The Clinical Presentation of Ehlers-Danlos Syndrome

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Abstract and Introduction

Abstract

Ehlers-Danlos syndrome (EDS), a heterogeneous group of inheritable connective tissue disorders, is attributed to mutations in connective tissue genes. These mutations cause defects in collagen. Collagen, a connective tissue protein that acts like glue, gives strength to the body and provides support and elasticity for movement. Thus, the altered gene affects the mechanical properties of skin, joints, ligaments, and blood vessels. Ehlers-Danlos syndrome is transmitted through autosomal dominant, autosomal recessive, or x-linked patterns of inheritance. The life expectancy of an affected infant varies with the type of EDS. This article provides an overview of the 6 major classifications of EDS, their unique clinical presentations, a focused physical assessment guide, considerations for nursing care, and resources for parents. Ehlers-Danlos syndrome can be a potentially debilitating syndrome. It requires preventative and protective measures starting at birth to preserve joint function to improve infant outcomes. Caring for patients with EDS requires an understanding of the potential associated complications to help minimize the physical and emotional impact of the syndrome and improve the quality of life for affected individuals.

Introduction

Ehlers-Danlos syndrome (EDS) is a group of heterogeneous connective tissue disorders involving the skin, organs, and joints.[1-7] The syndrome is named after Edvard Ehlers, a Danish dermatologist, and Henri-Alexandre Danlos, a French dermatologist, who presented the cases of patients with knee subluxations, joint lesions, hyperextensible skin, and joint laxity to the Paris Society of Syphilology and Dermatology in 1899 and 1908, respectively.[4,8] In 1936, English physician, Frederick Parkes-Weber suggested that the disorder be named Ehlers-Danlos syndrome.[8]

Classification and Prevalence of EDS

Originally there were 10 different classifications of EDS. These classifications were reorganized in 1997 into 6 major types of EDS and an "other types" category was created that encompasses a potpourri of rare forms of EDS that did not fit into the major types (Table 1).[1-7,9-47] This reclassification was aided by the ability to perform biochemical testing. The hypermobility and classical types of EDS are the most common forms of the disorder; however, they are difficult to diagnose in the infant or young toddler due to the general flexibility that all children possess.[7,25]

The estimated overall prevalence of EDS is 1 in 5000, depending on type.[2,3,7,11] It affects males and females of all racial and ethnic backgrounds equally.[5,6] Classical-type EDS occurs in 1 in 10,000 to 1 in 20,000 infants; it is one of the more common forms.[3,10] The EDS gene types may be inherited via autosomal dominant, autosomal recessive, or x-linked patterns of inheritance.[1]

The vascular and kyphoscoliosis types of EDS have more prominent characteristics present at birth and carry the poorest prognosis if unrecognized or untreated.[1,26-28] Facial features in infants with vascular-type EDS could provide clues to the diagnosis and prompt a more focused physical examination and detailed family history. It is also important to identify any sudden or unexpected deaths in first-degree relatives (parents, siblings, offspring).[1] In individuals affected by vascular-type EDS, the average age for arterial rupture is 23 years and the median age of death is 48 years.[28] If EDS is suspected, genetic counseling needs to be provided to the family.

Understanding the Genetics of EDS

Genes exist in pairs and are the blueprints for the development and function of every cell in the body.[2,46] A developing fetus receives one half of each gene pair from each parent, creating a new set of gene pairs that determine the infant's traits. There are 23 pairs of chromosomes: 22 pairs known as autosomes and a pair of chromosomes that determines the sex of an infant.[2]

The classical, hypermobile, vascular, and arthrochalasia types of EDS are inherited in an autosomal dominant manner.[1,7,10,25] Each affected infant has an affected parent. The altered gene is found on an autosome rather than the sex chromosome; therefore, males and females are equally affected.[2] The EDS gene is dominant, requiring only 1 gene to express EDS characteristics.[2,7] If 1 parent has EDS and 1 parent does not, they have a 50% chance of having a child with EDS and 50% chance of having an unaffected child.

