Down syndrome: Clinical features and diagnosis

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INTRODUCTION

Down syndrome (DS) is the most common chromosome abnormality among liveborn infants. It is the most frequent form of intellectual disability caused by a microscopically demonstrable chromosomal aberration. DS is characterized by a variety of dysmorphic features, congenital malformations, and other health problems and medical conditions. Not all of them are present in each affected person. The impact of DS for each person is individual, with some persons being profoundly impacted while others are healthy and able to live independently as adults. In general, persons with DS are now reaching fuller potentials secondary to better educational programs, medical advancements, community resources, and the support of family and friends.

The clinical features and diagnosis of DS will be presented here. The epidemiology, genetics, and management are discussed separately. (See "Down syndrome: Overview of prenatal screening" and "Congenital cytogenetic abnormalities", section on 'Trisomy 21 (Down syndrome)' and "Down syndrome: Management".)

DYSMORPHIC FEATURES

Upslanting palpebral fissures, epicanthic folds, and brachycephaly are nearly universal features of DS. The other characteristic dysmorphic features of DS are each present in 47 to 82 percent of cases [1,2]. These features predominantly affect the head and neck and the extremities.

Head and neck — Characteristic dysmorphic features of DS affecting the head and neck include:

- Upslanting palpebral fissures
- Epicanthic folds (picture 1)
- Flat facial profile/flat nasal bridge
- Folded or dysplastic ears
- Low-set, small ears
- Brachycephaly
- Brushfield spots
- Open mouth
- Protruding tongue (picture 1)
- Furrowed tongue
- Short neck
- Excessive skin at nape of the neck
- Narrow palate
- Abnormal teeth

Extremities — Characteristic dysmorphic features of DS affecting the extremities include:

- Short, broad hands
- Incurved fifth finger with hypoplastic middle phalanx
- Transverse palmar crease (picture 2)
- Space between the first and second toes (sandal gap)
- Hyperflexibility of joints

Neonatal features — Ten of the characteristic dysmorphic features are common in newborns with DS and are usually recognized soon after birth. In a series of 48 affected newborns, all had four or more features, and 89 percent had six or more [1,3]:

- Flat facial profile
- Slanted palpebral fissures
- Anomalous ears
- Hypotonia (picture 3)
- Poor Moro reflex
- Dysplasia of middle phalanx of fifth finger
- Transverse palmar (Simian) crease (picture 2)
- Excessive skin at nape of the neck
- Hyperflexibility of joints
- Dysplasia of pelvis

NEUROPSYCHIATRIC DISORDERS

Intellectual disability — Almost all individuals with DS have cognitive impairment, although the range is wide. Most are mildly to moderately intellectually disabled, with an intelligence quotient (IQ) in the 50 to 70 or 35 to 50 range, respectively, although some are severely impaired with an IQ of 20 to 35 [4]. (See "Intellectual disability (ID) in children: Clinical features, evaluation, and diagnosis".)

Developmental impairment becomes apparent in the first year of life. In general, the average age of sitting (11 months), creeping (17 months), and walking (26 months) is approximately twice the typical age [5]. The sequence of language development is the same, although the rate is slower, with the average age for the first word at 18 months [6]. The child with DS continues to learn new skills. However, IQ declines through the first 10 years of age, reaching a plateau in adolescence that continues into adulthood [2,7,8]. (See "Developmental-behavioral surveillance and screening in primary care", section on 'Approach to surveillance'.)

The profile of cognitive impairment in DS appears to differ from other forms of intellectual disability. The cognitive deficits are primarily in morphosyntax, verbal short-term memory, and explicit long-term memory [9]. The most common profile, in which language comprehension is equal to mental age and language production is more delayed, occurs in two-thirds of affected children [10]. In one-third, language comprehension, mental age, and language production are equal. Impairment in expressive language was noted in another study of children with DS, who had fewer different and total words and decreased mean length of utterance compared with controls matched for nonverbal mental age [11]. Vocabulary skills accelerated more rapidly than syntax (average sentence length and structure) and surpassed mental age in adolescence. Similar findings of increasing differences in comprehension with age were noted in another report, in which children with DS developed relatively stronger skills in vocabulary compared with syntax [12]. Other selective deficits have been described, such as greater difficulty understanding sequences or grammatical rules [2,13].

Behavioral and psychiatric disorders — Behavioral and psychiatric disorders are more common in DS than typical children but less common than in those with other causes of intellectual disability [8]. In one report, psychiatric disorders affected 17.6 percent of individuals with DS less than 20 years of age [14]. Disruptive behavioral disorders, such as attention-deficit hyperactivity disorder, conduct/oppositional disorder, or aggressive behavior, were most common. In the same study, psychiatric disorders, most often consisting of major depressive illness or aggressive behavior, affected 25.6 percent of DS adults. (See "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and diagnosis", section on 'Clinical features' and "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Unipolar

depression in adults: Assessment and diagnosis" and "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis".)

