia

Management

- Indication for treatment
  - Vitamin D therapy is necessary for infants and children who manifest clinical features of hypocalcemia as a result of vitamin D deficiency or rickets and when vitamin D levels are in the deficient range
- Vitamin D and calcium replacement
  - Vitamin D given daily for a 2- to 3-month period to normalize 25(OH)-D levels and replenish stores
  - Vitamin D_3 can be given 2000 IU PO daily or 50,000 IU PO weekly for 6 weeks
  - With therapy, radiologic evidence of healing is observed in 2–4 weeks, after which the dose of vitamin D can be reduced to 400 IU/day
  - Lack of compliance is an important cause of lack of response, and an option after the 1st month of life is to administer high doses of vitamin D in a single administration as "stoss therapy," instead of smaller doses over a longer period, followed by maintenance dosing
  - High-dose vitamin D may need to be intermittently repeated (usually every 3 months) if poor compliance persists with maintenance dosing
- Calcium replacement
  - Hypocalcemia should be treated with calcium supplements
  - Parenteral calcium as calcium gluconate becomes necessary in case of tetany or convulsions
  - Calcitriol may be necessary until calcium levels normalize
- Monitoring therapy
  - It is important to obtain calcium, phosphorus, and ALP levels 1 month after initiating therapy

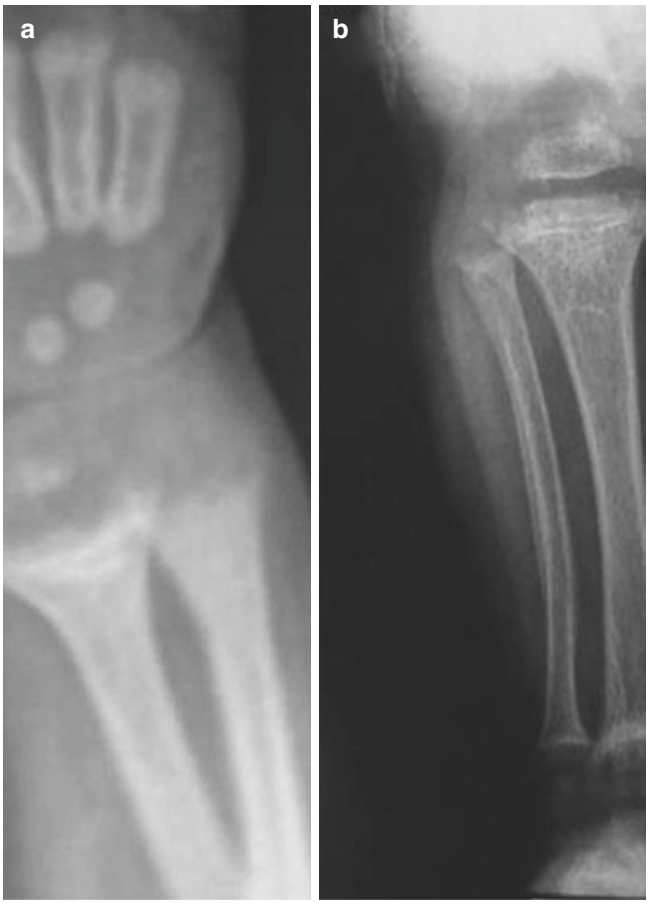

Fig. 12.7 Radiographs of rickets. Radiographs of the wrist (**a**) and leg (**b**) of a 3-year-old boy with nutritional rickets showing the cupping, fraying, and widening of the physis

  - With stoss therapy, a biochemical response occurs in 1 or 2 weeks, the first sign of which is an increase in phosphate
  - It is important to remember that ALP levels may actually increase in the short term as bone formation rates increase
  - Complete radiologic healing may take months, but changes are evident in 1 week
  - In 3 months, it is important to obtain calcium, phosphate, magnesium, ALP, 25(OH)D, and PTH levels, and one may consider obtaining a urine sample to determine the calcium/creatinine ratio
  - A radiograph should also be repeated at 3 months
  - 25(OH)D levels should be monitored yearly
- When to refer
  - If radiographic evidence of some healing is not observed with vitamin D and calcium replacement in 3 months
  - Considerations should include malabsorption, liver disease, or a lack of compliance with replacement therapy
  - Important to remember: Normal levels of ALP and 25(OH)D; very low or very high levels of 1,25-dihydroxyvitamin D; and high serum urea nitrogen and creatinine levels are red flags for considering other causes of rickets (e.g., inherited forms of hypophosphatemic rickets and vitamin D receptor mutations)
- Orthopedic referral if severe deformities have occurred

Prevention of vitamin D deficiency

- Supplementation with 400 IU of vitamin D should be initiated within days of birth for all breastfed infants
- Appropriate exposure to sunlight

Hypophosphatemic Rickets (X-Linked)

Background

- X-linked hypophosphatemic rickets is an X-linked dominant disorder
- Affects both males and females

Clinical presentation

- Failure to thrive
- Hypotonia
- Reluctance to bear weight when beginning to stand or walk
- Delayed dentition

Diagnosis

- Normal calcium level
- Low phosphorus
  - Concentration reference range for infants (5.0–7.5 mg/dL) is high compared with that for adults (2.7–4.5 mg/dL), e.g., 3 mg/dL is considered low in young children
  - Hypophosphatemia can easily be missed in an infant
- Very high ALP (significantly high)
- Normal HCO3
  - HCO3 is low in Fanconi syndrome or oculocerebrorenal dystrophy (Lowe syndrome), i.e., non-anion gap metabolic acidosis
- Radiography
  - Same as vitamin D deficiency rickets

Management (Table 12.3)

- Calcitriol and phosphorus

DISORDERS OF PUBERTY

General considerations

- Positive relation between degree of obesity and early puberty has been reported (African-American and Hispanic populations especially)
- Delayed puberty is common in gymnasts and marathon runners (lack critical adiposity)

Normal Variants of Puberty: Premature Adrenarche

Background

- Benign, self-limited
- Onset before age 6 years

Table 12.3 Types of rickets, differential diagnosis, and common laboratory findings

Disorder	Defect	Ca	Ph	PTH	25(OH) D	Calcitriol	ALP	Treatment
Vitamin D deficiency	Decreased vitamin D	N, L	L	H	L	N, L, H	H	Vitamin D
1-αhydroxylase mutation	25-(OH)D cannot be converted to calcitriol	N, L	L	H	N	Very L	H	Calcitriol
Vitamin D receptor mutation resistance	End-organ resistance to vitamin D	N, L	L	H	N	Very H	H	Ca
Chronic renal failure	Decrease activity of 1-αhydroxylase in the kidney	N, L	H	Very H	N	L	H	Ca and phosphate binders
Hypoparathyroidism	Low PTH	L	H	L	N	N	N	Ca, vitamin D, and calcitriol in some cases
X-linked hypophosphatemic rickets	Proximal tubular defect, Ph wasted in the urine	N, L	L	N, H	N	N, slightly L	H	Phosphate and calcitriol
Mostly due to *PHEX* mutation								
Pseudohypoparathyroidism (*Gsα* mutation)	PTH resistance	L	H	H	N	N	N	Ca and vitamin D
Fanconi syndrome	RTA	N	L	N	N	Slightly L or H	H	Phosphate, calcitriol, or 1α-hydroxy vitamin D3

Ca calcium, *Ph* phosphorus, *PTH* parathyroid hormone, *25(OH)D* 25-hydroxyvitamin D, *ALP* alkaline phosphatase, *N* normal, *H* high, *L* low, *RTA* renal tubular acidosis

Clinical presentation

- Early pubic hair and axillary hair development
- Increased sebaceous activity
- Adult-type body odor
- No sexual development (breast buds in girls; testicular enlargement in boys)
- Normal growth pattern

Diagnosis

- Bone age approximates chronological age or mildly advanced
- Other imaging studies are normal
- Slight increase in DHEA-S level
- Other adrenal steroid hormones are normal
- Normal sex hormones
- No CAH
- Consistent with prepubertal pattern

Management

- Reassurance

Isolated (Benign) Premature Thelarche

Background

- Premature thelarche refers to isolated breast development that occurs in the first 2 years of life
- Possible underlying cause must be investigated if it occurs after 3 years of age