Inheritance with the kyphoscoliosis and dermatosparaxis types of EDS is autosomal recessive; therefore, 2 copies of the altered gene must be present for EDS to occur.[1,7,35] Couples who have an affected child have a 25% chance of having another affected child with each subsequent pregnancy.[35,46]

The patterns of inheritance and the type of EDS remain consistent within a family.[2,3,46] A family with classical-type EDS will not develop vascular-type EDS without the introduction of those genes into the family. However, variations in the severity of EDS can occur within a family.

Vascular-type EDS can be identified by mutations in the COL3A1 gene.[1,4,9,29] The COL3A1 gene is 1 of several genes that provide instructions for making the components of collagen. Type III collagen is found in tissues such as the skin, lungs, intestinal walls, and the walls of blood vessels.[29] Currently, there are 320 mutations of the COL3A1 gene identified in vascular EDS.[29]

Complications of Pregnancy and Delivery

Because of the pregnancy-associated risks, and the potential for transmission, the optimal time to determine genetic risk is *before* pregnancy, especially if EDS has already been diagnosed in the family.[5,10,22-26,28,29,35,36,38,39] Genetic counseling for affected adult females is imperative.[2]

Ehlers-Danlos syndrome is associated with miscarriage and antepartum hemorrhage.[16] Pregnancy and postnatal complications are type specific (Table 1). Careful screening and follow-up can help decrease the potential complications of a surgical delivery, anesthesia, and postpartum hemorrhage.

Women with vascular-type EDS are particularly vulnerable to the increases in blood volume and cardiac output associated with pregnancy. Uncontrollable uterine hemorrhage often results in a hysterectomy after childbirth.[28] Pregnancy can be life-threatening, with the potential for gastrointestinal, uterine, or major vessel rupture; there is a 12% risk of death from peripartum arterial rupture or uterine rupture.[1,16,26-28] Women with vascular-type EDS should be considered at high risk and be cared for by maternal-fetal specialists at a high-risk perinatal center.[16]

A retrospective study of 46 Dutch women with EDS reported that pregnancy was well tolerated overall; the main complications in this population were pelvic instability (laxity and subluxation) and associated pelvic pain and postpartum hemorrhage.[22] No studies have justified the use of elective cesarean delivery to decrease mortality with EDS deliveries.[34] Escalated risks from vaginal delivery include extension of the episiotomy incision, tearing of the perineal skin, hematomas, or prolapse of the bladder or uterus related to delivery.[10] Use of forceps or vacuum assistance during the delivery of an infant with known or potential EDS should be avoided because of the risk of infant hematomas and skin lacerations.

Affected infants of mothers with classical- and hypermobility-type EDS have higher rates of premature rupture of membranes,[14,25] and precipitous deliveries (<4 hours).[25] The mechanism of premature rupture of membranes is likely an alteration in the collagen in the chorionic membrane of the affected fetus, which increases the risk of premature rupture of membranes and preterm labor, and ultimately results in preterm birth.[22,43] Premature birth occurs in approximately 50% of the reported cases of mothers with severe classical EDS.[10]

Breech presentation, potentially related to hypotonia, is also more common with an affected infant.[14,22] Other fetal malpositions (face and brow) as well as growth restriction have been reported with hypermobility-type EDS.[20,23,24]

Anesthesia during labor and delivery presents unique maternal risks for women affected with EDS. Epidural anesthesia may be technically difficult because of maternal skeletal abnormalities.[9] With general anesthesia, there is an escalated risk of injury to the cervical spine during intubation due to lax ligaments in the neck, as well as an increased risk of pneumothorax associated with positive pressure ventilation.[34]

Focused Physical Assessment

It is important to identify infants of affected women as high-risk infants. Scrutinize the maternal history and, when possible, determine the specific EDS type of the mother or affected family members. Although there may be variations in presentation, the type will remain consistent and may be useful in predicting risk. Early evaluation of an infant exhibiting major or minor criteria of EDS (Table 2) is a priority. Delivery room resuscitation and respiratory support may be necessary due to prematurity and/or hypotonia.