Autism is a common comorbidity of DS, affecting as many as 7 percent of children with DS [15]. The diagnosis is often delayed compared with children without DS [16]. Some children with DS present in the school-aged years with new-onset or worsening autistic-like features, cognitive decline to the point of dementia, and new-onset insomnia [17]. The term "Down syndrome disintegrative disorder" has been suggested to describe this cluster of clinical findings, although it is not clear if this is one disorder or several different ones with similar presentations. The etiology is not known, but autoimmunity is suspected. There are no established diagnosis or treatment recommendations for this clinical association. Some patients respond to psychiatric care. Further research is needed in this area. (See "Autism spectrum disorder in children and adolescents: Clinical features".)

Dementia/Alzheimer disease — Adults with DS usually develop neuropathologic and functional changes typical of Alzheimer disease by the sixth decade of life [8,18,19]. In one report, dementia was present in 49 of 96 (51 percent) DS individuals over the age of 35 years [18]. The average age of onset was 54 years, and seizures developed in 84 percent of patients. In another report, over 75 percent of patients over 65 years of age were affected [9]. (See "Evaluation of cognitive impairment and dementia".)

CARDIOVASCULAR DISEASE

Approximately one-half of individuals with DS have congenital heart disease [20-22]. In the largest population-based study, cardiovascular abnormalities were identified in 342 of 821 (42 percent) infants born with DS from 1985 to 2006 in the northeast region of England [22]. Twenty-three percent had more than one anomaly. The secondary lesion was most commonly an atrial septal defect (ASD) or patent ductus arteriosus (PDA). The following primary lesions were identified:

- Complete atrioventricular septal defect (CAVSD) – 37 percent
- Ventricular septal defect (VSD) – 31 percent
- ASD – 15 percent
- Partial atrioventricular septal defect (PAVSD) – 6 percent
- Tetralogy of Fallot (TOF) – 5 percent
- PDA – 4 percent
- Miscellaneous – 2 percent

The clinical features of these defects are discussed separately. (See "Isolated atrial septal defects (ASDs) in children: Classification, clinical features, and diagnosis" and "Isolated ventricular septal defects (VSDs) in infants and children: Anatomy, clinical features, and

diagnosis" and "Clinical manifestations and diagnosis of patent ductus arteriosus (PDA) in term infants, children, and adults" and "Tetralogy of Fallot (TOF): Pathophysiology, clinical features, and diagnosis".)

Some asymptomatic adolescents and adults without structural heart disease develop valve abnormalities [23,24]. In a series of 35 patients with DS, mitral valve prolapse occurred in 46 percent and aortic regurgitation in 6 percent at an average age of 20 years [23]. In another report of 30 adults, mitral valve regurgitation occurred in 17 percent [24].

Pulmonary hypertension is also common, occurring in 28 percent of patients with DS in one retrospective review [25]. The median age at diagnosis was five days in this review, with the majority (70 percent) having transient disease that lasted a median of eight months. Recurrent disease occurred in 15 percent and was associated with congenital heart disease, obstructive sleep apnea, recurrent pneumonia, and intermittent hypoxia. The remaining 15 percent had persistent disease. (See 'Pulmonary disorders' below.)

GASTROINTESTINAL ABNORMALITIES

Children with trisomy 21 are at increased risk for gastrointestinal tract anomalies, which occur in approximately 5 percent of cases [26]. Duodenal atresia or stenosis, sometimes associated with annular pancreas, is the most characteristic lesion, occurring in 2.5 percent [2]. Imperforate anus and esophageal atresia with tracheoesophageal fistula are seen less often. Conversely, DS affects 28 percent of patients with duodenal atresia or stenosis and 20 percent with annular pancreas. (See "Intestinal atresia" and "Annular pancreas" and "Prenatal diagnosis of esophageal, gastrointestinal, and anorectal atresia" and "Congenital anomalies of the intrathoracic airways and tracheoesophageal fistula", section on 'Tracheoesophageal fistula and esophageal atresia'.)

Hirschsprung disease is more common in DS than in the general population, although the risk is less than 1 percent [4]. Among children with Hirschsprung disease, approximately 2 percent have trisomy 21 (with a range of 2 to 15 percent) [27-31]. (See "Congenital aganglionic megacolon (Hirschsprung disease)".)