Diagnosis

- Normal bone age
- No other signs of puberty
- No growth acceleration
- All labs are normal for age
- Unilateral or bilateral with waxing and waning course
- Regression usually occurs within 18 months but may persist for 3–5 years
- Regression might not happen if presenting breast development is > Tanner II

Management
- Benign condition and self-limited
- However, patients should be followed at 3- to 6-month intervals, as studies have indicated that about 18% of premature thelarche will progress to central PP
- Thelarche after the first 3 years of life must be investigated

Premature Menarche

Background
- Premature menarche by itself is very rare

Differential diagnosis
- Foreign bodies
- Vulvovaginitis
- Sexual abuse

Clinical presentation
- Most girls with isolated premature menarche have only 1 to 3 episodes of bleeding, then puberty occurs at normal time

Diagnosis
- Gonadotropin levels are normal
- Estrogen may be elevated
- Ovarian cyst may be noted

Precocious Puberty (PP)

Definitions
- Thelarche: Breast development
- Adrenarche: Maturation of adrenal androgen production leading to body odor, acne, axillary and pubic hair development
- Pubarche: Pubic hair development; usually part of adrenarche
- Menarche: First vaginal bleeding
- Gonadarche: Earliest gonadal changes in response to pituitary gonadotropins

Background
- The hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gonadotrophs to release LH and FSH, which stimulate the gonads to release sex hormones (gonadarche: estrogen from ovaries and testosterone from testes)
- First manifestation of gonadarche in boys is testicular enlargement (> 3 ml in volume) and in girls is breast budding (Tanner II)
- Normal pubertal timing (gonadarche) is between 8 and 13 years in girls and 9 and 14 years in boys
- Pubertal signs are considered precocious if they happen before the age of 8 years in girls and 9 years in boys
- PP can be classified as gonadotropin-dependent (centrally mediated) and gonadotropin-independent (peripherally mediated)

Sexual Maturity Ratings (SMRs)

Sexual development in boys (Fig. 12.8, and Table 12.4)
- Thinning of scrotum
- Increased pigmentation of scrotum
- Enlargement of testis > 3 ml or 2.5 cm
- Pubic hair
- Height acceleration occurs late at SMR 4–5 (typically age 13–14)

Sexual development in girls (Fig. 12.9, and Table 12.5)
- Breast buds
- Pubic hair
- Height acceleration peak during SMR 2–3 (typically 11–12 years)
- Menarche takes usually 2–2.5 years after breast development but can take up to 6 years

Differential Diagnosis for Precocious Puberty

A. Gonadotropin-dependent PP = centrally mediated PP
- Idiopathic = most common cause
- CNS disorders

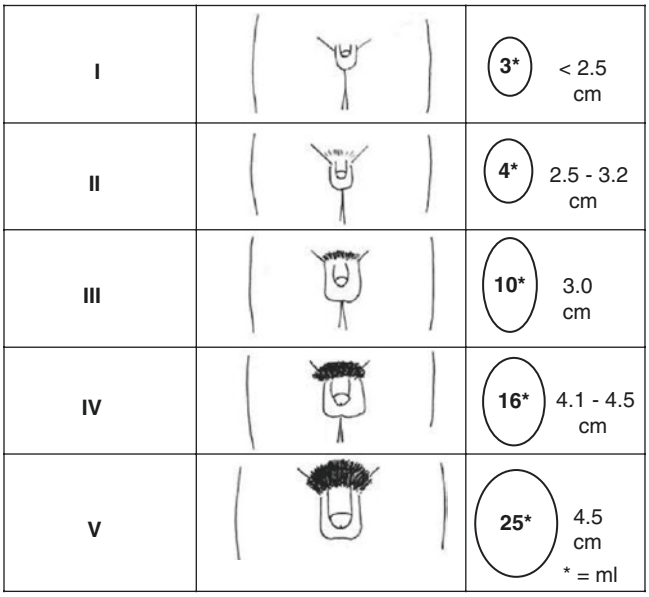

Fig. 12.8 Sexual maturity rating in boys

Table 12.4 Sexual maturity rating in boys

Stages	Pubic hair	Genitalia
1	Prepubertal	Prepubertal
2	Sparse, lightly pigmented at the base of the penis	Scrotum and penis enlarge slightly
3	Begins to curl, extend laterally	Testes and scrotum continue to grow
4	Coarse, curly, adult type but less in quantity	Large and darker scrotum, penis becomes large and increased in width, glans penis develops
5	Adult distribution and extends to medial thigh	Adult size scrotum and penis

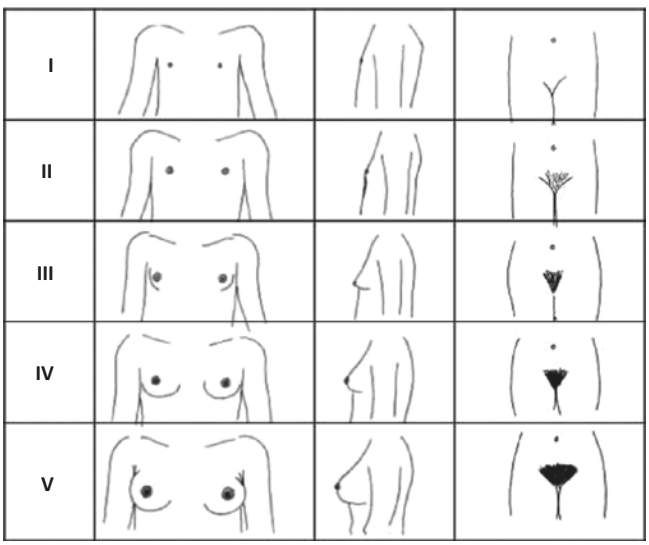

Fig. 12.9 Sexual maturity rating in girls

Table 12.5 Sexual maturity rating in girls

Stages	Pubic hair	Breasts
1	Prepubertal: no pubic hair present, fine hair may be noted	Prepubertal: Juvenile breast with small flat areola and elevated papilla
2	Sparse, lightly pigmented	Small mound and areolar diameter increases
3	Increased in amount and becomes darker, starting to curl	Breast and areola are larger, no separation of breast contour is noted
4	Abundant, coarse, curly, but less than adult	Areola and papilla form secondary mound, separation from contour is noted
5	Adult female triangle, extends to medial thigh	Mature, more projection of papilla, areola becomes part of general breast contour

  - Hypothalamic hamartomas: Most common identified CNS lesion. Benign and usually requires no intervention
  - Tumors (e.g., astrocytoma, gliomas, germ cell tumors secreting human chorionic gonadotropin [HCG])
  - Acquired CNS injury caused by inflammation, surgery, trauma, radiation therapy, or abscess
- Congenital anomalies (e.g., hydrocephalus, arachnoid cysts, suprasellar cysts)
- Genetic mutations: e.g., *MKRN-3, DLK-1, KISS1, KISSR1*
- Syndromes, e.g., neurofibromatosis type 1

B. Gonadotropin-independent PP = peripherally mediated PP

- Gonads
  - McCune Albright syndrome (see below)
  - Testotoxicosis (familial male gonadotropin-independent PP)
  - Tumors (e.g., theca cells, granulosa cells, Leydig cells, Sertoli cells)
- Adrenal gland
  - CAH (see below)
  - Tumors (adenoma or carcinoma)
- HCG-secreting tumors, e.g., hepatoblastoma (HCG acts as a gonadotropin)
- Exogenous exposure to estrogen or testosterone or endocrine disruptor chemicals
- Severe primary hypothyroidism (= Van Wyk–Grumbach syndrome)

C. Gonadotropin-dependent PP = centrally mediated

- PP increases the risk for psychological and social stress, including sexual abuse and compromise of final adult height in untreated cases

Clinical presentation

- PP in girls < 8 years
  - Breast enlargement, which may initially be unilateral
  - Pubic and axillary hair may appear first
  - Accelerated linear growth and bone age advancement
- PP in boys < 9 years
  - Testicular enlargement, a subtle finding that often goes unnoticed by patients and parents
  - Growth of the penis and scrotum
  - Accelerated linear growth and bone age advancement

