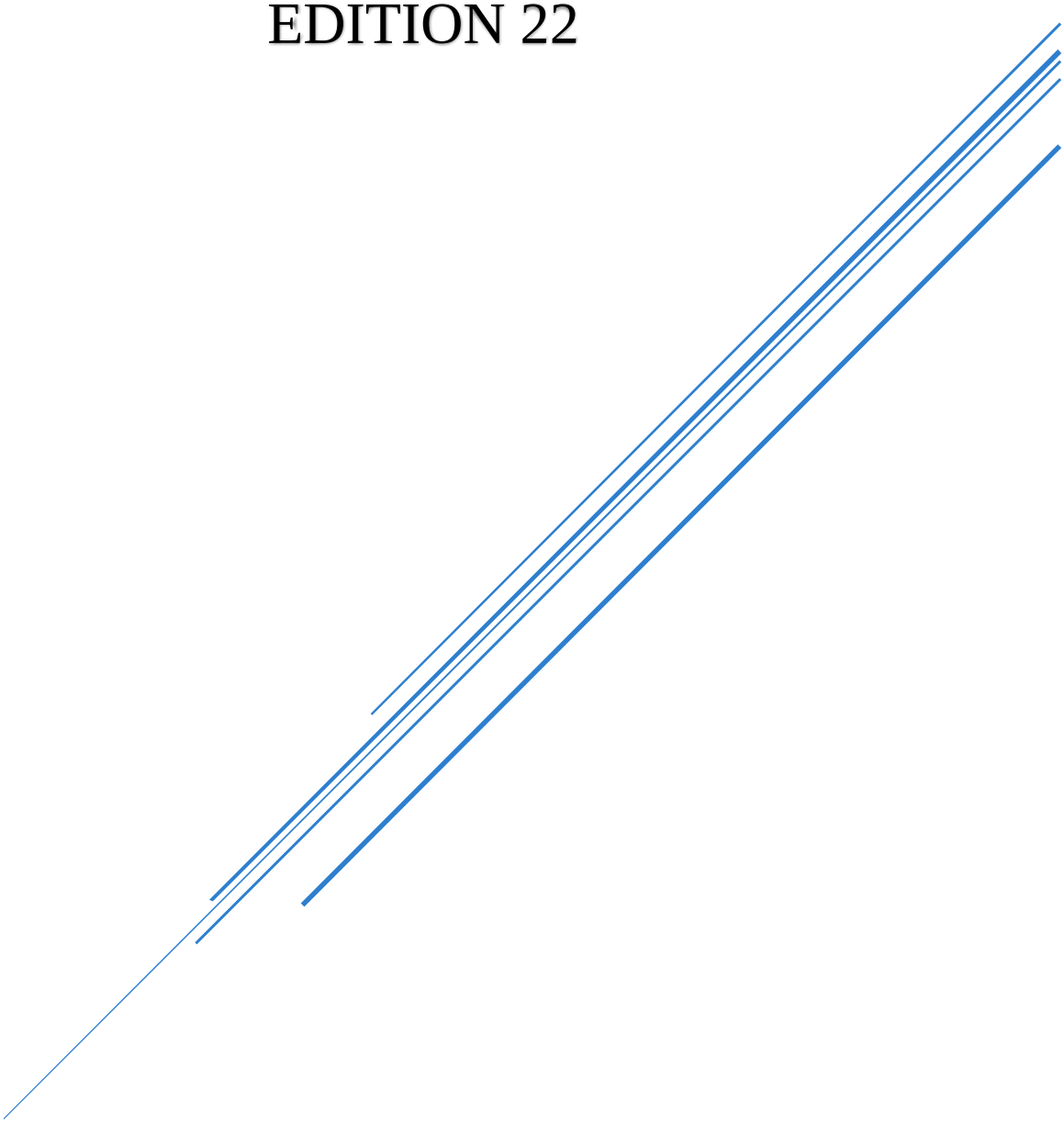
DEVELOPMENTAL DELAY AND INTELLECTUAL DISABILITY

NELSON TEXTBOOK OF PEDIATRICS EDITION 22



Assistant prof : Basma Adel Ibrahim
Pediatric neurologist

DEVELOPMENTAL DELAY AND INTELLECTUAL DISABILITY(ID)

The definition of ID requires significant impairment in general intellectual function (reasoning, memory, learning, problem solving) and adaptive behavior.

