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Newborn Presentation of Connective Tissue Disorders

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Author Disclosure
Dr Hoffman and Ms Estrella did not disclose any financial relationships relevant to this article.

Objectives After completing this article, readers should be able to:

1. Recognize the neonatal signs and symptoms of a connective tissue disorder.
2. Differentiate between the most common types of connective tissue disorders.
3. Diagnose types of connective tissue disorder using clinical and molecular techniques.
4. Treat a child who has a connective tissue disorder, paying special attention to appropriate involved systems.

Abstract
Connective tissue disorders are a relatively common group of disorders that should be considered in any baby who has hypermobility or related multisystem involvement. Early diagnosis can decrease morbidity and improve many features of connective tissue disorders, including gross motor development, ambulation, and vision and hearing outcomes. Early echocardiography can identify congenital defects that need to be addressed surgically, treated prophylactically, or followed over time. Timely orthopedic management can address serious issues such as scoliosis, hip dysplasia, or fractures that must be treated to assure the best outcome possible. A genetic specialist often can aid in the initial recognition of signs and symptoms, guide molecular or protein analysis, explain information regarding recurrence risk and prognosis, and provide coordination of care throughout life.

Introduction
Connective tissue disorders (CTDs) are a heterogeneous group of inherited conditions affecting multiple systems that occur in approximately 1 in 2,000 people. Most disorders primarily involve the joints, bones, skin, heart, and eyes. CTDs generally are caused by abnormalities in extracellular matrix proteins, ie, collagen and fibrillin. Molecular techniques have greatly advanced the ability to identify genes responsible for CTDs, expanding understanding of the pathophysiology of each disease. Such understanding allows for early identification of the disorders, which has been shown to improve care significantly, optimize quality of life, and considerably decrease morbidity and mortality.

Neonatal presentations of CTD can vary greatly. Most babies present with significant hypermobility or contractures of the joints. In addition, they may exhibit abnormally shaped bones, facial dysmorphisms, skin findings, or cardiac lesions. Initially, a child who has a CTD may appear to have hypotonia, which can shift the diagnostic focus to possible nervous system dysfunction or a muscular disorder. This may delay proper diagnosis and management of a CTD, with serious consequences.

Differential Diagnosis
This article addresses several common CTDs, such as Marfan syndrome, osteogenesis imperfecta, Stickler syndrome, and the Ehlers-Danlos syndromes (Table). We also address more

Abbreviations

CCA: congenital contractual arachnodactyly/Beals syndrome
CTD: connective tissue disorder
EDS: Ehlers-Danlos syndrome
LDS: Loey-Dietz syndrome
MFS: Marfan syndrome
nMFS: neonatal Marfan syndrome
SGS: Shprintzen-Goldberg syndrome
OI: osteogenesis imperfecta

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briefly some rare CTDs such as Beals, Shprintzen-Goldberg, Loeys-Dietz, and Larsen syndromes. Other genetic disorders, including Kabuki syndrome, Williams syndrome, Aarskog syndrome, and Menkes syndrome, may be associated with significant laxity of the joints, but more often are considered multiple congenital anomaly syndromes that have secondary connective tissue findings; they will not be discussed. Fragile X syndrome also may show laxity of the joints and aortic dilatation, overlapping features of a CTD.

Initial Assessment
During the initial assessment of a child who appears to have poor tone, it is important to determine whether the appearance is due to an abnormality of the joints, muscles, or nervous system. The differential diagnosis for hypotonia includes spinal muscular atrophy, which presents with poor muscle bulk, respiratory distress, and tongue fasciculations, and peripheral neuropathies such as Charcot-Marie-Tooth if absent or decreased reflexes are seen. Other causes of poor muscle tone include mitochondrial disorders and muscle diseases such as nemaline and myotubular myopathies, muscular dystrophies, and myotonic dystrophy. If the hypotonia is accompanied by dysphagia, apnea, and visual or hearing disturbances, the clinician must consider causes such as hypoxic-ischemic insult, neuronal migration disorders, and central nervous system malformations. If a newborn who exhibits hypotonia has facial dysmorphism, organ malformations, and significant hypermobility, chromosomal abnormalities and several genetic syndromes should be considered.