Compare the infant's overall tone and appearance to expectations appropriate for the infant's gestational age. Infants with classical-type EDS present with intrauterine growth restriction and/or prematurity.[9,34] The infant's general appearance may be similar to that of the infant with classic asymmetrical intrauterine growth restriction, including a normal occipital-frontal head circumference and a body that appears wasted by comparison (Fig 1). In contrast, infants affected with kyphoscoliosis-type EDS have a Marfan-like appearance, where the limbs are disproportionately longer than the rest of the body.[36]

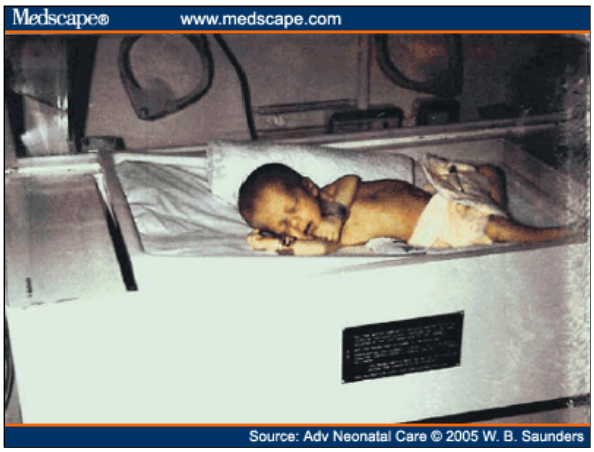

Figure 1.

Preterm infant born at 36 weeks gestation. Note the generalized lack of muscle tone and wizened facies characteristic of intrauterine growth restriction. Courtesy of K.H. Franklin. Reprinted with permission.

Skin Assessment

Examine the quality of the skin. Infants with classical and hypermobile EDS have skin that feels soft and velvet-like, a feature that is lifelong. The skin texture has also been described as doughy.[1,2,7,10] Note the presence, and pattern of distribution of ecchymosis. Dermatosparaxis-type EDS, presents with severe skin fragility and bruising.[1,4,39] Ongoing bruising and skin tears can be misdiagnosed as child abuse.[6]

Both classical and vascular types of EDS are characterized by translucent skin with prominent veins.[1] Relate these findings to norms for gestational age. In vascular-type EDS, veins are clearly visible on the thorax, shoulders, and abdomen.[9,26-28] Although the skin is fragile and bruises easily with both types, coagulation studies will be normal.[1,26] Observe for signs of acrogeria (the appearance of aging) on the hands and feet. In vascular-type EDS, the hands and feet may appear wrinkled and old.[1,26,28]

Observe for skin that splits easily, a finding common in classical- and hypermobility-type EDS. Gaping "fish mouth" type scars may occur over bony prominences. Inspect the forehead, chin, elbows, or knees for scarring.[1] The bruising and scarring will become more noticeable as the infant ages and becomes mobile. There are often severe scars, called cigarette paper scars, which resemble papyrus paper (Fig 2).[1,10,16,25] Slow wound healing with scars that widen after healing can be seen during the toddler years (Fig 3).[41] Palpate pressure points for mulluscoid pseudotumors, fleshy lesions associated with scars that develop over the pressure points (e.g., shins).[1,3,6,10]

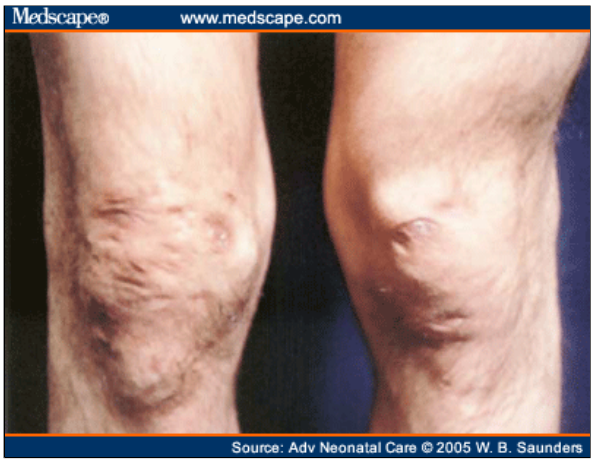

Figure 2.