Diagnosis

- Random gonadotropin and sex hormones may be elevated; however, in many occasions, random measurements are not diagnostic
- Definitive diagnosis of central PP may be confirmed by measuring LH (by ultrasensitive assay) levels 60 min after stimulation with a parenteral injection (subcutaneous or IV) with a short-acting GnRH analog
- Bone age radiograph is a quick and helpful means to estimate the likelihood of PP and its speed of progression

Management

- MRI of the brain is indicated in all boys (any age) with central PP and in girls with onset less than 6 years of age. There is no consensus on ordering MRI brain for girls between 6 and 8 years of age
- Long-acting GnRH analogs are the standard of care for central PP. They act by inhibiting the hypothalamic–pituitary–gonadal axis
- Treatment of the cause, e.g., surgical resection of tumor and irradiation

Gonadotropin-independent PP = peripherally mediated PP

- Clinical presentation and management will depend on the underlying cause
- Random and GnRH-stimulated levels of gonadotropins are suppressed with elevated sex hormone levels
- Adrenal androgens can be measured, including DHEA-S, androstenedione, and 17-hydroxyprogesterone
- Thyroid functions should be measured in all patients presenting with signs of PP to rule out severe primary hypothyroidism
- Ultrasound or imaging of gonads/adrenals may be needed

McCune–Albright Syndrome

Background

- Caused by an activating mutation of the *GNAS* gene
- Characterized by the following triad:
  - Polyostotic fibrous dysplasia
  - *Café-au-lait* skin pigmentation
  - Gonadotropin-independent PP

Clinical presentation

- PP
  - Breast development
  - Vaginal bleeding (may occur before breast development)
  - Genital maturation (with or without pubic hair growth)
  - Increased height velocity and advanced bone age
  - Macro-orchidism
- *Café-au-lait* pigmentation
  - Segmental distribution
  - Frequently predominating on one side of the body without crossing the midline
- Polyostotic fibrous dysplasia
  - Multiple pathologic fractures
  - Gait anomalies
  - Visible bony deformities (including abnormal bone growth of the skull), bone pain, and joint stiffness with pain

- Other signs of *GNAS* activation: e.g., hyperthyroidism or hypercortisolism

Diagnosis

- Elevation of sex hormones (estrogen in girls and testosterone in boys) with suppressed gonadotropins (both random and GnRH analog stimulated)
- Plain radiography can show multiple patchy areas of bony lysis

Management

- No specific treatment for this syndrome
- Treatment of PP
  - Aromatase inhibitors

Delayed Puberty

- In boys, puberty is considered delayed if testicular volume is less than 4 ml by 14 years of age or if started before 14 years of age and is taking more than 5 years to complete
- In girls, puberty is considered delayed if no breast development is happening by 13 years of age or if no menarche by age 16 years or 3 years after breast budding

Differential diagnosis of delayed puberty includes the following

- Constitutional delay of growth and puberty (normal variant of normal pubertal timing)
  - The most common cause of delayed puberty
  - Positive family history is usually present
- Functional disorders and chronic systemic illness
  - Chronic illnesses
  - Nutrition disorders, e.g., malnutrition, anorexia nervosa, etc.
  - Endocrinopathies
  - Psychological stress
  - Medications, e.g., steroids
- Central causes or hypogonadotropic hypogonadism
  - Congenital causes
    - Kallmann syndrome (delayed puberty and anosmia (loss of smell sensation)
    - Bardet–Biedl syndrome
    - Prader–Willi syndrome
    - Congenital panhypopituitarism
  - Acquired causes: Tumors, radiation, or surgery affecting the hypothalamus and/or pituitary gland
- Primary gonadal failure or hypergonadotropic hypogonadism, e.g., Turner syndrome and Klinefelter syndrome

Primary Hypogonadism

Causes

- Primary hypogonadism in males or vanishing testis syndrome
- Developmental anomalies associated with the genital system (e.g., hypospadias, micropenis, and cryptorchidism)
- Mumps orchitis, trauma, radiation exposure of the head or testes, and chemotherapy can cause testicular failure
- Spironolactone, cyproterone, marijuana, heroin, and methadone can inhibit the synthesis of testosterone
- Klinefelter syndrome

Clinical presentation

- In male infants, the testicles are abnormally small
- Failure to develop secondary sexual characteristics
- Eunuchoid body habitus

Diagnosis

- Elevated FSH and LH

Klinefelter Syndrome (See Also Chap. 4 "Genetic Disorders")

Background
- Most common major sexual differentiation abnormality
- 47,XXY karyotype
- Abnormalities of nondisjunction during meiosis

Clinical presentation
- Gynecomastia
- Male breast cancer
- Mild intellectual disability
- Small penis
- Testes are small and firm (usually < 2 cm or 2 ml)
- Azoospermia
- Decreased facial hair, but the pubic hair is abundant

Diagnosis
- Karyotype
- Elevated FSH and LH
- Low inhibin B level
- Increased estradiol to testosterone ratio

Management
- Testosterone replacement after age 11 years (intramuscular [IM], or transdermal)
  - Testosterone 25–50 mg IM every 3–4 weeks
  - Increase the dose by 50 mg every 6–9 months
  - Goal: 200–250 mg every 3–4 weeks
- Breast cancer surveillance

Gynecomastia

Background
- Gynecomastia is a benign enlargement of the male breast (usually bilateral but sometimes unilateral) resulting from a proliferation of the glandular component of the breast
- Presence of a rubbery or firm mass extending concentrically from the nipples
- Gynecomastia should be differentiated from pseudogynecomastia (lipomastia), which is characterized by fat deposition without glandular proliferation
- Common in adolescence

Causes
- Estrogen–androgen imbalance
- Pubertal (physiologic gynecomastia)
- Klinefelter syndrome
- Testicular tumor
- Ectopic production of HCG, e.g., germ cell tumor
- Chronic liver disease
- Hyperthyroidism
- Adrenal tumor
- Familial gynecomastia
- Prolactinoma

Approach and considerations
- Asymptomatic and pubertal gynecomastia does not require further tests and should be reevaluated in 6 months
- Red flags
  - Breast size greater than 5 cm (macromastia)
  - A lump that is tender, of recent onset, progressive, or of unknown duration
  - Signs of malignancy (e.g., hard or fixed lymph nodes or positive lymph node findings)
- Further investigation if abnormal underlying cause is considered

Treatment
- Generally, no treatment is required for physiologic gynecomastia
- Pubertal gynecomastia resolves spontaneously within several weeks to 3 years in approximately 90% of patients

Turner Syndrome (See also Chap. 4 "Genetic Disorders")

Background

- More than 95% of adult women with Turner syndrome are short and infertile
- 45,X chromosome

Clinical presentation

- Short stature
- Ovarian failure
- Heart murmur
  - Bicuspid aortic valve (most common heart defect)
  - Coarctation of the aorta
- Hypertension
- Lymphedema at birth
- Webbed neck
- Madelung deformity
- Hypothyroidism

Diagnosis

- Karyotype: Diagnosis is confirmed by the presence of a 45,X cell line or a cell line with deletion of the short arm of the X chromosome (Xp deletion), also mosaic forms
- The buccal smear for Barr bodies is obsolete
- Y-chromosomal material should be investigated for possibility of mixed 45,X/46,XY mosaicism may have mixed gonadal dysgenesis and are at a high risk for gonadoblastoma
- LH and FSH rise to menopausal level after age of 10 years
- TSH and thyroid study must be followed due to high risk of hypothyroidism

Management

- GH to improve final height
- Estrogen replacement therapy is usually required
- Estrogen is usually started at age 12–15 years after height optimized
- Treatment can be started with continuous low-dose estrogens at 12 years
- These can be cycled in a 3-weeks on, 1-week off regimen and after 6–18 months; progestin can be added later

ADRENAL DISORDERS

For the purpose of this review, the following disorders will be discussed:

- Disorders of the adrenal cortex: Cushing syndrome, Addison disease, and hyperaldosteronism. CAH syndrome will be discussed under disorders of sexual differentiation
- Disorders of the adrenal medulla: Pheochromocytoma