The American Association on Intellectual and Developmental Disabilities (AAIDD) classifications of adaptive behavior address three broad sets of skills: conceptual, social, and practical.

- ✓ Conceptual skills include language, reading, writing, time, number concepts, and self-direction.
- ✓ Social skills include interpersonal skills, personal and social responsibility, self-esteem, gullibility, naiveté, and ability to follow rules, obey laws, and avoid victimization.
- ✓ Practical skills involve performance of activities of daily living (dressing, feeding, toileting/bathing, mobility), instrumental activities of daily living (e.g., housework, managing money, taking medication, shopping, preparing meals, using phone and mail systems), occupational skills, and maintenance of a safe environment.

For a deficit in adaptive behavior to be present, a significant delay in at least one of the three skill areas must be present.

Global developmental delay (GDD) is a term often used to describe young children with delays across multiple domains of development that have not yet resulted in a diagnosis of ID. In DSM- 5, GDD is a diagnosis given to children <5 years of age who display significant delay (>2 SDs) in acquiring early childhood developmental milestones in two or more domains of development.

These domains include receptive and expressive language; gross and fine motor function; cognition, social and personal development; and activities of daily living. Typically, it is assumed that delay in two domains will be associated with delay across all domains evaluated, including cognitive and intellectual abilities.

It is important to distinguish the medical diagnosis of GDD from the federal disability classification of "developmental delay". This classification requires that a child have delays in only one domain of development with subsequent need for special education.

ETIOLOGY

Numerous identified causes of ID may occur prenatally, during delivery, postnatally, or later in childhood. These include infection, trauma, prematurity, hypoxia-ischemia, toxic exposures, metabolic dysfunction, endocrine abnormalities, malnutrition, and genetic abnormalities. Most people with ID will not have a readily identifiable underlying

However, several reasons beyond disease modification should prompt providers to seek etiologic answers in patients with ID. These include insight into possible associated medical or behavioral comorbidities; information on prognosis and life expectancy; estimation of recurrence risk for family planning counseling, increased access to services, or specific supports.

Mild and more severe forms of ID have different but overlapping risk factors and etiologies.

Nongenetic risk factors that are often associated with **mild** ID include low socioeconomic status, low maternal education levels, residence in a developing country, malnutrition, and poor access to healthcare. The most common biologic causes of, or risk factors for, **mild** ID include intrauterine growth restriction; prematurity; perinatal insults; intrauterine exposure to drugs of abuse (including alcohol); postnatal exposure to neurotoxic substances (including lead); and some genetic syndromes. Familial clustering is common.

In children with more **severe** ID, a biologic cause (usually with prenatal onset) can be identified in about three fourths of all cases. Causes include chromosomal (e.g., Down, and other genetic disorders (e.g., fragile X, Rett, and Angelman syndromes), abnormalities of brain development (e.g., lissencephaly), and inborn errors of metabolism and mitochondrial disorders (e.g., mucopolysaccharidoses).

CLINICAL MANIFESTATIONS

Early diagnosis of ID facilitates earlier intervention, identification of abilities, realistic goal setting, monitoring for potential comorbid conditions, easing of parental anxiety, and greater inclusion of the child in the community. Children with ID may first come to the pediatrician's attention because of dysmorphisms (often in infancy), associated developmental disabilities, or failure to meet age- age-appropriate developmental milestones. Physical exam findings are nonspecific, but constellations of dysmorphisms may be consistent with certain genetic syndromes.

- In early infancy, failure to meet age- age-appropriate expectations can include a lack of visual or auditory responsiveness, unusual muscle tone (hypotonia or hypertonia), or posture and feeding difficulties.
- Between 6 and 18 months of age, gross motor delay (lack of sitting, crawling, walking) is the most common concern.
- Language delay and behavior problems are common concerns after 18 months of age .
- For some children with mild ID, the diagnosis remains uncertain during the early years and becomes clearer as the demands of the school setting increase. With increasing expectations for independence at home and socially, limitations among those with mild ID become more salient.
- Older school-age children and adolescents with mild ID might not be appreciated, even by professionals such as healthcare providers. Because of the stigma associated with ID, adolescents may refer to themselves as learning disabled, dyslexic, language disordered, or slow learners.