Kabuki, Williams, Aarskog, and Menkes syndromes all present in the neonatal period with syndrome-specific dysmorphic features, hypotonia, organ malformations, and hypermobility. Consultation with a geneticist may help narrow the differential diagnosis for a child who has such a complex combination of features. If the child has persistent laxity of the joints combined with the other signs of a CTD in commonly affected systems (ocular, cardiac, bone, or dermatologic), further evaluation for a CTD is warranted.

Fibrillinopathies
Description and Genetics
A family of extracellular matrix proteins, the fibrillin-LTBP gene family, was discovered in the 1990s and helped to elucidate the structure and function of microfibrils. Mutations in fibrillin-1, -2, and -3 genes were discovered and found to be associated with several connective tissue disorders. The most common of the fibrillinopathies are Marfan, Beals, Shprintzen-Goldberg, and Loeys-Dietz syndromes.

Marfan Syndrome (MFS)
MFS is an autosomal dominant disorder that has an estimated incidence of 1 in 5,000. Its most prominent features are skeletal, cardiovascular, and ocular. Most cases of MFS are due to mutations in the fibrillin-1 gene (*FBN1*) on chromosome 15. Approximately 25% of cases are believed to occur sporadically. The mutations are scattered throughout the gene. The clinical course is variable, with inter- and intrafamilial variability in patients who have the same mutation. Genotype-phenotype correlations have been difficult in classic MFS because most mutations are private.

Classic MFS may be difficult to diagnose in the newborn period without a family history. Affected babies may be long and have mild contractures of the elbows and fingers. Hypermobility of the large joints may be appreciable. Infants are unlikely to demonstrate the cardiac features seen later in life, such as mitral valve prolapse or aortic dilatation. Classic facial features, such as down-slanted eyes, flattening of the malar region, a prominent nose, ear proptosis, and a high arched palate, may be overlooked easily in a newborn. Pectus deformities, scoliosis, and protrusion acetabulae usually are not noted early in life. Affected patients develop a characteristic body habitus that is characterized by disproportionately long arms, legs, hands, and feet and described as dolichostenomelia. Occasionally, ectopia lentis can present in the newborn period and should prompt further consideration of MFS.

*FBN1* analysis can be pursued if there is significant concern for MFS in a baby who does not meet published criteria fully. Mutation analysis of *FBN1* detects mutations in approximately 80% of patients who eventually develop classic MFS. Testing for mutations in transforming growth factor-beta receptor 2 (*TGFBR2*), another member of the fibrillin-LTBP gene family, should be considered if *FBN1* testing results are negative. A negative molecular result does not rule out MFS, and further follow-up is important to prevent the morbidity associated with unmonitored cardiac, skeletal, and ophthalmologic involvement.

A subset of patients who have MFS and present in the neonatal period have been shown to have mutations confined to a “hot spot” in the *FBN1* gene. The neonatal Marfan syndrome (nMFS) is much less common, but significantly more severe on the clinical spectrum than classic MFS. Early hallmarks of nMFS include arachnodactyly, pectus deformities, congenital flexion contrac-
tures, crumpled ears, loose and redundant skin, and an “aged or senile” facial appearance. Severe cardiac valve regurgitation and dilatation of the proximal aorta are common. The prognosis for a newborn who has nMFS is directly correlated with the severity of the cardiac involvement, with congestive heart failure expected within the first neonatal year. FBN1 mutations for nMFS usually are clustered between exons 23 to 32, and in most cases, these mutations are de novo. This observed clustering of mutations facilitates molecular diagnosis in a newborn suspected of having nMFS.

Beals Syndrome (Congenital Contractural Arachnodactyly)

Beals syndrome, also known as congenital contractural arachnodactyly (CCA), is an autosomal dominant CTD that has considerable phenotypic overlap with MFS. Affected newborns frequently have crumpled ears, dolichostenomelia, arachnodactyly, and chest wall deformities, similarly to patients who have nMFS. In addition, newborns frequently exhibit joint contractures of the fingers, elbows, and knees. The severe contractures can cause motor delay. Mitral valve prolapse with or without regurgitation can be seen. Scoliosis and high-arched palate also are common in CCA. Ocular and life-threatening cardiac complications are absent in most affected patients, although a severe, lethal type of CCA has been reported. In this form of CCA, structural cardiac and gastrointestinal malformations are seen.