Cushing Syndrome

Background

- Caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids
- Exogenous glucocorticoid exposure is the most common overall cause. ACTH therapy is another cause of hypercortisolism but is much less common
- Endogenous causes
  - ACTH-secreting pituitary adenoma
    - Most common endogenous cause (75%)
    - More common above 7 years of age
  - Adrenal causes of Cushing (adenoma, carcinoma, and bilateral hyperplasia)
    - More common below 7 years of age
  - Ectopic ACTH-secreting tumors represent less than 1% of cases and is very rare in children
- Cushing syndrome causes can be classified as ACTH-dependent (Cushing disease and ectopic secretion) and ACTH-independent (exogenous exposure or adrenal causes)

Clinical presentation

- Excessive weight gain, especially in the face (moon facies), supraclavicular region, upper back (buffalo hump), and torso
- Failure to grow or short stature
- Hypertension
- Purple stretch marks, easy bruising, and other signs of skin thinning
- Proximal muscle weakness
- Depression, cognitive dysfunction, and emotional lability may develop
- Hypertension
- DM or glucose intolerance
- Decreased bone density and fractures

Diagnosis

- Evidence of hypercortisolism
  - Elevated 24-h urinary free cortisol
  - Low-dose dexamethasone suppression test showing no suppression of 8:00 AM cortisol
  - Loss of normal circadian rhythm, i.e., elevated cortisol at midnight
- If there is evidence of hypercortisolism → ACTH levels will be elevated in Cushing disease and ectopic secretion and will be low in adrenal causes
- Imaging is recommended: e.g., brain MRI to look for Cushing disease (pituitary) and abdominal CT for adrenal causes
- Nonspecific laboratory evidence: Elevated white blood cell count greater than 11,000/mm^3, hyperglycemia, and hypokalemic metabolic alkalosis

Management

- Depends on lesion and location
- Unilateral adrenalectomy for benign adrenal tumor
- Treatment of choice for pituitary adenoma: Transsphenoidal pituitary microsurgery

Remember

- Children with obesity are usually tall
- Children with Cushing syndrome (and other endocrine causes of short stature) are obese and short

Hyperaldosteronism

Background

- Rare in children
- Primary hyperaldosteronism usually due to adrenal tumor
- Secondary hyperaldosteronism, e.g., nephrotic syndrome, congestive heart failure, and liver cirrhosis

Clinical presentation

- Hypertension
- Headache
- Hypokalemia-related symptoms, e.g., constipation and weakness

Diagnosis

- Primary hyperaldosteronism
  - Elevated aldosterone level
  - Low renin level
  - Hypertension
  - Hypokalemia
- Secondary hyperaldosteronism
  - Elevated plasma renin activity (PRA)

Management

- Surgical removal of adenoma
- Prednisone for glucocorticoid-suppressible hyperaldosteronism

Adrenal Insufficiency

- Can be classified into **primary adrenal insufficiency** and **secondary or central adrenal insufficiency**
- The most common cause of **primary adrenal insufficiency** is autoimmune adrenal insufficiency, also known as Addison disease

- The most common cause of **secondary/central adrenal insufficiency** is chronic use of exogenous supraphysiological doses of corticosteroids (iatrogenic adrenal insufficiency)
- It is important to note that chronic use of corticosteroids will inhibit ACTH secretion with resulting adrenal gland atrophy
- Sudden cessation or withdrawal of corticosteroids in these patients will lead to acute adrenal insufficiency or crisis
- A similar scenario will happen if the patient is on physiological doses of steroids but is exposed to stress (e.g., surgery, illness) with no additional replacement

Addison Disease

Background

- Addison disease is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex
- Idiopathic autoimmune Addison disease tends to be more common in females and children

Associated autoimmune diseases

- Diabetes mellitus (DM) type 1
- Celiac disease, Hashimoto thyroiditis
- Graves disease
- Vitiligo
- Alopecia areata, totalis, and universalis
- Premature ovarian or testicular failure
- Pernicious anemia
- Autoimmune polyglandular syndrome (APS) type 2

Other causes

- Tuberculosis, sarcoidosis, histoplasmosis, blastomycosis, and cryptococcosis could involve the adrenal glands

Acute Addison Disease

Causes

- Bilateral adrenal hemorrhage, e.g., meningococcemia
- Failure to increase steroids in patients with adrenal insufficiency in time of stress, e.g., surgery

Clinical presentation

- Hyperpigmentation
  - Caused by the stimulant effect of excess adrenocorticotropic hormone (ACTH) on the melanocytes to produce melanin
- Vitiligo
- Hypotension
- Myalgias and flaccid muscle paralysis may occur due to hyperkalemia
- Acute adrenal crisis
  - Nausea, vomiting, and vascular collapse
  - Shock; may appear cyanotic and confused
  - Acute abdomen
  - Hyperpyrexia, with temperatures reaching 105 °F or higher
  - In acute adrenal hemorrhage, the patient is usually in an acute care setting, deteriorates with sudden collapse, abdominal or flank pain, and nausea with or without hyperpyrexia

Diagnosis

- High-dose ACTH stimulation test (Cortrosyn, cosyntropin, or Synacthen)
- Low cortisol with elevated ACTH suggestive
- Hyponatremia
- Hyperkalemia
- Mild non-anion-gap metabolic acidosis due to the loss of the sodium-retaining and potassium and hydrogen ion-secreting action of aldosterone

Management of adrenal crisis

- In stress situations, the normal adrenal gland output of cortisol is approximately 100 mg/m^2 of bovine serum albumin (BSA) in 24 h
- IV access should be established urgently
- Infusion of isotonic NaCl to restore volume deficit and correct hypotension
- IV bolus of hydrocortisone and then 100 mg/m^2/day divided into three or four times a day until resolution of crisis, then consult endocrinology to discontinue or taper

Pheochromocytoma

Background

- Rare catecholamine-secreting tumor that arises from chromaffin cells of the sympathetic nervous system (adrenal medulla and sympathetic chain)

Clinical presentation

- Headache is the most frequent symptom in children (75%)
- Sweating in two-thirds of patients
- Nausea and vomiting in half of patients
- Hypertension
- Palpitation with or without tachycardia
- Weakness or exhaustion
- Chest pain
- Dyspnea
- Epigastric pain
- Tremor
- Nervousness or anxiety
- Numbness or paresthesia
- Blurred vision

Diagnosis

- High blood pressure or recurrent hot flushes that are indicative of blood pressure peaks
- An adrenal mass
- Family history of MEN type 2 (MEN-2) or von Hippel–Lindau disease
- Measurement of urinary catecholamines and their metabolites in a 24-h specimen
  - Homovanillic acid (HVA)
  - Vanillylmandelic acid (VMA)
  - Epinephrine
  - Norepinephrine
- Abdominal ultrasound may detect large adrenal tumor
- CT scan of adrenal gland

Management

- Treat with surgical removal and pretreat with alpha-blockade
- During a hypertensive crisis, immediately institute alpha-blockade with phenoxybenzamine
- Nitroprusside should also be used for uncontrolled hypertension

Polycystic Ovarian Syndrome (PCOS)

Background

- Women with PCOS have abnormalities in the metabolism of androgens and estrogen and in the control of androgen production
- PCOS can result from abnormal function of the hypothalamic–pituitary–ovarian (HPO) axis

Clinical presentation

- Menstrual dysfunction due to anovulation
- Hirsutism
- Infertility
- Obesity
- Metabolic syndrome
- DM
- Obstructive sleep apnea
- Virilizing signs
- Acanthosis nigricans
- Hypertension

Diagnosis

- FSH levels are within the reference range or low
- LH levels are elevated for Tanner stage, sex, and age
- The LH to FSH ratio is usually greater than 2–3
- Elevated testosterone (or free testosterone) level
- Recommended tests:
  - TSH and free thyroxine
  - Serum prolactin level
  - Total and free testosterone
  - Serum hCG level
  - Glucose level
  - Insulin level
  - Lipid panel
  - 17-hydroxyprogesterone level (to exclude late onset CAH)
  - Karyotype usually excludes mosaic Turner as a cause of primary amenorrhea

- Ovarian ultrasonography
  - Enlarged ovaries and cysts may or may not be present