Table 56.6 Common Presentations of Intellectual Disability by Age

AGE	AREA OF CONCERN
Newborn	Dysmorphic syndromes, (multiple congenital anomalies), microcephaly Major organ system dysfunction (e.g., feeding, breathing)
Early infancy (2-4 mo)	Failure to interact with the environment Concerns about vision and hearing impairments
Later infancy (6-18 mo)	Gross motor delay
Toddlers (2-3 yr)	Language delays or difficulties
Preschool (3-5 yr)	Language difficulties or delays Behavior difficulties, including play Delays in fine motor skills: cutting, coloring, drawing
School age (>5 yr)	Academic underachievement Behavior difficulties (e.g., attention, anxiety, mood, conduct)

Table 56.7 Suggested Evaluation of the Child with Intellectual Disability (ID) or Global Developmental Delay (GDD)

TEST	COMMENT
In-depth history	Includes prenatal, perinatal, and postnatal events (including seizures); developmental attainments; and three-generation pedigree in family history (focusing on neurologic or developmental abnormalities, miscarriages, consanguinity, etc.)
Physical examination	Particular attention to minor or subtle dysmorphisms; growth issues; neurocutaneous findings; eye and skull abnormalities; hepatosplenomegaly; and neurologic examination for focality Behavioral phenotype
Vision and hearing evaluation	Essential to detect and treat; can mask as developmental delay
Gene microarray analysis	A ~15% yield overall Better resolution than with karyotype; may identify up to twice as many abnormalities as karyotyping Often included in exome testing
Karyotype	No longer a first-line test Reserve use when concerned for trisomic/monosomic conditions, inversions and balanced insertions, or reciprocal translocations
Fragile X screen	Combined yield of 2%, preselection on clinical grounds can increase yield to 7.6%
Next-generation gene sequencing	Detects inherited and de novo point mutations, especially in nonsyndromic severe intellectual disability Whole exome sequencing gives an additional yield of about 30–40% Pilot studies of whole genome sequencing (WGS) reveal additional yield of about 15%
Neuroimaging	MRI preferred; positive findings increased by abnormalities of skull contour or microcephaly and macrocephaly or focal neurologic examination (30–40% if indicated, 10–14% if screening) Identification of specific etiologies is rare; most conditions that are found do not alter the treatment plan; need to weigh risk of sedation against possible yield
Thyroid (T_4, TSH)	Near 0% in settings with universal newborn screening program
Serum lead	If there are identifiable risk factors for excessive environmental lead exposure (e.g., low socioeconomic status, home built before 1950)
Metabolic testing	Yield of 0.2–4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and capillary blood gas Focused testing based on clinical findings is warranted if lack of newborn screen results or suggestive history/exam (e.g., regression, consanguinity, hepatosplenomegaly, course facies) Tandem mass spectrometry newborn screening has allowed for identification of many disorders in the perinatal period and has decreased yield in older children; other disorders have emerged, such as congenital disorders of glycosylation (yield 1.4%) and disorders of creatine synthesis and transport (yield 2.8%)
MECP2 for Rett syndrome	1.5% of females with criteria suggestive of Rett (e.g., acquired microcephaly, loss of skills) 0.5% of males
EEG	May be deferred in absence of history of seizures or significant language regression
Repeated history and physical examination	Can give time for maturation of physical and behavioral phenotype; new technology may be available for evaluation

EEG, Electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG binding protein 2; T_4, thyroxine; TSH, thyroid stimulating hormone

TRISOMY 21 SYNDROME

Fig. 57.6 Appearance of two 2-year-old children with trisomy 21. The facial appearance of children with trisomy 21 is often characterized by a low nasal bridge, small nose, small ears, up-slanting almond-shaped eyes, and epicanthal folds. *(Photos courtesy of Children's Hospital of Philadelphia.)*

Fig. 57.5 Down syndrome in the neonatal period. A, Brushfield spots. B, Loose nuchal skin. C, Wide space between toes 1 and 2. D, Poor tone. E and F, Accentuation of typical face when crying. (From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022: Fig. 3, p. 7.)