A strong association appears to exist between DS and celiac disease. The prevalence of biopsy-proven celiac disease has been reported to be between 5 and 16 percent, representing a 5- to 16-fold increase compared with the general population [32-36]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children", section on 'High-risk groups'.)

GROWTH

Birth weight, length, and head circumference are less in DS compared with typical infants. Newborns with DS weigh approximately 0.18 to 0.37 kg less than their siblings [37]. Mean length at birth is approximately 0.5 standard deviations less than control newborns [38]. In a study of 105 children with DS, growth parameters remained lower until puberty, with the growth spurt being earlier (age 11 years in males and 9.5 years in females), and were blunted compared with controls [39]. Weight gain during the first three years of life has improved since the 1980s, as has stature in males [40-42].

Short stature — Growth rate is reduced in DS compared with typical children, especially in infancy and adolescence. Growth is most reduced in children with severe congenital heart disease [38,40]. In adults with DS, the average height in males and females was 61.7 and 57 inches (157 and 144 cm), respectively, and the average weight was 157 and 140 lb (71 and 64 kg) in males and females in a 1998 study [43]. Measurement of growth in patients with DS is discussed separately. (See "Down syndrome: Management", section on 'Growth'.)

The cause of DS-associated growth retardation remains unknown. Low circulating levels of insulin-like growth factor (IGF) 1 and diminished provoked and spontaneous secretion of growth hormone (GH) have been reported in some patients [44,45]. Serum GH levels are not low in children with DS [46,47], but suboptimal endogenous GH production as a result of hypothalamic dysfunction has been demonstrated [48]. Selective deficiency of IGF-1, but not IGF-2, has been seen in DS patients who are older than two years [49,50]. IGF-1 receptors are present in brain cells from fetuses with trisomy 21 [50].

Obesity — The prevalence of obesity (defined as a body mass index [BMI] >27.8 kg/m^2 in adult males and >27.3 kg/m^2 in adult females) is greater in DS than in the general population (45 versus 33 percent, 56 versus 36 percent, for males and females, respectively) [43]. This is thought to result from the reduced resting metabolic rate in children and adults with DS [51,52]. In general, weight is less than expected for length in infants with DS and then increases disproportionally so that the majority of children are obese by age three to four years [8]. (See "Down syndrome: Management", section on 'Obesity prevention'.)

EYE PROBLEMS

Ophthalmologic disorders that require monitoring and intervention affect the majority of children with DS. Disorders that are the most common include [8,53-57]:

- Refractive errors (myopia, hyperopia, astigmatism) – 35 to 76 percent
- Strabismus – 25 to 57 percent
- Nystagmus – 18 to 22 percent

Cataracts occur in 5 percent of newborns. Starting in the second decade of life, many individuals develop corneal opacities. Children occasionally develop glaucoma. (See "Overview of glaucoma in infants and children" and "Cataract in children", section on 'Clinical features'.)

The frequency of ocular disorders increases with age. In one report, eye abnormalities occurred in 38 percent of infants 2 to 12 months of age and 80 percent of children age 5 to 12 years [53]. These abnormalities may be more prevalent in adults. In one report of 30 institutionalized adults with DS, only one had nearly normal ocular status [58]. Nine had keratoconus, an abnormal shape or thinning of the cornea that impairs visual acuity.

HEARING LOSS

Hearing impairment affects 38 to 78 percent of individuals with DS [8,59,60]. Otitis media is a frequent problem, affecting 50 to 70 percent of DS children, and it is often the cause of hearing loss in this population [4]. Monitoring for this condition is important to preserve hearing. Congenital hearing loss is also more common in DS, identified in 15 percent of newborns with DS compared with 0.25 percent in the total neonate population in one retrospective review [61].

The characteristics of hearing loss were illustrated by a study of 47 children with DS, 2 months to 3.5 years of age, evaluated by auditory brainstem response testing [60]. The following findings were noted:

- The loss was unilateral or bilateral in 28 and 38 percent, respectively; 34 percent of patients had normal hearing.
- The loss was conductive in 19 ears, sensorineural in 16, and mixed in 14.
- The extent of loss was mild, moderate, and severe to profound in 33, 13, and 3 ears, respectively.

Another series of 332 children with DS born in Utah found that [62]:

- Forty-six percent had hearing loss, 32 percent of whom were identified on newborn screening and the rest in later infancy.
- Most newborns and infants had conductive hearing loss due to serous otitis media and required placement of tympanostomy tubes, although a few children were identified with sensorineural or mixed hearing loss, primarily identified by newborn screening.

ENDOCRINE DISORDERS

Endocrine abnormalities in DS include thyroid dysfunction and diabetes.