Management

- Diet and exercise are considered first-line treatment
- Oral contraceptive to induce regular menses
- Metformin for insulin resistance

DISORDERS OF SEXUAL DEVELOPMENT (DSD)

Background

- Congenital conditions in which the genetics (chromosomes), gonads, or genitals (anatomic sex) are atypical
- Current classification is based on genetics and does not use the phenotype, as in the past. Terms such as "hermaphrodite," "pseudohermaphrodite," or "sex errors of body" are no longer acceptable
- The embryonic mesoderm develops the genital ridge and primitive kidney. The genital ridge then develops into the bipotential gonad
- The most common cause of atypical genitalia is CAH due to 21-hydroxylase deficiency leading to a virilized female phenotype
- The screening laboratory level for 21-hydroxylase deficiency is 17-hydroxyprogesterone, which will be markedly elevated and is screened for on the newborn screen

In 46 XY males

- The presence of *SRY* (sex-determining region on the Y chromosome) in addition to other autosomal genes will lead the bipotential gonad to differentiate in testis
- The Leydig cells in the testes produce testosterone, which will lead to the development of the Wolffian structures, including epididymis, vas deferens, seminal vesicles, and ejaculatory ducts
- Testosterone is further converted into dihydrotestosterone (DHT) by the action of 5-alpha-reductase enzyme
- DHT is essential for complete masculinization of the external genitalia
- Both testosterone and DHT bind to the androgen receptors to exert their effects; however, DHT has a higher affinity to the androgen receptor
- The Sertoli cells produce anti-Müllerian hormone (AMH), which leads to regression of the Müllerian structures
- The result is normal testicular development with normal male-appearing external genitalia

In 46 XX females

- In the absence of *SRY,* the bipotential gonad develops into an ovary. This also requires interaction of multiple autosomal genes, and the notion that ovarian development is passive is no longer accepted
- In the absence of AMH, the Müllerian structures also under control of autosomal genes will develop into the uterus, fallopian tubes, and upper third of the vagina
- In the absence of androgens, the external genitalia will develop into the normal female phenotype

Classification of DSD is quite complex and the following is a suggested classification

46 XY DSD

- Disorders of testicular development
  - Complete gonadal dysgenesis (Swyer syndrome)
  - Partial gonadal dysgenesis
- Disorders of androgen synthesis or action
  - LH receptor defects → Leydig cell hypoplasia/aplasia
  - Steroidogenic pathway defects: e.g., 17-hydroxysteroid dehydrogenase deficiency, steroidogenic acute regulatory

protein (StAR) deficiency, and 5-alpha-reductase deficiency
  - Androgen receptor defects: Complete and partial androgen insensitivity syndromes
- Disorders of AMH and its receptor, e.g., persistent Müllerian duct syndrome

46 XX DSD
- Disorders of ovarian development
- Disorders of androgen excess
  - 21-hydroxylase deficiency, 11-hydroxylase deficiency, aromatase deficiency, maternal exogenous exposure to androgens
- Others, e.g., vaginal atresia

Sex chromosome DSD
- 45 XO (Turner syndrome)
- 47 XXY (Klinefelter syndrome)
- Mixed gonadal dysgenesis syndrome (45 X/46 XY)
- Ovotesticular DSD (46 XX/46 XY)

Clinical approach to a child with ambiguous genitalia
1. Refer to newborn as "infant" without assigning a gender
2. Consult endocrinology, psychology, urology, genetics, and social services
3. History and physical exam with careful description of genitalia
   (a) Is the newborn a genetic 46 XX female exposed to excess androgens (virilized female)?
   (b) Is the newborn a genetic 46 XY male with underproduction of androgens or decreased action (undervirilized male)?
   (c) Is a gonad palpable? In almost all cases, palpable gonads are testes
4. Laboratory evaluation
   (a) Karyotype
   (b) First 24 h of life: Testosterone, DHT, LH, FSH, AMH
   (c) After 48 h of life: Electrolytes, 17-hydroxyprogesterone, PRA (plasma renin activity)
5. Imaging: Abdominal/pelvic ultrasound to look for uterus, ovaries/testes (gonads)

Congenital Adrenal Hyperplasia (CAH)

Background
- The term encompasses a group of autosomal recessive disorders, each of which involves the deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both

Causes
- The most common form of CAH is due to mutations or deletions of *CYP21A,* resulting in 21-hydroxylase deficiency
- 17-hydroxylase deficiency
- 11-beta-hydroxylase deficiency
- 3-beta-hydroxysteroid deficiency

Clinical presentation in females
- Severe form of CAH
  - Ambiguous genitalia at birth due to excess adrenal androgen production in utero
- Mild forms of 21-hydroxylase deficiency (simple virilizing adrenal hyperplasia)
  - Usually females are identified later in childhood
  - Precocious pubic hair
  - Clitoromegaly
  - Accelerated growth and skeletal maturation due to excess postnatal exposure to adrenal androgens may occur
- Milder deficiencies of 21-hydroxylase or 3-beta-hydroxysteroid dehydrogenase activity (nonclassic adrenal hyperplasia)
  - May present in adolescence or adulthood
  - Oligomenorrhea
  - Hirsutism and/or infertility
  - This is termed nonclassic adrenal hyperplasia
- Females with 17-hydroxylase deficiency
  - Phenotypically female

  - Do not develop breasts or menstruate in adolescence because of inadequate estradiol
  - May present with hypertension

Clinical presentation in males

- 21-hydroxylase deficiency
  - Generally, not identified in the neonatal period because the genitalia are normal
- Severe form of 21-hydroxylase deficiency in males (classic salt-wasting congenital adrenal hyperplasia)
  - Usually results in salt wasting at age 1–4 weeks
  - Failure to thrive
  - Recurrent vomiting
  - Dehydration
  - Hypotension
  - Hyponatremia
  - Hyperkalemia
  - Shock
- Mild form of 21-hydroxylase deficiency (simple virilizing adrenal hyperplasia)
  - May present later in childhood
  - Early development of pubic hair
  - Phallic enlargement
  - Accelerated linear growth and advancement of skeletal maturation
- In male infants, CAH may be misdiagnosed as pyloric stenosis
- Hypertension: Associated with two forms
  - 11-hydroxylase deficiency
  - 17-hydroxylase deficiency

Diagnosis

- High serum concentration of 17-hydroxyprogesterone (usually > 1000 ng/dL)
- Salt-wasting forms
  - Low serum aldosterone concentrations
  - Hyponatremia
  - Hyperkalemia
  - Elevated PRA
- Hypertensive forms of adrenal hyperplasia (i.e., 11-beta-hydroxylase deficiency and 17-alpha-hydroxylase deficiency)
  - Suppressed PRA
  - Hypokalemia
- Karyotype
  - It is essential in the evaluation of an infant with ambiguous genitalia to establish the patient's chromosomal sex

Management

- Stabilization of patient with IV fluids if presenting in shock or dehydration
- IV dextrose if hypoglycemic
- IV hydrocortisone (50–100 mg/m^2 or 1–2 mg/kg initial dose if signs of adrenal insufficiency, e.g., hypotension)
- Followed by 50–100 mg/m^2/day IV divided every 6 h
- Long-term treatment
  - Hydrocortisone oral
  - Fludrocortisone (0.05–0.2 mg/day PO) to patients with mineralocorticoid deficiency
  - Oral NaCl (2–5 g/day) to infants with salt-wasting form

Remember

- 11-Hydroxylase deficiency
  - Non-salt wasting; hypertension is the most presenting symptom, virilization can cause very large clitoris mistaken for penis
- 17-Hydroxylase deficiency
  - Same as 11-hydroxylase deficiency with hypertension but no sex hormone or virilization in females, very rare
- 3β-Hydroxysteroid dehydrogenase deficiency
  - Can be confused with 21-hydroxylase and 11-B with late-onset and salt-wasting forms

Denys–Drash Syndrome

Background

- Occurs in 46, XY individual
- Complete Müllerian ducts usually found in these patients

Clinical presentation

- Nephropathy

- Renal failure usually by 3 years of age
- Ambiguous genitalia
- Wilms tumor

Swyer Syndrome (XY Pure Gonadal Dysgenesis)