Down syndrome (trisomy 21) is the most common genetic cause of intellectual disability, with an incidence of 1 in 700 live births in the United States.

- The Down syndrome phenotype can occur as a result of full trisomy 21 (95%), partial trisomy 21 (part of the 21st chromosome in triplicate), mosaic trisomy 21, or translocation.
- Maternal nondisjunction in meiosis is the most common cause of trisomy 21.

CLINICAL CHARACTERISTICS

Children with Down syndrome are at increased risk for a variety of congenital anomalies and comorbid medical conditions. Typically, they have a characteristic facial appearance and other physical characteristics that allow clinical recognition of trisomy 21 in the newborn period

Table 57.4 Frequency of Medical Conditions in Trisomy 21

SYSTEM	CONDITION	ESTIMATED FREQUENCY (IF KNOWN)
EYE		
	Cataracts (birth/later)	1.4%/5–37 %
	Glaucoma	1%
	Nystagmus	18–30%
	Strabismus	19–34%
	Refractive errors	80%
	Astigmatism	67–74%
	Nasolacrimal duct obstruction	11–30%
ENT		
	Stenotic ear canals	50%
	Choanal atresia	
	Bifid uvula/mucosal cleft	5%
	Laryngomalacia	
	Middle ear effusions	50–90%
	Adeno/tonsillar hypertrophy	
	Hearing loss	37–78%
DENTAL		
	Tooth agenesis	54–58%
	Malocclusion	>70%
	Periodontal disease	~100% under 30 years
ENDOCRINE		
	Congenital hypothyroidism	1:113 to 1:141 live births
	Acquired hypothyroidism	13–34%
	Subclinical hypothyroidism	7–40%
	Hyperthyroidism	6.5%
	Type 1 diabetes mellitus	0.3–1%
CARDIAC		
	Congenital heart disease	44–54%
	AV canal defects	42% (of CHD)
	VSD	22–35%
	ASD	8–16%
	Tetralogy of Fallot	2–4%
	Acquired mitral, tricuspid, or aortic regurgitation PDA	5–7%

Table 57.4 Frequency of Medical Conditions in Trisomy 21—cont'd

SYSTEM	CONDITION	ESTIMATED FREQUENCY (IF KNOWN)
PULMONARY		
	Pulmonary hypertension	1–5%
	Subglottic stenosis	6%
	Tracheo/laryngomalacia	33% (of ENT-referred population)
	Tracheal bronchus	
	Obstructive sleep apnea	~50%
GASTROINTESTINAL		
	Esophageal atresia	0.5–0.9%
	Duodenal malformations	4%
	Rectoanal malformations	1%
	Hirschsprung disease	3%
	Celiac disease	5–9.8%
	GERD	14–40%
	Constipation	30–49%
GENITOURINARY		
	Renal/urinary tract findings	Up to 25%
HEMATOLOGY/ONCOLOGY		
	Transient myeloproliferative disease (TMD)	5–10%
	Acute megakaryoblastic leukemia (AMKL)	10–20% with TMD, first 4 years of life
	Acute lymphocytic leukemia	0.1–0.2%
ORTHOPEDICS		
	Atlantoaxial instability (AAI)	9–27%
	Symptomatic AAI	1–2%
	Recurrent joint dislocations (shoulder, knee, elbow, thumb)	1–7%
	Pes planus	91%
	Juvenile idiopathic arthritis	~1%
DERMATOLOGY		
	Alopecia/vitiligo	1–11%
	Hidradenitis suppurativa	2%
	Xerosis/eczema	
	Seborrheic dermatitis	
	Psoriasis	0.5–8%
NEUROLOGY		
	Infantile spasms	2–5%
	Seizure disorders	8% (lifetime)
	Strokes and moyamoya	
	Autism spectrum disorder	7–16%
	Early onset Alzheimer disease	~50% >50 yr
	Down syndrome disintegrative disorder	<1%

ENT, Ear/nose/throat; AV, atrioventricular; CHD, congenital heart disease; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; GERD, gastroesophageal reflux disease.