Thyroid disease — Thyroid disorders are common in DS. The prevalence varies, depending in part upon the population studied and the age of testing. The prevalence of hypothyroidism ranged from 3 to 54 percent in reports of adults with DS [63]. Hyperthyroidism is also relatively common, occurring in 2.5 percent of institutionalized adults [64].

Thyroid disease is also frequently seen in children with DS, as indicated in the following reports:

- In a longitudinal study of 85 DS patients up to 25 years of age, 35 percent had hypothyroidism. One-half developed the disorder before age eight years [63]. Two percent had hyperthyroidism.
- In 320 children with DS aged five days to 10 years, 28 percent had abnormal thyroid function tests [65]. Of these, diagnoses included primary congenital hypothyroidism in 6, acquired hypothyroidism in 1, transient hyperthyrotropinemia in 2, compensated hypothyroidism (T4 concentration normal or close to the lower limit of normal and increased thyroid-stimulating hormone [TSH] level) in 16, and mild compensated hypothyroidism (mildly elevated TSH concentration) in 65. None had hyperthyroidism.
- In a retrospective cohort study of 122 infants less than four months of age with DS, 17.5 percent had primary hypothyroidism that required therapy, and 15 percent had compensated hypothyroidism [66].

However, there is a shift in thyroid hormone levels in patients with DS who have no overt symptoms of thyroid disease, suggesting that normal values may be different in this group. In a large cohort from a neonatal screening program, T4 concentrations in newborns with DS had a normal distribution but were shifted to lower concentrations than the general population [67]. Mean TSH concentration was significantly increased (9.76 versus 3.96 milli-international units/L), and T4-binding globulin was normal compared with controls. The distribution plots for TSH and free T4 were shifted to higher values in another study of patients with DS (median age 10 years; range six months to 64 years) [68]. This was attributed to a resetting of the hypothalamic-pituitary-thyroid axis rather than subclinical hypothyroidism, and, therefore, the recommendation was to only treat if TSH remained above the 95th percentile (>9 milli-international units/L) [68] or if there were clinical symptoms.

Diabetes — The risk of type 1 diabetes appears to be increased in DS [36,69-71]. Data from a Dutch study in children up to 14 years of age suggest the risk of type 1 diabetes is three times greater in DS than in the general population (50 versus 12.4 per 100,000 per year) [70,71]. In another study, the estimated prevalence of type 1 diabetes in DS children up to

nine years of age was eight times greater than the age-matched control population (335 versus 40 per 100,000) [70].

HEMATOLOGIC DISORDERS

Hematologic abnormalities affecting red blood cells, white blood cells, and platelets are common in DS, particularly during childhood. The lifetime risk of leukemia in DS is 1 to 1.5 percent [72,73].

Approximately 65 percent of newborns with trisomy 21 have polycythemia [74]. In one report, plasma erythropoietin concentration measured in umbilical cord blood was higher in infants with DS compared with controls, suggesting that chronic fetal hypoxemia may explain the high incidence of polycythemia [75]. (See "Neonatal polycythemia".)

Children with DS often have macrocytosis [74,76]. In one study, mean corpuscular volume (MCV) was greater in DS children age two to six years compared with controls (86.9 versus 80.6 fL), and MCV >95th percentile for age was more likely to occur (66 versus 11 percent) [76]. Hematocrits were higher in the DS patients (39.1 versus 36.9 percent), although all were normal for age. (See "Macrocytosis/Macrocytic anemia".)

White blood cell counts are decreased in DS [74,76]. In the study cited above, white blood cell counts <5th percentile for age occurred more often in DS than controls (33 versus 6 percent) [76]. The macrocytosis and leukopenia were not explained by folate deficiency, because serum and red blood cell folate concentrations were similar between the patients and controls. Thrombocytosis is common in infancy, and thrombocytopenia is rare [74].

Transient myeloproliferative disorder — Transient myeloproliferative disorder (TMD), also known as transient leukemia or transient abnormal myelopoiesis (TAM), is a form of leukemia that almost exclusively affects newborns with DS. It is typically detected on routine screening with a complete blood count (identification of blasts on the peripheral smear). The majority of newborns are asymptomatic, with spontaneous resolution of the disorder by two to three months (median 54 days), although some develop severe disease including hydrops fetalis, hyperleukocytosis, liver failure, and cardiopulmonary failure. TMD is discussed in greater detail separately. (See "Transient abnormal myelopoiesis (TAM) of Down syndrome (DS)".)