Background
- Most patients have mutation in *SRY* gene
- Y chromosome is cytogenetically normal
- The gonads are undifferentiated streaks

Clinical presentation
- Complete female phenotype at birth
- Presence of vagina and fallopian tubes
- At puberty, no breast development and no menstruation

Prognosis
- Development of gonadoblastoma is the highest risk

Management
- Gonads must be removed as soon as the diagnosis is made

5-Alpha-Reductase Deficiency

Background
- Autosomal recessive
- Due to defect in androgen action on external genitalia
- This causes ambiguity of external genitalia
- Peripheral action of testosterone is normal

Clinical presentation
- Newborn with small penis, bifid scrotum, urogenital sinus, and a blind vaginal pouch
- Testes are in inguinal canal
- Most infants are raised as female and changed to male at the time of puberty
- At puberty
  - Virilization occurs
  - Male hair distribution
  - Enlargement of penis and scrotum
  - Sperm formation
- Normal adult height

Androgen Insensitivity Syndrome (AIS)

Background
- X-linked disorder
- Due to defect in androgen receptor gene
- All infants are 46, XY
- All infants have testes and normal testosterone levels

Clinical presentation
- Infant is phenotypically female at birth
- Most infants raised as female and identify with female gender
- External genitalia are female and the vagina ends in a blind pouch
- No uterus
- Fallopian tubes may or may not be present
- Testes are usually intra-abdominal
- At puberty, breasts develop normally
- No menses
- Sexual hair does not appear
- Normal male adult height
- Testosterone may be normal or high

Summary of DSD (Table 12.6)

DIABETES MELLITUS

Type 1 Diabetes Mellitus

Background
- Type 1 DM is a chronic illness characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas
- Most pediatric patients with DM have type 1 and a lifetime dependence on exogenous insulin

Table 12.6 Keywords of common causes of disorders of sexual development

Description of DSD	Diagnosis
XX newborn	Congenital adrenal hyperplasia (CAH)
Virilization of external genitalia	
Ultrasound: normal Müllerian structures	
17 hydroxyprogesterone is very high	
XY female phenotype (raised female)	Androgen insensitivity syndrome (AIS)
Breast, no menses, no sexual hair	
Blind vaginal pouch (MIS is normal)	
Undescended testes	
Elevated testosterone level → estradiol → breast	
XY female phenotype (raised female)	Swyer syndrome (XY pure gonadal dysgenesis)
No breast, no menses, no sexual hair	
Has vagina, uterus, and fallopian tube	
Streak gonads	
Low testosterone	
XY female phenotype at birth	5-Alpha-reductase deficiency (no dihydrotestosterone)
No breast, no menses	
Develop sexual hair, enlarging penis	
No internal Müllerian structures	
Testes are inguinal canal	
XY normal male phenotype	Persistent Müllerian duct syndrome
Inguinal hernia, undescended testes	
Mullerian structure found incidentally	

Clinical presentation

- Hyperglycemia
- Glycosuria
- Polydipsia
- Unexplained weight loss
- Nonspecific malaise
- Symptoms of ketoacidosis

Diagnosis

- Diagnostic criteria by the American Diabetes Association (ADA) include the following:
  - Fasting plasma glucose (FPG) level ≥ 126 mg/dL (7.0 mmol/L), *or*
  - 2-hour plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT), *or*
  - Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
  - HbA1C≥ 6.5%
- Glycated hemoglobin
  - Measurement of HbA1c levels is the best method for medium- to long-term diabetic control monitoring
  - New target for HbA1C in children is < 7.5%
  - Benefits of tight glycemic control include not only continued reductions in the rates of microvascular complications but also significant differences in cardiovascular events and overall mortality
- Positive autoimmune markers (glutamic acid decarboxylase [GAD], insulin islet cell, and Zn transporter antibodies)
- Blood glucose tests
  - Capillary blood samples, reagent sticks, and blood glucose meters are the usual methods for monitoring day-to-day diabetes control

Management

- Insulin therapy
  - All children with type 1 DM require insulin therapy
  - Most require two or more injections of insulin daily, with doses adjusted on the basis of self-monitoring of blood glucose levels
  - Insulin replacement is accomplished by giving basal insulin and a preprandial (premeal) insulin
  - The basal insulin is either long-acting (glargine or detemir) or intermediate-acting (neutral pH protamine [NPH]). The preprandial insulin is either rapid-acting (lispro, aspart, or glulisine) or short-acting (regular)

- Diet and activity
  - The aim of dietary management is to balance the child's food intake with insulin dose and activity and to keep blood glucose concentrations as close as possible to reference ranges, avoiding extremes of hyperglycemia and hypoglycemia
  - Carbohydrates should provide 50–55% of daily energy intake; no more than 10% of carbohydrates should be from sucrose or other refined carbohydrates
  - Fat should provide 30–35% of daily energy intake
  - Protein should provide 10–15% of daily energy intake
- Exercise
  - An important aspect of diabetes management
  - Has real benefits for a child with diabetes
  - Patients should be encouraged to exercise regularly

Screening for associated autoimmune conditions:

Thyroid screening

- Autoimmune thyroiditis is the most common autoimmune disease associated with type 1 DM
- Screening start and frequency: At diagnosis and then annually

Celiac screening

- Celiac disease is the second most common autoimmune disease associated with type 1 DM
- Clinical picture: Classic symptoms include abdominal pain, diarrhea, or constipation. Some patients present with growth failure, reduced insulin requirement, or hypoglycemia due to erratic absorption of nutrients. Many children especially at a younger age are completely asymptomatic
- Screening start and frequency: At diagnosis and then annually
- How to screen: tTG IgA (in addition to a total IgA level)
- Positive screening: High tTG IgA titer
- Positive screening management: Refer to gastroenterologist to confirm diagnosis before starting a gluten-free diet

Addison disease

- Rare association with type 1 DM, so no universal screening warranted
- Suspect if patient is having unexplained hypoglycemia or decreased insulin requirements, losing weight, increased pigmentation of the skin and gingival mucosa, salt craving, weakness, and postural hypotension

Important to know: Consider the diagnosis of **autoimmune polyglandular syndrome type II** in patients with type 1 DM, autoimmune thyroiditis, and autoimmune adrenal insufficiency

Screening for associated comorbidities/ complications

Dyslipidemia

- Screening starts and frequency: 10 years of age or when puberty starts, whichever comes first, and then annually
- Risk factors: Family history of early cardiovascular disease (< 55 years of age)
- How to screen: Non-fasting lipid panel
- Positive screening management
  - Positive screening: Low-density lipoprotein (LDL) 100 mg/dl or above
  - Start by lifestyle change and Step II American Heart Association (AHA) diet
  - If lifestyle not effective, a statin is warranted if the child is 10 years or older

Retinopathy screening (dilated eye exam)

- Screening starts: 10 years of age or above and DM duration of 3–5 years
- How frequent: Annually if normal

Nephropathy screening

- Screening starts: At puberty or age ≥ 10 years, whichever is earlier, once the child has had DM for 5 years

- How to screen: Spot urine albumin to creatinine ratio. (12–24 h urine collections did not improve detection of albuminuria and are more burdensome)
- Positive screening management
  - Positive if ratio 30 mg/gm creatinine or above
  - If persistently positive (2 out of 3 samples): Treatment with an ACE inhibitor is warranted

Type 2 Diabetes Mellitus

Background

- Characterized by
  - Hyperglycemia
- Insulin resistance
  - Family history of type 2 DM in first- or second-degree relative
- Obesity strongly associated with type 2 in children and adolescents

Clinical presentation

- Slow and insidious onset
- Signs of insulin resistance, e.g., acanthosis nigricans
- Strong family history of type 2 DM: Familial lifestyle risk factors leading to obesity may be present; family history of cardiovascular disease or metabolic syndrome
- PCOS
- Hypertension
- Retinopathy