PHENYLKETONURIA

Metabolic disease caused by a deficiency of Phenylalanine hydroxylase enzyme, which converts phenylalanine to tyrosine, that is necessary for the production of neurotransmitters such as epinephrine, norepinephrine, and dopamine.

Phenylalanine is an essential amino acid, so deficiency of the enzyme phenylalanine hydroxylase (PAH) causes accumulation of phenylalanine and its metabolites in body fluids and the brain. excess phenylalanine is metabolized to phenyl ketones (phenylpyruvate and phenylacetate), which are excreted in the urine, giving rise to the term *phenylketonuria* (PKU).

Clinical Manifestations

- The affected infant appears normal at birth. Profound intellectual disability gradually develops if the infant remains untreated. Cognitive delay may not be evident for the first few months in untreated patients.
- Vomiting, sometimes severe enough to be misdiagnosed as pyloric stenosis, may be an early symptom.
- Older untreated children become hyperactive and show autistic behaviors, including stereotypic hand movements and rhythmic rocking.
- Untreated and undertreated infants are lighter in their complexion than unaffected siblings.
- Some may have a seborrheic or eczematoid rash, which is usually mild and disappears with age.
- Affected children have an odor of phenylacetic acid, which has been described as musty or “mousey.”
- Neurologic signs include seizures (approximately 25%), spasticity, hyperreflexia, tremors, and athetosis; >50% have electroencephalographic (EEG) abnormalities.
- Microcephaly, prominent maxillae with widely spaced teeth, enamel hypoplasia, and growth retardation are other common findings in untreated children.
- Low bone mineral density and osteopenia have been reported in affected individuals of all ages.

Diagnosis

Because of the gradual and nonspecific nature of early clinical symptoms, PKU is usually diagnosed through a newborn screening test. (NBS) which is an effective and relatively inexpensive method. A few drops of blood are placed on a filter paper test using tandem mass spectrometry, in the first 24-48 hours of life after feeding protein.

In infants with positive screening results, the diagnosis should be confirmed by quantitative measurement of plasma phenylalanine concentration.

Treatment

The mainstay of treatment of PKU is a *low-phenylalanine diet*. The goal of therapy is to reduce phenylalanine levels in the plasma and brain. Formulas free of or low in phenylalanine are commercially available. The diet should be started as soon as the diagnosis is established.

Because phenylalanine is not synthesized endogenously, the diet should provide phenylalanine to prevent phenylalanine deficiency. Phenylalanine deficiency is manifested by lethargy, failure to thrive, anorexia, anemia, rashes, diarrhea, and even death.

Special food items low in phenylalanine are commercially available for dietary treatment of affected children and adults throughout life. Discontinuation of therapy, even in adulthood, may cause deterioration of neurocognitive performance.

CONGENITAL HYPOTHYROIDISM

The incidence of congenital hypothyroidism was initially reported to be 1 in 4,000 infants.

Etiology
.Most cases of congenital hypothyroidism are caused by abnormal formation of the thyroid gland (thyroid dysgenesis), and ~30% of cases are due to inborn errors of thyroid hormone synthesis (dyshormonogenesis) or other causes.
Most infants with congenital hypothyroidism are detected by newborn screening programs in the first week after birth, before significant clinical signs or symptoms develop. In regions without newborn screening, severely affected infants usually manifest features within the first week of life, but in infants with milder hypothyroidism, the clinical manifestations may not be evident for weeks or months.