CCA has been linked to the FBN2 gene on chromosome 5. As seen in nMFS, mutations have been found to cluster between exons 23 to 34 in FBN2. Interestingly, mutations in both CCA and nMFS cluster in homologous domains of FBN1 and FBN2, indicating an important conserved function for this protein domain.

Shprintzen-Goldberg and Loeys-Dietz Syndromes

Other syndromes that mimic features of MFS are Shprintzen-Goldberg syndrome (SGS) and Loeys-Dietz syndrome (LDS) type I. Children who have these syndromes present with dolichostenomelia, arachnodactyly, chest wall deformities, and cardiovascular anomalies. They are distinguished from patients who have MFS by the additional features of craniosynostosis, significant hypotonia, and mental retardation. The characteristic facial appearance of both includes hypertelorism, downslanting palpebral fissures, micrognathia, and low-set ears. The distinguishing features of LDS are bifid uvula and arterial tortuosity, although recent reports have described bifid uvula in newborns who have SGS.

LDS is an autosomal dominant disorder, with mutations found in two related genes, TGFBR1 and TGFBR2, located on chromosome 9. Sporadic cases of SGS have been found to have mutations in both the FBN1 and TGFBR2 genes. Microfibrils comprised of both fibrillin-1 and fibrillin-2 can bind to several members of the TGF-beta cell signaling superfamily, including TGFBR1 and TGFBR2. Therefore, it is uncertain, whether SGS and LDS are truly separate disorders or, due to their significant clinical overlap, may be genetically heterogenic with each other and MFS.

Management

Early diagnosis of the fibrillinopathies is important for early intervention due to the significant and sometimes severe cardiovascular involvement. Early diagnosis is also important in providing prognosis and recurrence risk information to families. Children who have a fibrillinopathy require an initial cardiac evaluation that includes echocardiography to assess the need for medical interventions such as surgery or beta blockers and the frequency of further cardiac follow-up. Frequent ophthalmologic evaluations are needed to assess for ectopia lentis, retinal detachment, or severe myopia. Orthopedic evaluation is important to treat contractures, monitor pectoral deformities that may impinge on cardiac function, and assess and treat severe scoliosis and pes planus. Physical therapy is important to decrease the severity of contractures and allow for more comfortable ambulation. Patients who have SGS should receive initial radiographic studies to look for craniosynostosis.

Osteogenesis Imperfecta (OI)

Description and Genetics

OI is a heterogeneous group of disorders resulting in multiple fractures of the bones due to unstable architecture. Affected people often have short stature, thinning of the skin, poorly developed muscles, blue sclera, dentinogenesis imperfecta, and hearing loss. OI is estimated to affect approximately 1 in 10,000 people and does not have sex or ethnic preference.

OI type II

Babies who have the perinatal lethal form of OI, type II, often exhibit shortening and bowing of the long bones on prenatal ultrasonography due to multiple fractures as well as large, sometimes wormian skulls. They are more likely to be preterm and have low birthweight. Their sclera may appear dark, and the nose may appear beaked. Affected infants generally cannot survive the trauma of delivery due to disease severity and often are unable to
sustain respirations postnatally due to abnormal ribs, lung hypoplasia, and a small thoracic cavity. Approximately 60% of babies who have OI type II die in the first day after birth, and up to 80% die within the first month from respiratory failure, infections, and congestive heart failure. If a prenatal diagnosis is made, cesarean delivery is not recommended because it has not been found to increase the survival rate. OI type II generally results from a sporadic mutation that causes integration of abnormal collagen fibrils into collagen I. Rare cases of autosomal recessive inheritance have been documented. The recurrence risk is estimated at 6% to 7% due to the possibility of parental mosaicism.