Screening and diagnosis

- Screening for type 2 DM should be considered when a patient is overweight or obese and has one or more of the following:
  - Family history of type 2 DM in first- or second-degree relative
  - Signs of insulin resistance or conditions associated with insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, PCOS and SGA birth weight)
  - Race/ethnicity: Native American, African-American, Latino, Asian American, or Pacific Islander
  - Maternal history of DM or gestational DM during the child's gestation
- Screening should start at 10 years of age or at the start of puberty if it occurs at a younger age
- Screening should be repeated every 3 years
- Diagnosis is established in the presence of one of the following criteria:
  - A random plasma glucose concentration of 200 mg/dL or greater in association with classic symptoms of hyperglycemia (polyuria, polydipsia, or nocturia) or a hyperglycemic crisis
  - FPG value of 126 mg/dL or greater
  - 2-hour plasma glucose value of 200 mg/dL or greater during an OGTT
  - HbA1c levels equal or greater than 6.5%
- Other laboratory results that are suggestive of type 2 DM but not needed for diagnosis are as follows:
  - Elevated fasting C-peptide level
  - Elevated fasting insulin level
  - Absence of autoimmune markers (see Type 1 DM)

Management

- Diabetes education and lifestyle changes (diet, exercise, and weight control)
- The only pharmacologic therapy that is FDA-approved in children is metformin and insulin
- Metformin is the initial drug of choice for treatment of type 2 DM in metabolically stable patients (A1C < 8.5% and asymptomatic) if renal functions are normal
- Children with marked hyperglycemia (blood glucose ≥ 250 mg/dL, A1C ≥ 8.5%) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while metformin is initiated and titrated

- In patients with ketosis/ketoacidosis, treatment with subcutaneous or IV insulin should be initiated to rapidly correct the hyperglycemia and metabolic derangement.
- Once ketosis/ketoacidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued

Management of Comorbidities/ Complications

Nephropathy screening

- Screening starts: At diagnosis and then annually if normal
- How to screen: Spot urine albumin to creatinine ratio. (12–24 h urine collections did not improve detection of albuminuria and are more burdensome)
- Positive screening management
  - Positive if ratio is 30 mg/gm creatinine or above
  - If persistently positive (2 out of 3 samples): Treatment with an ACE inhibitor is warranted

Hypertension

- Increases risk for cardiovascular and renal disease
- Blood pressure should be measured accurately and reviewed at each visit
- Both systolic and diastolic blood pressures should be below the 90th percentile for age, gender, and height
- Pharmacological therapy with an ACE inhibitor is indicated if hypertension persists after 6 months of lifestyle modifications

Dyslipidemia

- Screening starts and frequency: At diagnosis and then annually
- How to screen: Non-fasting lipid panel
- Positive screening management
  - Positive screening: LDL 100 mg/dl or above, or high-density lipoprotein (HDL) 35 mg/dL or lower, triglycerides 150 mg/dL or above
  - Start by lifestyle change and Step 2 AHA diet
  - If lifestyle is not effective after 6 months, a statin is warranted with a goal of LDL below 100 mg/dl

Retinopathy screening (dilated eye exam)

- Screening starts and frequency: At diagnosis and then annually

Neuropathy screening:

- Screening starts and frequency: At diagnosis and then annually
- How to screen: Examination should include inspection, assessment of foot pulses, pinprick, and 10-g monofilament sensation tests; testing of vibration sensation using a 128-Hz tuning fork, and ankle reflexes

Nonalcoholic fatty liver disease

- Screening starts and frequency: At diagnosis and then annually
- How to screen: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels
- Positive screening management: Lifestyle modifications and referral to gastroenterologist

PCOS

- Screening is indicated if showing signs/symptoms of PCOS
- Metformin may be beneficial in the treatment of girls with type 2 DM and PCOS. Oral contraceptives can also be used

Obstructive sleep apnea

- Start screening at diagnosis and at each visit
- Refer to a pediatric sleep specialist for evaluation and a sleep study if showing positive symptoms (snoring, insufficient or disrupted sleep, circadian rhythm dysregulation)

Depression

- The prevalence of clinically significant symptoms of depression were reported to be at 14.8% in the TODAY cohort of youth with type 2 DM
- Screen using age-appropriate tools and refer to specialty care when indicated

Summary

- Treatment goals include improvement of glycemia (HbA1c) levels (< 7%), dyslipidemia (LDL level < 100 mg/dL, triglyceride < 150 mg/dL, HDL level > 35 mg/Dl), and hypertension (blood pressure < 90th percentile for age, sex, and height)

Diabetes Ketoacidosis (See Chap. 7 also "Emergency Medicine")

Precipitating factors that could lead to the onset of DKA

- Infection
- Insulin omission
- Insulin pump failure
- Failure to match insulin dosing to metabolic requirements during illness or stress

Diagnosis

- Blood glucose level greater than 200 mg/dL
- Presence of serum/urine ketones
- Venous pH < 7.30 or a bicarbonate level less than 15 mmol/L

Severity of DKA can be classified according to the severity of the acidosis

- Mild
  - Venous pH 7.21–7.30
  - Bicarbonate (mmol/L) 11–15
- Moderate
  - Venous pH 7.11–7.20
  - Bicarbonate (mmol/L) 6–10
- Severe
  - Venous pH < 7.10
  - Bicarbonate (mmol/L) < 5

Management

- Hydration is the most important first step
  - IV fluid replacement is begun as soon as the diagnosis of DKA is established
  - Initial fluid resuscitation begins with 10 mL/kg of isotonic fluid, 0.9% saline administered over 1 h
  - After the initial fluid resuscitation, the remainder of the fluid deficit is replaced evenly over 48 h (most patients are 6% dehydrated)
  - Maintenance fluid requirements are added to this deficit replacement to provide the total fluid requirements, which rarely exceed 1.5 times the usual daily fluid requirement
  - The 0.9 saline with added 30–40 mEq/L of potassium is continued as the hydration fluid until the blood glucose value declines to less than 300 mg/dL
  - Replacement fluid should be changed to D5 0.45% with added potassium when glucose value declines to less than 300 mg/dL
  - If the blood glucose concentration declines below 150 mg/dL (8.3 mmol/L), dextrose content may need to be increased to 10% or even 12.5%

Insulin

- Time of insulin initiation is controversial
- Insulin is administered as a continuous IV infusion of regular insulin at a rate of 0.05–0.1 units/kg/h
- Bolus of insulin should not be given at the start of therapy
- If IV administration of insulin is not possible, short- or rapid-acting insulin injected subcutaneously every 2 h can be effective

Resolution of the acidosis in DKA

- Acidosis (pH > 7.3)
- Bicarbonate > 15 mEq/L
- IV insulin therapy should continue as long as the patient is still acidotic

- Decrease IV insulin rate if there is persistent hypoglycemia despite maximum dextrose administration
- Subcutaneous insulin must be started before discontinuation of IV insulin when acidosis is resolved

Monitoring
- Vital signs
- Mental status and neurologic evaluation
- Serum glucose, electrolytes including serum phosphorus (including blood urea nitrogen and creatinine), and pH and urine ketones should be measured at presentation
- Serum glucose and pH should be measured hourly
- Serum electrolytes and urine ketones assessed every 2–3 h
- If phosphate is administered, serum calcium concentrations must be monitored

Outpatient Management of Sick Days in Patient with Diabetes Mellitus

Management steps
- Check blood glucose level every 2–3 h until feeling well. Urine ketones should be checked frequently
- It is important to teach families that adjustments in the insulin doses are necessary during intercurrent illness, but a complete cessation of all insulin replacement will quickly lead to diabetic ketoacidosis
- Encourage fluid intake. Ideally, give 1 oz (30 mL) per year of age per hour in small, frequent sips
  - If glucose level is ≥ 200 mg/dL, sugar-free fluids should be given
  - If glucose level is < 200 mg/dL, sugar-containing fluids should be included

Factors warranting medical evaluation
- Persistent vomiting (e.g., vomiting more than twice after starting sick day rules) with moderate to large urine ketone levels (or blood ketone levels greater than 1.5 mmol/L)
- Inappropriately rapid breathing
- Altered mental status
- Inability to perform sick day rules

Maturity-Onset Diabetes of Youth (MODY)

Background
- MODY is the most common form of monogenic diabetes
- The genes involved control the pancreatic beta cell development, function, and regulation, hence leading to defects in glucose sensing and insulin secretion
- Onset is usually before 25 years of age
- Inherited in an autosomal dominant pattern