Note the cigarette paper scars on both knees and the thin and fragile appearance of the skin. Courtesy of and reprinted with permission from eMedicine.com, Inc, 2005. Ceccolini E, Schwartz RA. Ehlers-Danlos Syndrome. eMedicine Journal [serial online]. 2005. Available at: http://www.emedicine.com/derm/topic696.htm.

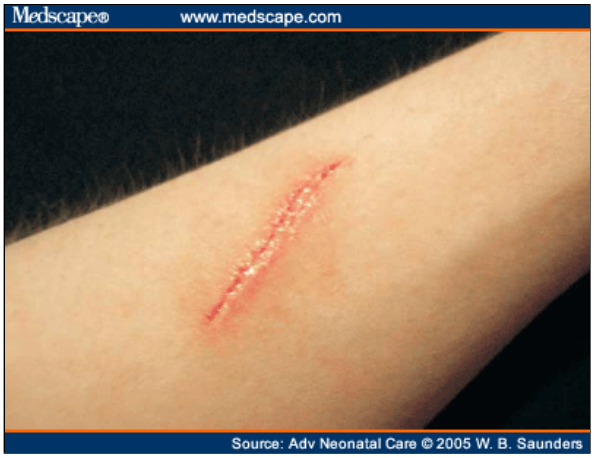

Figure 3.

Widened scarring and slow wound healing characteristic of EDS. Courtesy of Jo Husband. Reprinted with permission.

Inspect and palpate for piezogenic papules, which can be seen in classical-type EDS as early as birth. Piezogenic papules are small, soft lumps that appear on the side of the heel when the person is standing but which disappear when the foot is elevated.[1,10] Small, mobile, spherical hard bodies are palpable and may be present on the forearms or shins.[1,2,5,6] These can calcify and be visible on radiographs.[5,10] Spheroids develop over time as subcutaneous fat necrosis occurs.[44]

The skin of an infant with classical-type EDS has hyperextensible or hyperelastic properties not seen as a manifestation of vascular-type EDS.[1,26] To accurately assess for hyperextensible skin, test the skin in a neutral site such as the palm side of the forearm.[1,10] Pull the skin up until resistance is felt. Hyperextensible skin extends easily and snaps back after releasing it. Hyperelasticity is more easily noted at the neck, elbows, or knees (Fig 4).[1] This is in contrast to the presentation of cutis laxa, where the skin lacks elasticity, hangs in loose folds, and does not rebound rapidly after extended.[10] This test may be difficult to perform in newborns because subcutaneous fat may impair the assessment.

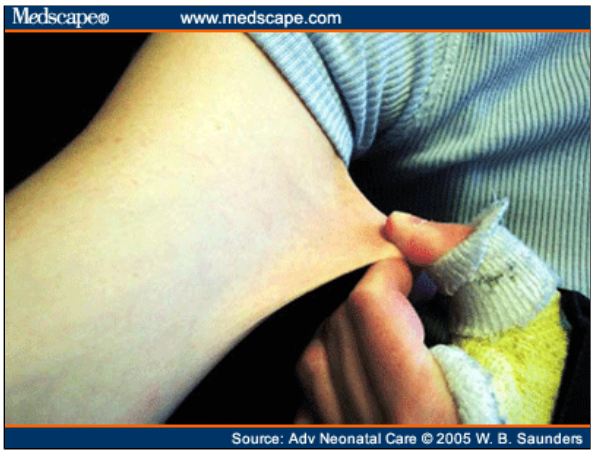

Figure 4.

Testing for hyperelastic skin at the palm side of the arm. Courtesy of Jo Husband. Reprinted with permission.