Acute megakaryoblastic leukemia — In prospective and retrospective studies, up to 26 percent of infants with transient leukemia later developed the French-American-British (FAB) classification system M7 subtype of acute myeloid leukemia (AML-M7), also known as acute megakaryoblastic leukemia (AMKL) or myeloid leukemia of DS (ML-DS) [77-79]. AMKL occurs

in approximately 1 in 50 to 200 children with DS. The incidence is approximately 500 times greater in children with than without DS. (See "Acute myeloid leukemia: Classification".)

AMKL develops during the first four years of life. It is most commonly seen by two years of age and is invariably associated with variants in guanine-adenine-thymine-adenine (GATA) binding factor 1 gene (*GATA1*) [73,78,80-85]. In contrast, myeloid leukemias in people with DS aged four years or older are usually negative for *GATA1* variants, and their prognosis does not differ from AML in patients without DS. Many affected patients (20 to 69 percent) present with myelodysplastic syndrome, consisting of progressive thrombocytopenia followed by anemia [72]. Some develop hepatomegaly and liver failure due to fibrosis [86]. Neutropenia and infection rarely are seen [86]. Treatment issues are complex as children with DS and either acute lymphoblastic leukemia (ALL) or AMKL are subject to high initial rates of treatment-related mortality [87].

There is evidence that these *GATA1* variants are acquired in utero and that finding such variants at birth might serve as a biomarker for an increased risk of transient leukemia and subsequent AMKL [88,89]. In one study, three of four children with DS and AMKL had the same *GATA1* variant in a neonatal blood spot (Guthrie card) that was found at the time of clinical diagnosis of AMKL 12 to 26 months later [90].

Gene expression profiling may help in distinguishing transient leukemia from AMKL [91] and identifying those at risk of progressing from transient leukemia to AMKL [92], as well as distinguishing the AMKL seen in children with DS from AMKL seen in those without DS [93].

Acute lymphoblastic leukemia — The risk of developing ALL is approximately 10 to 20 times higher in DS compared with children without DS [36,94-96] and accounts for 1 to 3 percent of all patients with ALL. The clinical presentation is similar to that in children without DS. (See "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children".)

In a report comparing ALL in children with and without DS, the following findings were noted at presentation [72,94]:

- Leukocyte count and leukemic cell mass were similar.
- Age distribution and immunophenotype were similar.
- Clinically, they were indistinguishable [73].
- Mediastinal mass (1.6 versus 8.9 percent) and central nervous system (CNS) leukemia (0 versus 2.7 percent) were less common in DS, both favorable prognostic signs.
- Less T cell leukemia or translocation of (9;22) or t(4;11) were seen in DS, both unfavorable prognostic signs.

- Cytogenetic differences occurred, including less hyperdiploidy in DS, an unfavorable prognostic sign.

Children with DS who develop ALL often respond to chemotherapy, similar to children without DS. The treatment and outcome for children with DS and ALL are discussed separately. (See "Acute lymphoblastic leukemia/lymphoblastic lymphoma: Outcomes and late effects of treatment in children and adolescents".)

PULMONARY DISORDERS

Sixty percent of 208 children with DS in a 2004 survey were reported by their parents to have respiratory conditions, including sleep apnea and asthma [97], although this may be an underestimate based upon results from other studies [98]. Other pulmonary complications that are more common in children with DS include disorders of the pulmonary vasculature, parenchymal lung disease, upper and lower airway abnormalities, and chronic aspiration [99]. Respiratory tract infections are also more frequent and often more severe than in children without DS.

Sleep apnea — Obstructive sleep apnea (OSA) occurs in at least 30 to 75 percent of children with DS, including those who are not obese [98,100-106]. In a population of 65 unselected 3.5 year olds with DS, polysomnograms were classified as abnormal with evidence of OSA in 57 percent. Among the 45 children whose parents reported no sleep problems, 54 percent had abnormal results [98]. The mechanism includes soft tissue and skeletal alterations that lead to upper airway obstruction. In infants with DS, OSA was associated with dysphagia, gastrointestinal conditions such as gastroesophageal reflux disease, and congenital heart disease [106]. Intermittent hypoxemia may lead to pulmonary hypertension and contribute to mental impairment [107]. (See "Mechanisms and predisposing factors for sleep-related breathing disorders in children".)

SKIN DISORDERS

The majority of DS children have associated skin disorders, which are considered benign [108-110]. In one series, 62 of 71 children (87 percent) had skin abnormalities in the following proportions [111]:

- Palmoplantar hyperkeratosis – 41 percent
- Seborrheic dermatitis – 31 percent
- Fissured tongue – 20 percent
- Cutis marmorata – 13 percent
- Geographic tongue – 11 percent

- Xerosis – 10 percent
- Alopecia areata – 8 percent [108,109]

In adolescents, dermatologic problems become particularly bothersome. The most common condition in this age group is folliculitis, which affects 50 to 60 percent of patients [112].