**OI Types III/IV**

Babies who have types III and IV OI have abnormal collagen fibrils mixed with normal fibrils, resulting in more fragile bones than in children who have type I. Some babies develop fractures in utero, producing short stature. The calvarium is undermineralized and wormian, and the anterior fontanelle often is large. Affected infants rarely survive the first postnatal year without sustaining a fracture. Type III involves more severe deformations, more frequent fractures, and shorter stature than type IV. In both types, reports of heat intolerance and increased sweating have led to concerns about hyperpyrexia. Therefore, caution should be exercised with anesthesia. Babies have light blue-to-normal sclera and develop dentinogenesis imperfecta. Basilar compression may occur, resulting in progressive signs of sleep apnea, headache, and peripheral nervous system involvement. People who have OI types III and IV may develop hearing loss in adulthood. Progressive deformity of the thorax and kyphoscoliosis can result in cardiopulmonary dysfunction and reduced life expectancy. Many people who have OI type III are wheelchair-bound. Both OI types III and IV are usually autosomal dominant, but rare recessive cases have been reported.

**OI Type I**

Babies who have OI type I may be overlooked in the newborn period due to the lack of early fractures. They are unlikely to have bone deformations or short stature at birth, although they occasionally have congenital bowing. Fractures may occur during diaper changes or may not develop until the baby begins to walk. The babies may have bluish sclera due to abnormal collagen content. They may pass the initial newborn hearing screening, but can develop conductive and sensorineural hearing loss later. Rarely, children may develop cardiac involvement such as mitral valve prolapse, aortic insufficiency, or aortic dilatation. Some children have ligamentous laxity. Others have thin-appearing skin and bruising. OI type I most commonly is due to decreased or absent synthesis of type I procollagen from one COL1A1 allele, with the remaining collagen having normal formation, which explains the milder phenotype than that seen in type II. OI type I has an autosomal dominant inheritance.

**Diagnosis**

Until recently, the diagnosis of OI required a skin biopsy for collagen analysis. With the discovery of the collagen I genes (COL1A1 and COL1A2), the type of OI can be predicted based on mutational analysis of a blood sample. Abnormalities are classified into the less severe mutations that decrease the amount of collagen I versus the more severe mutations that cause the production of abnormal collagen that integrates in the normal collagen and greatly affects the bone architecture. The combination of molecular results and physical examination findings allows for more accurate OI classification and prognosis. Biochemical techniques remain available for collagen analysis in cases in which molecular analysis is unrevealing.

**Management**

Although there is no cure for OI, treatment can minimize fracture frequency and severity, with the goal of decreasing pain and improving overall quality of life. Intravenous pamidronate has become standard for children who have more severe types of OI. The first several doses usually are administered in the hospital due to the possibility of postinfusion hypocalcemia. Pamidronate increases overall bone density and improves stature. Proper diapering techniques must be used, and children must be treated with the utmost care before they learn to protect themselves from fractures as they grow older. The long bones sometimes are braced to increase stability of the joints and limbs. Fractures must be stabilized with minimally invasive techniques. Scoliosis must be evaluated frequently, and rods often are required to prevent further curvature. Cardiac surveillance can detect aortic dilatation and valve abnormalities. Physical therapy can be used to increase joint mobility, minimize contracture formation, allow for increased independent ambulation, and provide overall increased quality of life.

**Larsen Syndrome**

Larsen syndrome is primarily a skeletal dysplasia, but it involves significant laxity of the joints and multiple dislocations, mimicking a CTD. Second-trimester ultrasonography may show abnormal positioning of the
joints. Neonatal presentation may include dislocations of the hips, knees, and ankles; ligamentous laxity; and hydrocephalus with a normal ventricular system. Among the facial features are bossed forehead, depressed nasal bridge, hypertelorism, midfacial hypoplasia, and cleft palate or uvula. Cervical vertebral may be unstable, resulting in severe kyphosis and death if untreated. Larsen syndrome is autosomal dominant in most cases. Mutations in filamin B (FLNB), a gene located on 3p21.1–4.1, have been found to be the cause of most cases of Larsen syndrome. Filamin B protein is important in joint formation, vertebral segmentation, and ossification.

The Ehlers-Danlos Syndromes (EDSs)
Description and Genetics
The EDSs are a heterogeneous group of syndromes that most frequently involve laxity of the joints, abnormalities of the skin, skeletal changes, cardiovascular abnormalities, and ophthalmologic findings.