Facial Features

The infant with vascular-type EDS has distinctive facial features. Observe for bulging eyes with telangiectasis (dilated capillaries forming a red lesion) on the eyelids.[1,25,26,30] Examine the infant for epicanthal folds (redundant skin folds on the eyelids)[1,41] that may make the nose appear broad.[28] Facial bones may be prominent with sunken cheeks as well as thin, fine upper lips that are unpuckered in appearance.[26] The infant with kyphoscoliosis-type EDS will have scleral fragility. Minor trauma can cause rupture of the ocular globe.[1,35] Examine the size of the eyes, specifically evaluating for small corneas.[1,35,36] Inspect the nose for a proportionately large and thin "pinched" appearance.[26] Inspect the scalp hair distribution, which may be thin in affected infants. Inspect and palpate the earlobes; lobeless ears may be present in infants with vascular-type EDS.[31,41]

Cardiorespiratory Assessment

Auscultate the lung fields and observe for signs of respiratory distress, such as nasal flaring, grunting, retractions, or decreased air exchange that may indicate a pneumothorax. Newborns with vascular-type EDS are at risk of developing a spontaneous pneumothorax.[28] If a murmur is present in the newborn period, a pediatric cardiology consultation and an echocardiogram are indicated to evaluate for dysplastic valves (mitral and tricuspid), a dilated aorta or pulmonary trunk, or heart failure.[45]

Aortic root dilation has been reported in classical and hypermobile types of EDS in children <15 years old.[19] These cardiac findings were in contrast to former studies where mitral valve prolapse was the most common cardiac finding in EDS.[19] In the absence of cardiac symptoms or a murmur, at a minimum, the aortic root size should be measured by 5 years of age with repeat echocardiograms every 5 years even if the original echocardiogram is normal.[35]

Abdominal and Genitourinary Findings

Inspect the abdomen and groin for inguinal hernias or a large umbilical hernia.[1,39] Palpate the abdomen and bladder. Observe for lower abdominal tenderness. If possible, observe the strength of the urinary stream, especially in male infants. A weak urinary stream despite a full bladder associated with tenderness may warrant further investigation. Male children with EDS are at increased risk of giant bladder diverticula, which may cause urethral obstruction.[17]

Musculoskeletal Involvement

Examine the feet for talipes equinovarus (clubfoot).[1] Up to 12% of neonates born with vascular-type EDS have a clubfoot and 3% have congenital dislocation of the hips.[26,28,39] Joint hyperlaxity dislocatabilty is a common feature of EDS (Figs 5 and 6).[1,10] Evaluate the infant's overall tone and posture. Assess the joints for stability using Beighton's criteria (Table 3). A score of at least 5 out of 9 defines hypermobility.[1,2,10] Be alert for dislocated hips or shoulders, which may be associated with breech presentation and delivery in infants affected with classical-type EDS.[10,38]

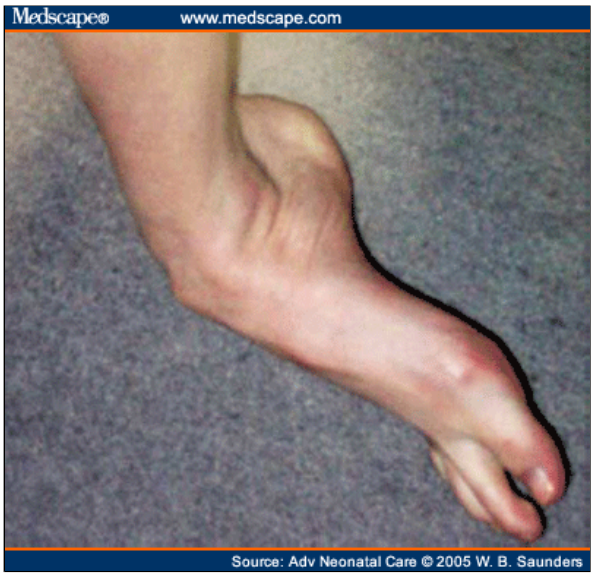

Figure 5.

Right ankle hypermobility. The ankle turns inward beyond the normal range of motion. Courtesy of Jo Husband. Reprinted with permission.

Figure 6.

Hyperflexible finger in a neonate. Courtesy of David A. Clark. *Atlas of Neonatology: A Companion to Avery's Diseases of the Newborn.* Philadelphia, Pa: WB Saunders; 2000. Reprinted with permission.