REPRODUCTION

Females with DS are fertile and may become pregnant. In one series, 30 pregnancies in 26 women resulted in 10 offspring with DS, 18 (including one set of twins) without DS, and 3 spontaneous abortions [113]. Appropriate counseling should be provided for management of menstruation and contraception [114].

Nearly all males with DS are infertile. The mechanism is impairment of spermatogenesis [115]. However, cases have been reported of offspring from fathers with DS [116,117].

UROLOGIC ABNORMALITIES

Studies suggest an increased incidence of urologic abnormalities in individuals with DS. These include hypospadias (1 in 250 males), cryptorchidism (14 to 27 percent of males), testicular cancer, and kidney malformations (3.5 percent) [118]. (See "Hypospadias: Pathogenesis, diagnosis, and evaluation" and "Undescended testes (cryptorchidism) in children: Clinical features and evaluation" and "Clinical manifestations, diagnosis, and staging of testicular germ cell tumors" and "Overview of congenital anomalies of the kidney and urinary tract (CAKUT)".)

ATLANTOAXIAL INSTABILITY

Atlantoaxial instability (AAI), defined as excessive mobility of the articulation of the atlas (C1) and the axis (C2), may lead to subluxation of the cervical spine [119]. Approximately 13 percent of individuals with DS have asymptomatic AAI, while spinal cord compression due to the disorder affects approximately 2 percent [120]. The diagnosis is made by lateral neck radiographs taken in neutral position, flexion, and extension. (See "Down syndrome: Management", section on 'Atlantoaxial instability'.)

Patients with symptomatic spinal cord compression may have neck pain, torticollis, gait abnormalities, loss of bowel or bladder control, or signs of quadriparesis or quadriplegia and require immediate stabilization. Asymptomatic individuals appear to remain asymptomatic whether or not physical activity is restricted [121,122]. In one study, DS children with AAI were randomly assigned to participate or not in athletic activities considered to be risky and

evaluated after one year. The groups were similar in motor function, frequency of neurologic signs, and changes in atlantoaxial distance and were also similar to children with DS and without AAI [121].

ARTHROPATHY

DS arthropathy has a prevalence of 8 to 10 per 1000, or approximately six times the prevalence of juvenile idiopathic arthritis in the general population [123]. In a review of 30 cases, 17 had polyarticular disease at symptom onset, and 13 had oligoarticular disease at symptom onset, but 7 of these progressed to polyarticular disease. Average delay from symptom onset to diagnosis was two years.

IMMUNODEFICIENCY

DS is associated with a variety of immunologic impairments that are thought to be related to the increased susceptibility to infection, autoimmune disorders, and malignancies [124-128]. Chemotactic defects [129], decreased immunoglobulin G4 (IgG4) levels [130], and quantitative and qualitative abnormalities of the T cell and B cell systems have been inconsistently demonstrated [124-126,131]. Whether these represent an inborn error of immunity (also known as a primary immunodeficiency) or early senescence of the immune system is uncertain.

Support for an intrinsic immunodeficiency is provided by a cross-sectional study in which immunophenotyping was used to evaluate lymphocyte subpopulations in 96 children with DS who ranged in age from 1 to 20 years [132]. In another study, children with DS had a diminished expansion of T and B cells in the first years of life compared with previously published data on healthy children without DS [133]. B cells remained diminished (with 88 percent of values below the 10^{th} percentile), although T cells eventually approximated normal levels. Reduced naive mature and memory B cell numbers and evidence of impaired antigen selection for IgM+ and IgA+ memory B cells were seen in one small study [134].

DIAGNOSIS OF DOWN SYNDROME

The diagnosis of DS is often made by prenatal screening. (See "First-trimester combined test and integrated tests for screening for Down syndrome and trisomy 18" and "Maternal serum marker screening for Down syndrome: Levels and laboratory issues".)

When no prenatal diagnosis is available, DS is usually recognized from the characteristic phenotypic features present in the newborn (see 'Dysmorphic features' above). Diagnosis

should be confirmed with a genetic test (eg, a karyotype performed on a blood sample). Alternative methods (eg, interphase fluorescent in situ hybridization [FISH] for trisomy 21 or quantitative fluorescence-polymerase chain reaction [QF-PCR]) may be used to expedite diagnosis, but these investigations should always be followed by a full karyotype in order to detect DS due to translocations (eg, Robertsonian translocations involving chromosome 21) or mosaic DS.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Down syndrome".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Down syndrome (The Basics)")
- Beyond the Basics topic (see "Patient education: Down syndrome (Beyond the Basics)")

SUMMARY

- **Diagnosis** – The diagnosis of Down syndrome (DS) is often made by prenatal screening. DS is otherwise usually recognized from the characteristic phenotypic features present in the newborn. A clinical diagnosis of DS should be confirmed by genetic testing whenever possible. (See 'Diagnosis of Down syndrome' above and "First-trimester combined test and integrated tests for screening for Down syndrome and trisomy 18" and "Maternal serum marker screening for Down syndrome: Levels and laboratory issues" and 'Neonatal features' above.)