Arthrochalasia (EDS VIIA and B)
This type of EDS is most likely to be recognized in the newborn period. Affected babies initially present with bilateral hip dislocations that almost always require surgical intervention. Babies also may present with hyperextension of the knees due to congenital patellar dislocations. They frequently exhibit hypotonia due to excessive joint laxity and may be breech in presentation due to hyperlaxity. Children have frequent, recurrent joint dislocations and often develop postural thoracolumbar scoliosis. The joint abnormalities lead to delayed gross motor development, and scoliosis may result in short stature. EDS VIIA and B are inherited in an autosomal dominant pattern and are caused by mutations in exon 6 of the COL1A1 or COL1A2 genes that lead to abnormalities in the alpha-1 or -2 chains of type I collagen in most cases.

Kyphoscoliotic Type (EDS VI)
The kyphoscoliotic/ocularscoliotic type of EDS most often is recognized by the presence of congenital kyphoscoliosis, severe hypotonia, and generalized joint laxity in the newborn period. Ophthalmologic findings include severe fragility of the ocular globe that leads to early rupture, microcornea, retinal detachment, and blue-appearing sclera. The babies often have difficulty latching on and feeding, delayed motor milestones, and a weak cry. There is some overlap with the skeletal features of MFS, such as dolichostenomelia and thoracic cage abnormalities. The kyphoscoliotic type of EDS usually is due to autosomal recessive inheritance of mutations in the PLOD1 gene that lead to lysyl hydroxylase deficiency. Lysyl hydroxylase activity can be evaluated in urine by measurement of pyridinoline cross-links.

Dermatosparaxis (EDS VIIC)
This rare, autosomal recessive type of EDS is seen in multiple animal species. The initial presentation includes breech position, preterm delivery, inguinal hernias, and extremely redundant and lax skin. The soft and doughy skin bruises and tears easily. The face may appear dysmorphic due to micrognathia, sagging facial skin, blue sclera, and a swollen appearance around the eyes due to excessive peri-orbital skin. The joints tend to become more hypermobile as the child ages. Dermatosparaxis is caused by an abnormality in procollagen N-proteinase, which is necessary to process collagens I and II and provide proper organization of collagen fibrils. The gene for this protein, ADAMTS2, is located on chromosome 5q23. Molecular analysis has revealed a predominance of one common mutation, which facilitates genetic testing in this disorder.

Classic EDS (EDS I/II)
EDS I/II once was classified as two separate entities, but it is now believed to be a disorder that has a continuous spectrum of presentation severity. The more severe phenotype (I) is referred to as gravis, while the less severe phenotype (II) is referred to as mitis. Classic EDS is difficult to diagnose in the newborn period. A high rate of preterm delivery is reported in the literature. On focused examination, affected children have hyperextensibility of velvety smooth skin; widened, atrophic scars; and joint hypermobility. The joint hypermobility is likely to present as a delay in gross or fine motor skills in the first postnatal year, accompanied by hypotonia. Hiatal hernia or anal prolapse may occur early in life. Bruising and bleeding may occur without significant injury. A significant percentage of patients exhibit mitral valve prolapse; fewer patients exhibit aortic dilatation. The classic form of EDS most often has an autosomal dominant inheritance, with inter- and intrafamilial variability. Mutations in the genes for both collagen 5A1 and 5A2 account for approximately 50% of all cases. Tenascin X recently has been found to cause a smaller portion of classic cases of EDS, acquired in an autosomal recessive pattern. Affected patients tend to lack the atrophic scars seen in people who have collagen 5A1 and 5A2 abnormalities.
Hypermobile EDS (III)

EDS III is one of the more common types of EDS. It may present in the newborn period with severe hypermobility of all joints causing delays in the acquisition of fine and gross motor skills. Frequent dislocations of the shoulders, mandible, and patella as well as other joints occur. Although the skin often is extremely smooth and velvety, affected children are less prone to the hyperextensible skin seen in classic EDS and do not have widened atrophic scars. They may have significant bruising and an increased risk for bleeding. They are likely to have gastrointestinal involvement such as severe gastroesophageal reflux, gastric dysmotility, and irritable bowel symptoms. Children who have hypermobile EDS may complain of significant fatigue with routine activities such as walking short distances due to their ligamentous laxity and need to provide joint stabilization through increased muscle tone. Because of the association of cardiac defects such as mitral valve prolapse and aortic dilatation in some, early diagnosis is important for further management. The lack of a single genetic cause raises some concern that hypermobile EDS may include a range of disorders from the upper limit of normal for mobility, familial hypermobility syndrome, to severe autosomal dominant hypermobile EDS. A few cases of hypermobile EDS due to heterozygosity for a tenascin X mutation have been described. A single case of hypermobile EDS was attributed to a COL3A1 gene, but due to the age of the patient, it is still possible that the patient eventually will be diagnosed with the vascular type of EDS with hypermobile features.