Kyphoscoliosis-type EDS presents with joint laxity and severe muscle hypotonia at birth.[1,4,35,38] Examine the spine carefully. Kyphoscoliosis, characterized by progressive deformity of the spine consisting of lateral and posterior curvatures, is present at birth and progressively worsens.[35,38]

Differential Diagnosis of EDS

There are many varieties of EDS making the differential diagnosis challenging. Other causes of hypotonia or fragile skin must also be considered. These include:

- Cutis laxa syndromes (inelastic skin that hangs in redundant folds)
- Marfan syndrome
- De Barsy syndrome (acrogeria, mental retardation)[10]
- Familial joint hypermobility syndrome
- Tenascin X deficiency

In adults the joint pain and fatigue associated with hypermobility-type EDS can be misdiagnosed as chronic fatigue syndrome, hypochondriasis, or depression.[25] Vascular-type EDS may also be confused with the kyphoscoliosis type.

Diagnosis of EDS is based on family history and clinical examination.[1-3,10,25,28,35] The presence of 1 or more major criteria is necessary for clinical diagnosis.[35] Minor criteria are less specific indicators; however, the presence of 1 or more minor criteria aids in delineating the specific type of EDS.[1,2,10,25,28,35]

If the infant has suspicious findings, explore the family history to identify any other family members who have major or minor diagnostic criteria of EDS

(Table 2). The physical manifestations of EDS evolve over time (Fig. 7A-F). See Sidebar 1 for one family's story. A genetics referral, along with a complete pedigree and careful examination of parents, siblings, or other family members may be useful. This will allow the care team to focus concerns to a specific type of EDS using the major and minor diagnostic criteria.

Diagnosis should be confirmed by laboratory testing whenever possible.[1,2,10,25,28] Obtaining the correct biochemical or molecular genetic tests is the final step in the diagnostic process. A skin biopsy will show structural defects in the pro-alpha1 or pro-alpha2 type III collagen.[1,29] Classical-type EDS will have abnormal electrophoretic mobility of the collagen.[1]

Figure 7.

The series of pictures of David Daniel Bowen III, who has vascular-type EDS, provide a very real face to a rare syndrome. The features of EDS may not be immediately recognizable in infants at birth; however, caregivers may note the compatible features in the parents, siblings, or other family members. The physical features often become more prominent over time; Fig 7A-F illustrate the changing face of EDS over time.(A) Birth photograph. Note the large eyes, lobeless ears, and small mouth. David also had bilateral inguinal hernias, hydroceles, cryptorchidism, and hypospadius that were corrected at 6 months of age.(B) David at 5 months of age. Again note the characteristic lobeless ears; his earlobe appears to attach directly to the head.(C) David at 2 years of age; note the thin pinched appearance to his nose that is more prominent now that he has lost his "baby fat." The lobeless ears are still apparent.(D) David at age 5, playing in the bathtub; note the thin skin and prominent veins on his chest wall.(E) David in 6th grade; note how his face has evolved, his nose now has the more classic pinched appearance. He also has strikingly large eyes and thin lips.(F) David at age 13.5 years of age: The eyes, nose, lips, and ears are all consistent with vascular-type EDS. David ultimately died from complications related to surgery for spontaneous bowel perforation. He was not seen by a geneticist until days before his death. At that time the diagnosis of EDS was suspected and later confirmed by biopsy (EDS Type IV). Genetic testing of mother, father, and a female sibling were all negative suggesting a spontaneous new mutation of EDS. David's memory lives on. His mother continues to be a strong advocate striving to increase education and awareness of EDS around the world. Photographs courtesy of David's mother Cathy Bowen, with permission.