- **Dysmorphic features** – The characteristic dysmorphic features of DS predominantly affect the head and neck and the extremities (picture 1 and picture 2). Ten of the characteristic dysmorphic features are common in newborns with DS and are usually recognized soon after birth. (See 'Dysmorphic features' above.)

- **Neuropsychiatric disorders** – Almost all persons with DS have cognitive impairment, although the range is wide. Most are mildly to moderately intellectually disabled, although some are severely impaired. Behavioral and psychiatric disorders are more common in DS than typical children but less common than in those with other causes of intellectual disability. (See 'Neuropsychiatric disorders' above.)

- **Cardiovascular disease** – Approximately one-half of persons with DS have congenital heart disease. Septal defects are the most common. Some asymptomatic adolescents and adults without structural heart disease develop valve abnormalities. (See 'Cardiovascular disease' above.)

- **Gastrointestinal abnormalities** – Children with trisomy 21 are at increased risk for gastrointestinal tract anomalies, including duodenal atresia or stenosis, imperforate anus, and esophageal atresia with tracheoesophageal fistula. They are also at increased risk for celiac disease and Hirschsprung disease. (See 'Gastrointestinal abnormalities' above.)

- **Growth** – Birth weight, length, and head circumference are less in DS compared with typical infants. The growth rate for height is reduced in DS compared with typical children. In general, weight is less than expected for length in infants with DS and then increases disproportionally so that the majority of children are obese by age three to four years. (See 'Growth' above.)

- **Eye and hearing problems** – Ophthalmologic disorders are common in patients with DS and increase in frequency with age. These disorders include refractive errors, strabismus, nystagmus, cataracts, and keratoconus. Hearing loss is also common, and otitis media is a frequent problem. (See 'Eye problems' above and 'Hearing loss' above.)

- **Endocrine disorders** – Endocrine abnormalities in DS include thyroid dysfunction and type 1 diabetes. (See 'Endocrine disorders' above.)

- **Fertility and reproduction –** Females with DS are fertile and may become pregnant. However, nearly all males with DS are infertile. (See 'Reproduction' above.)

- **Atlantoaxial instability** – Persons with DS are at increased risk of atlantoaxial instability (AAI), defined as excessive mobility of the articulation of the atlas (C1) and the axis (C2), although spinal cord compression due to subluxation of the cervical spine is uncommon. (See 'Atlantoaxial instability' above.)

- **Hematologic abnormalities** – Hematologic abnormalities affecting red cells, white cells, and platelets are common in DS and include polycythemia, macrocytosis, leukopenia, thrombocytosis, and leukemia (transient, acute megakaryoblastic, and acute lymphoblastic). (See 'Hematologic disorders' above.)

- **Immunologic abnormalities** – DS is associated with a variety of immunologic impairments that are thought to be related to the increased susceptibility to infection, autoimmune disorders, and malignancies. However, these defects are inconsistently demonstrated. Whether these represent an inborn error of immunity (also known as a primary immunodeficiency) or early senescence of the immune system is uncertain. (See 'Immunodeficiency' above.)

- **Other abnormalities** – Increased rates of urologic abnormalities, arthropathy, pulmonary disease, and benign skin disorders are also seen in patients with DS. (See 'Urologic abnormalities' above and 'Arthropathy' above and 'Pulmonary disorders' above and 'Skin disorders' above.)