Vascular EDS (IV)

Vascular EDS (IV) is the most life-threatening type of EDS. It is autosomal dominant, and affected women have up to a 28% risk of uterine rupture with each pregnancy. If there is a family history of vascular EDS, a relative who had sudden death, or maternal uterine rupture, vascular EDS should be considered. Very few signs of vascular EDS are seen in the newborn period other than clubfoot. Older children and adults have an aged appearance due to a lack of facial adipose tissue, with translucent, velvety skin. The faces are distinctive, with a gaunt look, proptotic eyes, a long and thin nose, and prominent forehead veins. The hands are likely to be the only site of hypermobility and often have little subcutaneous adipose tissue, which contributes to the overall aged appearance. A prominent venous pattern is notable over most of the trunk. People who have vascular EDS bruise extremely easily and often do not recall the cause of their bruises. Unfortunately, many patients are diagnosed initially at the time of an arterial rupture in the third or fourth decade of life. No specific recommendations are available regarding screening or preventive care because repair of dilating or aneurysmal vessels is highly risky due to wound dehiscence, poor scar formation, and the risk of further damage to vessels during surgery. Cardiac ultrasonography is prudent, but intervention usually is postponed as long as possible.

Vascular EDS is due to abnormalities of collagen III caused by mutations in the COL3A1 gene. More recently, multiple cases of vascular EDS without mutations in COL3A1 have been found to have mutations in TGFBR1 and TGFBR2. Vascular EDS can be diagnosed by fibroblast analysis of collagen III or molecular analysis of the COL3A1 gene. Molecular analysis of TGFBR1 and TGFBR2 should be considered if collagen III analysis is unrevealing.

Diagnosis

Molecular and fibroblast analysis is available for most types of EDS, excluding the hypermobile form. Many patients are diagnosed clinically, based on medical history, physical examination, and family history. Laboratory analysis may be useful in providing recurrence risk information for families as well as differentiating between vascular EDS and the less life-threatening types.

Management

For those types of EDS involving significant hypermobility, early initiation of physical therapy can improve muscle bulk, tone, and overall stability of the joints. Avoidance of high-impact activities and hyperextension of the joints can decrease joint pain and delay the symptoms of early-onset arthritis. Yearly orthopedic evaluation is useful in assessing the progression of scoliosis and other bony deformities that might benefit from early intervention. Initial cardiac evaluation with echocardiography is recommended to look for mitral valve prolapse, aortic root dilatation, or tortuous vessels that must be followed closely. Further follow-up intervals are based on the initial examination. Medical management of gastrointestinal symptoms such as constipation, gastroesophageal reflux, gastric dysmotility, and irritable bowel syndrome can greatly improve quality of life and nutrition and prevent bowel rupture. A yearly eye examination by an ophthalmologist skilled in the diagnosis of connective tissue changes of the eyes is recommended. Many people who have EDS experience significant pain of the joints and fatigue due to muscle compensation for the unstable joints. Children may require extra time to complete tasks, modified physical education to minimize high impact on
joints, and an educational plan that allows for their needs and avoids a label of being lazy. Unmanaged chronic pain and fatigue can lead to depression that requires professional interventions.

**Stickler Syndrome**

Stickler syndrome, also called hereditary arthro-ophthalmopathy, is a multisystem connective tissue disorder involving the ocular, orofacial, auditory, and musculoskeletal systems. It has an incidence of approximately 1 in 10,000 and an autosomal dominant inheritance. Most affected patients have mutations in three collagen genes: *COL2A1*, *COL11A1*, and *COL11A2*. These genes code for type II and type XI collagens that are expressed primarily in cartilage, the vitreous of the eye, and the middle and inner ear. Based on the molecular findings, Stickler syndrome has been classified into three subtypes (Table).