Types
- MODY 1–MODY 6 are the most common identified gene mutations, with MODY 3 (hepatocyte nuclear factor-1 alpha = *HNF1A*) being the most common, representing about 50% of monogenic diabetes cases

Diagnosis
- Suspect in individuals with the following characteristics:
  - Diabetes diagnosis before 25 years of age
  - Autosomal dominant pattern of inheritance of diabetes (> 2 generations affected)
  - Nonobese (usually)
  - Negative islet antibodies (markers of type 1 DM)
- Genetic testing is readily available

Treatment
- MODY 4–6 are treated with insulin
- MODY 1 and MODY 3 are treated with sulfonylureas
- MODY 2 is treated with diet and exercise but may require insulin during illness or pregnancy

Obesity

Background

- The most commonly used measure is body mass index (BMI)
- BMI is defined as kilograms (kg) of body weight per height in square meters (m^2)
- Overweight: BMI between 85th and 94th percentile
- Obesity: BMI at or above 95th percentile

Causes

- Idiopathic or familial obesity
  - Poorly understood
  - Most common cause of childhood obesity
- Hormonal, e.g.,
  - Hypothyroidism
  - GHD
  - Hypogonadism
  - Cushing syndrome
  - PCOS
- Syndromic, e.g.,
  - Down syndrome
    - Hypotonia
  - Prader–Willi syndrome
    - Hypotonia, hypogonadism, hyperphagia, small hands and feet
  - Albright hereditary osteodystrophy
    - Short stature and skeletal defect
  - Bardet–Biedl syndrome
    - Retinal dystrophy, renal abnormalities, mental retardation
  - Fragile X syndrome
    - Macro-orchidism and large ears
- Genetic, e.g.,
  - Melanocortin 4 receptor deficiency (*MC4R*)
  - Congenital leptin deficiency
  - Leptin receptor defect

Definition of *Pediatric Metabolic Syndrome* (International Diabetes Federation Criteria)

- Central obesity (required feature) > 90th percentile for age, gender, and ethnicity with waist circumference ≥ 94 cm in men or ≥ 80 cm in women
- Plus at least two of the following four clinical risk factors:
  - BP ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or drug treatment for hypertension
  - HDL < 40 mg/dL in men or < 50 mg/dL in women or treatment for lipid abnormalities
  - Triglyceride level ≥ 150 mg/dL
  - FPG level ≥ 100 mg/dL or previously diagnosed type 2 DM

Obesity-related conditions

- Depression and isolation are the most common complications of obesity in children and adolescents
- Liver
  - Fatty liver infiltration (nonalcoholic steatohepatitis [NASH]) 25–83%
  - Cholelithiasis (50% are obese)
- Pulmonary
  - Obstructive sleep apnea
  - Metabolic alkalosis and respiratory acidosis
  - Hypoventilation
  - Pulmonary hypertension
  - Right-sided heart failure
  - Obesity hypoventilation syndrome
  - Asthma
  - Renal
- Nocturnal enuresis
  - Related to obstructive sleep apnea and excess secretion of atrial natriuretic peptide (ANP)
- Cardiovascular
  - Hypertension (60% are obese)
  - Systolic blood pressure > 95% for age, sex, and height
  - Dyslipidemia
  - HDL < 40 mg/dL
  - LDL > 130 mg/dL
  - Triglyceride > 150 mg/dL
  - Total cholesterol > 200 mg/dL
- Musculoskeletal complications
  - Slipped capital femoral epiphysis (30–50% are obese)

  - Blount disease or tibia vara (70% are obese)
  - Severe leg bowing of tibia, knee pain, and limp
  - Osteoporosis
  - Back pain
  - Joint pain
- Acanthosis nigricans and insulin resistance (Fig. 12.10)
  - Not a criteria of metabolic syndrome diagnosis
  - High concentration of insulin in obese patients may exert potent proliferative effects via high-affinity binding to IGF-1, which stimulate epidermal keratinocyte and dermal fibroblast proliferation

Management

- Multidisciplinary approach
- Weight reduction
- Diet and exercise
- Management of obesity-related conditions
- Treatment of the cause if applicable

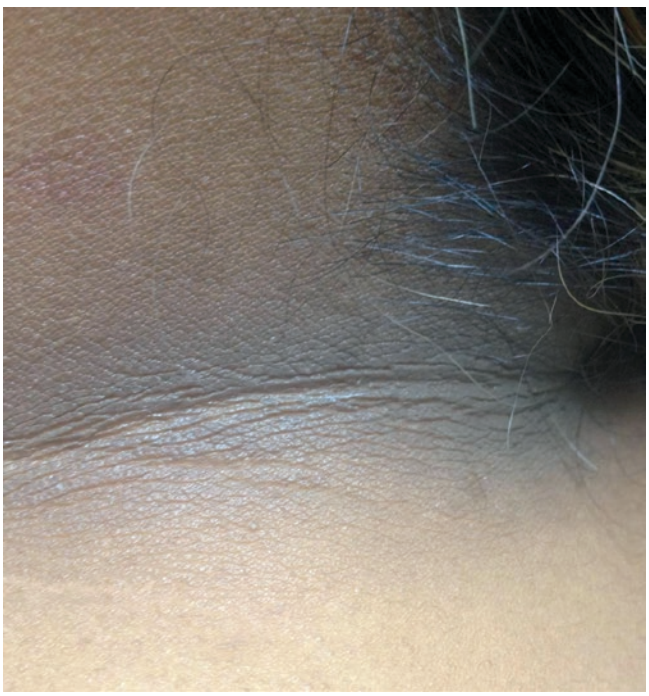

Fig. 12.10 **A** 17-year-old female with obesity and metabolic syndrome. Weight 180 lbs, height 60 in., BMI 35th percentile, blood pressure 140/90 mmHg. She has poorly defined, velvety hyperpigmentation of the skin around the neck

PEARLS AND PITFALLS

- Assessing growth velocity (linear growth) is as important as assessing height percentiles when assessing short stature in children.
- Bone age radiograph is a useful tool that can be used to differentiate between different causes of short stature or poor linear growth.
- Growth hormone is not the major determinant of growth in the first 4–6 months of life.
- Signs of congenital hypopituitarism include hypoglycemia and micropenis (in boys).
- Congenital hypothyroidism is the most common cause of preventable intellectual disability. Treatment with thyroid hormone replacement should not be delayed.
- Children presenting with normal variants of puberty (premature thelarche, premature adrenarche) need to be followed more closely than regular well-child visits, as they may be presentations for true precocious puberty in 18–20% of cases.
- Klinefelter syndrome is the most common cause of hypergonadotropic hypogonadism with a prevalence of 1 in 700 males.
- Always consider the diagnosis of Turner syndrome when evaluating a girl with short stature, as it may be the only presenting sign.
- Be aware of the different potencies of oral steroids commonly used. Hydrocortisone is equivalent to our endogenous cortisol (×1), prednisone (4 × hydrocortisone equivalent), dexamethasone (40 × hydrocortisone equivalent).
- Inhaled corticosteroids are associated with endocrine effects, including hyperglycemia, iatrogenic adrenal insufficiency, and linear growth effects.
- When interpreting an endocrine laboratory result, it is important to use pediatric reference ranges. Also, a normal value might not always be considered normal in certain scenarios. For example, a low normal TSH level with a low normal thyroid hormone level is suspicious of central hypothyroidism despite both values being in the normal range.

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Suggested Reading

American Diabetes Association. 13. Children and adolescents: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S148–64. Review.

Anderson BJ, Edelstein S, Abramson NW, Katz LE, Yasuda PM, Lavietes SJ, et al. Depressive symptoms and quality of life in adolescents with type 2 diabetes: baseline data from the TODAY study. Diabetes Care. 2011;34(10):2205–7.

Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPE-LWPES GnRH Analogs Consensus Conference Group, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009;123(4):e752–62. Review.

Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society, et al. 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(6):361–97.

Lee PA, Houk CP, Ahmed SF, Hughes IA, International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006;118(2):e488–500.

Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(11):4043–88.

Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, Pediatric Endocrine Society, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. J Pediatr. 2015;167(2):238–45.