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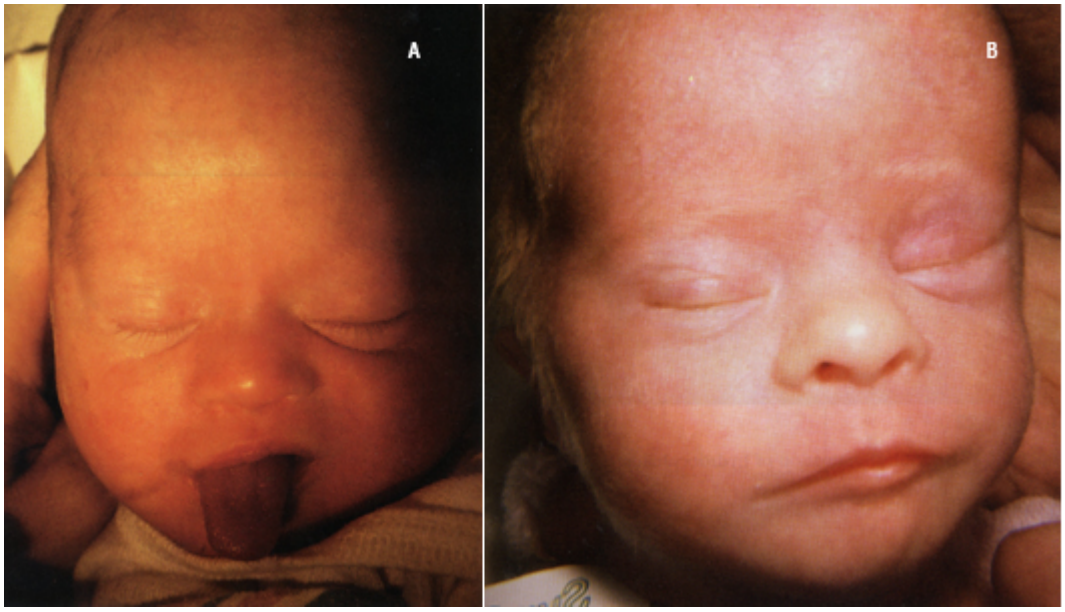
Topic 2917 Version 32.0

GRAPHICS

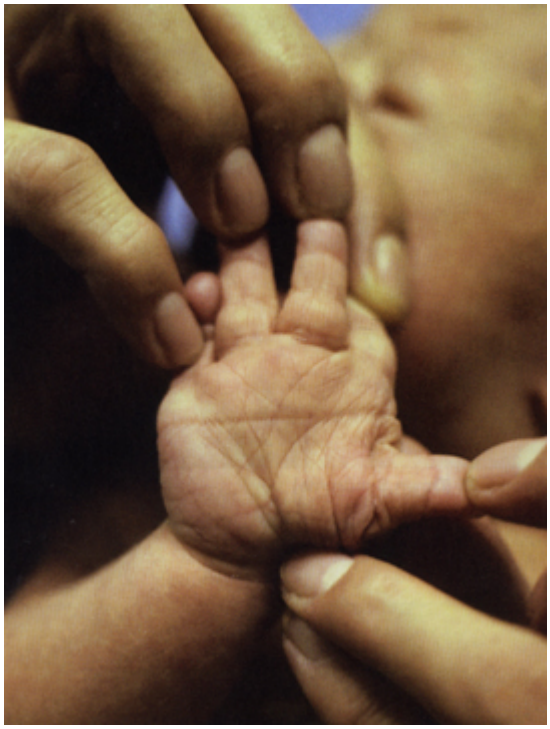
Down syndrome facies



Characteristic facial features of Down syndrome depicted in a term (A) and preterm (B) infant include: epicanthal folds, slanted palpebral fissures, flat nasal bridge, and protruding tongue.

Graphic 64030 Version 2.0

Transverse palmar crease



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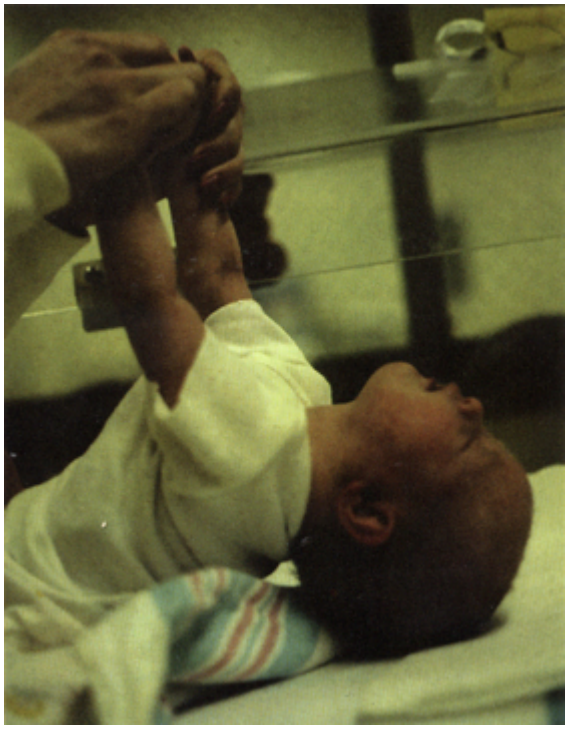
Graphic 79414 Version 2.0

Hypotonia: Severe head lag



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