Newborns who have Stickler syndrome present with a flat facial profile, telecanthus, epicanthal folds, and Pierre Robin sequence (micrognathia, cleft palate, glossoptosis). Severe micrognathia may compromise the upper airway, necessitating tracheostomy in the newborn period. Neonatal eye findings include high myopia (greater than −3 diopters) that is nonprogressive and vitreous abnormalities. A predisposition to retinal tears and detachment as well as premature cataract are seen frequently, especially with a family history of cataract. Joint laxity may be seen in the newborn period, but tends to resolve over time. Nearly all patients have radiographic findings consistent with mild spondyloepiphysical dysplasia with or without other spinal abnormalities (scoliosis, kyphotic deformities, spondylolisthesis). Premature osteoarthritis is common, as are complications such as Legg-Perthes disease, slipped epiphysis, or other femoral head abnormalities. Both sensorineural and conductive hearing loss are common in all types of Stickler syndrome, although it is most severe in types II and III. The conductive hearing loss may develop over time due to recurrent ear infections associated with cleft palate or a defect of the ossicles of the middle ear.

**Diagnosis**

Stickler syndrome can be diagnosed on a clinical basis by thorough medical and family history as well as physical examination. Molecular testing is also available for all three collagens involved (*COL2A1*, *COL11A1*, *COL11A2*). Molecular information may be useful in predicting the prognosis for eye involvement as well as for testing other relatives who may be affected.

**Management**

Although Stickler syndrome is a relatively common multisystem connective tissue disorder, it often is unrecognized due to its interfamilial variability. Studies have shown that 10% of patients who had isolated cleft palate and 12% of patients who had Pierre Robin sequence had undiagnosed Stickler syndrome. Early recognition of this disorder can have life-altering medical consequences by preventing early blindness and hearing loss. Affected patients should be followed by an ophthalmologist, audiologist, otorhinolaryngologist, and orthopedist at frequent intervals to ensure prevention and treatment of any complications.

**Suggested Reading**


NeoReviews Quiz

1. Connective tissue disorders are a heterogeneous group of inherited conditions that affect multiple organ systems. Neonatal presentations of connective tissue disorders are highly variable. Of the following, the most common presentation of neonatal connective tissue disorder is:
   A. Abnormal joint mobility.
   B. Abnormal bone shape.
   C. Cardiac lesion.
   D. Facial dysmorphism.
   E. Rash.

2. A term newborn has dolichostenomelia (long arms, hands, legs, and feet), joint contractures of elbows and knees, scoliosis, and a high-arched palate. An autosomal dominant disorder involving extracellular matrix proteins is suspected and confirmed by the finding of mutations in the fibrillin-2 gene on chromosome 5. Of the following, the most likely connective tissue disorder in this infant is:
   A. Beals syndrome.
   B. Larsen syndrome.
   C. Loeys-Dietz syndrome.
   D. Shprintzen-Goldberg syndrome.
   E. Stickler syndrome.

3. A preterm newborn has multiple fractures of long bones, wormian skull, dark blue sclera, and beaked nose. Osteogenesis imperfecta type II is suspected. Genetic molecular tests are ordered for confirmation of the diagnosis. Of the following, the genetic mutation in this infant is most likely to involve the:
   A. ADAMTS2 gene.
   B. Collagen 1A1 gene.
   C. Fibrillin-1 gene.
   D. Filamin B gene.
   E. Transforming growth factor receptor 1 gene.

4. Ehlers-Danlos syndromes (EDS) are a heterogeneous group of syndromes that are characterized by laxity of joints, abnormalities of skin, skeletal changes, cardiovascular anomalies, and ophthalmologic findings. Of the following, the type of EDS most likely to be recognized in the newborn period is:
   A. EDS type I/II (classic).
   B. EDS type III (hypermobile).
   C. EDS type IV (vascular).
   D. EDS type VI (kyphoscoliotic).
   E. EDS type VII (arthrochalasia).
Newborn Presentation of Connective Tissue Disorders
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