Etiologic Classification of Congenital Hypothyroidism
PRIMARY HYPOTHYROIDISM
Defect of thyroid development (dysgenesis) Agenesis Hypoplasia Ectopia
Defects in thyrotropin (TSH) responsiveness TSH receptor–blocking antibodies Pathogenic variants in TSH receptor (TSHR) Defects in Gsα (GNAS)—pseudohypoparathyroidism
Defect in thyroid hormone synthesis (dyshormonogenesis) Defective iodide uptake into follicular cell:sodium–iodide symporter (NIS) Defective iodide transport from follicular cell into colloid:Pendred syndrome (SLC26A4) Iodide ramification defects: thyroperoxidase (TPO), dual oxidase 2 (DUOX2), dual oxidase maturation factor 2 (DUOXA2) Thyroglobulin synthesis defect: thyroglobulin (TG) Deiodination defect: iodotyrosine deiodinase (IYD) Thyroid hormone transport defect:monocarboxylate transporter 8 (SLC16A2)—X- linked
Iodine deficiency (endemic goiter)
Iodine excess
Maternal medications Iodides, amiodarone Methimazole, propylthiouracil,Radioactive iodine

Clinical Manifestations
most affected infants are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This is because of the transplacental passage of maternal T4.

- Birth weight and length are normal, but head size may be slightly increased
- The anterior and posterior fontanels are open widely, and the presence of this sign at birth may be a clue to early recognition of congenital hypothyroidism.
- Prolonged jaundice (indirect hyperbilirubinemia) may be present because of delayed maturation of hepatic glucuronide conjugation.
- Affected infants cry little, sleep much, have poor appetites, and are generally sluggish.
- Feeding difficulties, choking spells during nursing.

- Respiratory difficulties, partly caused by macroglossia, include apneic episodes, noisy respirations, and nasal obstruction.
- There may be constipation that does not respond to treatment. The abdomen is large, and an umbilical hernia is often present.
- The temperature may be subnormal (often <35°C/95°F), and the skin may be cold and mottled, particularly on the extremities.
- Edema of the genitals and extremities may be present.
- The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common.
- Macrocytic anemia is often present.
- Approximately 10% of infants with congenital hypothyroidism have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported.
- Infants with congenital hypothyroidism may have associated hearing loss.

If congenital hypothyroidism goes undetected and untreated, the clinical manifestations progress. Delay of physical and mental development becomes more severe over time, and by 3- 6 months of age,the clinical picture is fully developed.

- In the patient with untreated congenital hypothyroidism, growth is stunted, extremities are short, and head size is normal or increased. The anterior fontanel is large, and the posterior fontanel may remain open. The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow, and the eyelids are swollen. The mouth is kept open, and the thick, broad tongue protrudes. Dentition is delayed. The neck is short and thick.The hands are broad, and the fingers are short. The skin is dry and scaly, and there is little perspiration. Myxedema occurs mainly in the skin . Carotenemia can cause a yellow discoloration of the skin, but the sclerae remain white. The hair is coarse, brittle, and scanty. The hairline reaches far down on the forehead.
- Development is usually delayed. Hypothyroid infants appear lethargic and are late in acquiring gross and fine motor skills. The voice is hoarse, and they do not learn to talk. The degree of physical and intellectual delay increases with age. Sexual maturation may be delayed or even absent. Affected older children can have an athletic appearance because of pseudohypertrophy, particularly in the calf muscles.

LABORATORY FINDINGS

- Because symptoms appear gradually and may be nonspecific, the clinical diagnosis of neonatal hypothyroidism is often delayed. The newborn screening test is the most important method for identifying infants with congenital hypothyroidism. Blood obtained by heel prick between 1 and 5 days of life is placed on a filter paper card and sent to laboratory.
- Most screening programs measure the level of TSH, T4 . Patients with congenital hypothyroidism have low serum levels of T4 and free T4. Serum levels of T3 are often normal and are not helpful for diagnosis. If primary hypothyroidism is present, levels of TSH are elevated, often to >100 mU/L in severe cases.
- Delay of osseous development can be shown radiographically at birth in approximately 60% of congenitally hypothyroid infants .The distal femoral and proximal tibial epiphyses, which are normally present at birth, are often absent in congenital hypothyroidism .
- In untreated patients, the discrepancy between chronologic age and osseous development increases over time.
- Deformity (beaking) of the 12th thoracic or 1st or 2nd lumbar vertebra is common. X- rays of the skull show large fontanels and wide sutures, and wormian bones are common.
- Ultrasound of the thyroid can document the presence or absence of an anatomically normal gland.

TREATMENT

- Levothyroxine (L-T4) given orally is the treatment for congenital hypothyroidism. The recommended initial dose of L- T4 is 10- 15 µg/kg/day .tablets should not be mixed with iron, or calcium because these can inhibit l- T4 absorption. Although it is often recommended to administer l- T4 on an empty stomach and avoid food for 30- 60 minutes, this is not practical in an infant .

PROGNOSIS

- Thyroid hormone is critical for normal neurodevelopment, particularly in the early postnatal months. Prompt diagnosis and initiation of adequate treatment of congenital hypothyroidism in the first 2 weeks of life are essential to prevent irreversible brain damage and normal growth and development. In most infants detected by newborn screening, verbal development, psychomotor development, and global IQ scores are similar to unaffected siblings.
- Delay in diagnosis or treatment, failure to rapidly correct the initial hypothyroidism, inadequate treatment, or poor adherence to treatment the first 2- 3 years of life may result in variable degrees of neurodevelopmental impairment.
- Without treatment, severely affected infants have profound intellectual disability and growth stunting.

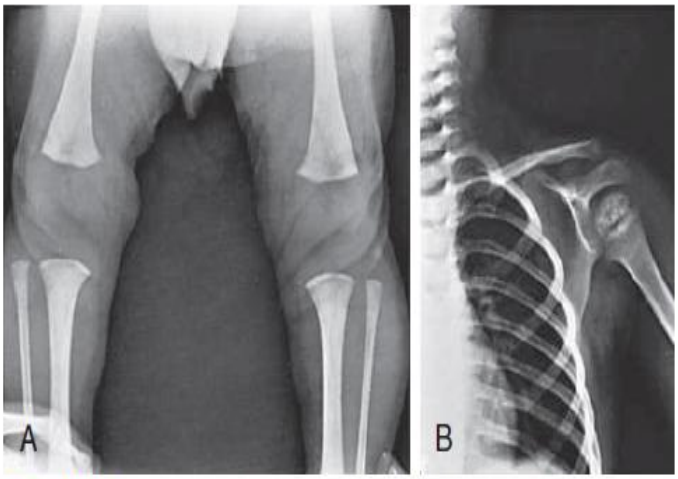


Fig. 603.2 Congenital hypothyroidism. A, Absence of distal femoral epiphyses in a 3-mo-old infant who was born at term. This is evidence for onset of the hypothyroid state during fetal life. B, Epiphyseal dysgenesis in the head of the humerus in a 9-yr-old girl who had been inadequately treated with thyroid hormone.

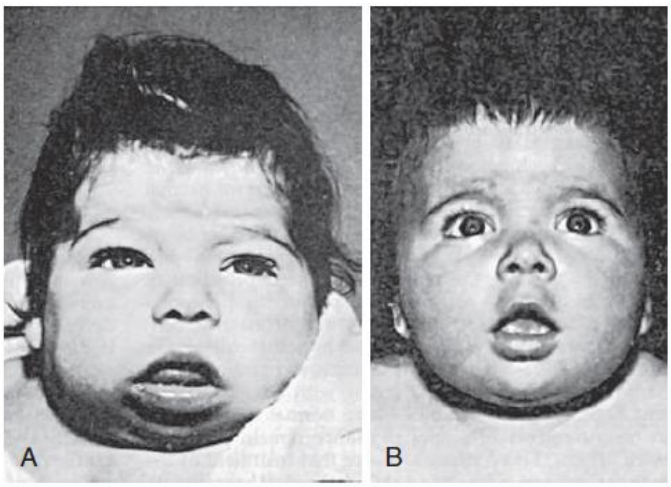


Fig. 603.1 Congenital hypothyroidism in an infant 6 mo of age. The infant ate poorly in the neonatal period and was constipated. She had persistent nasal discharge and a large tongue, was very lethargic, and had no social smile and no head control. A, Notice the puffy face, dull expression, and hirsute forehead. Tests revealed a negligible uptake of radioiodine. Osseous development was that of a newborn. B, Four months after treatment, note decreased face puffiness, decreased hirsutism of the forehead, and the alert appearance.