Prognosis

Prognosis is dependent on the type of EDS involved. Early diagnosis of vascular-type EDS may improve life expectancy. Sudden death from vascular rupture or perforation is not uncommon.[28,31,33] Vascular complications are not limited to adults. Investigation of a basilar arterial aneurysm in a 5-year-old child revealed that she had vascular-type EDS.[32] Vascular-type EDS should be considered part of the differential diagnosis of cerebral vascular accidents or strokes in infancy and early childhood.[32]

Individuals with classical- and hypermobile-type EDS have a normal lifespan.[10,25] People affected by kyphoscoliosis-type EDS may have a normal lifespan; however, in the most severe cases, they are at risk of respiratory compromise and arterial rupture.[35] The severe hypotonia in kyphoscoliosis-type EDS leads to motor developmental delays.[35] By the second or third decade of life, many of these patients are unable to walk.[1]

Nursing Care of Infants With Suspected EDS

Ehlers-Danlos syndrome is a chronic condition. Parents will need accurate information regarding their infant's care. Resources about EDS and information on support groups may be useful for parents, day care providers, family members, and later teachers and friends (Table 4).[43]

A general understanding of EDS is important in caring for the infant and family.[2] An infant suspected of having EDS will require careful handling to

prevent bruising during procedures. The joints, particularly the shoulders and hips, need to be supported and protected during repositioning and handling.[46]

Treatment in most types of EDS is limited to therapies that manage or minimize symptoms. A multidisciplinary team approach, with careful collaboration between nurses, social workers, physical therapists, orthopedists, surgeons, pain control specialists, cardiologists, and the genetics team, is required.[46]

Early intervention with physical therapy and a developmental clinic will ensure the best possible future for the infant. Hypermobility and dislocations of the small joints of the hand are common. Over time, this leads to problems with gripping and strength. Depending on the type of EDS, braces to stabilize joints and physical and occupational therapy to help strengthen muscles and preserve their mobility may be required.[2,25] Physical therapy can strengthen large muscle groups and help prevent recurrent shoulder dislocation.[2,35] Affected individuals should avoid activities that hyperextend or lock a joint.[46] Children may intentionally put their body in strange or unusual positions to entertain others.[2] These types of maneuvers put them at risk of joint degeneration, and affected children need to be educated from an early age to preserve their body and joint function.

The infant that is starting to crawl or the unstable toddler needs to wear protective gear (headgear, elbow pads, knee pads, and shin pads) to prevent damage to their fragile skin.[6,10] Simple safety measures, such as padding the edges of coffee tables and sharp corners, will help safeguard fragile skin. Prevention of scarring and disfigurement is important.[3] Daily vitamin C supplements may improve wound healing and bruising.[5]

If surgical intervention is required, wound closure and healing can be a challenge. Dermal wounds should be closed without tension and deep stitches should be applied generously.[10] Cutaneous stitches should be left in place twice as long as usual; in addition, the adjacent skin may be taped to help support the approximation of the incision and prevent stretching of the scar.[10]

Children with EDS may need to avoid physically stressful activities and contact sports to prevent joint strain and damage.[2] Swimming, a non–weight-bearing activity, will not stress the joints yet helps with muscle development and coordination in infants and children. It can be initiated in infancy by the parents.[10,25] Stationary bicycling, golfing, or walking are other recommended forms of exercise for older children and adults.[35]

Cardiac problems are associated with both classical- and hypermobile-type EDS. Individuals with mitral valve prolapse and/or regurgitation require antibiotic prophylaxis to prevent bacterial endocarditis before dental or surgical procedures.[10] An unusually high prevalence of aortic dilation (28%) in individuals affected with both these types of EDS has been reported.[19] An increased risk of aortic dissection is associated with this significant dilatation.[25] Baseline echocardiograms should be initiated at age 5 to measure aortic diameter,[10,35] and follow-up should occur every 3 to 5 years depending on severity.[25]

Affected young adults may be otherwise healthy and become frustrated and experience self-doubt that limits their self-actualization.[48] Emotional support and behavioral and psychological therapy may be necessary to help the individual cope and accept this condition.[14]

Chronic pain is a serious complication of classical and hypermobility-type EDS. It can be both physically and mentally disabling; may present caregiving challanges for affected mothers.[25,47] This pain is described as an aching, throbbing pain similar to the pain associated with fibromyalgia; however, it is distinctly different from the pain associated with joint dislocations.[25] The neuropathic etiology of the pain explains the burning, shooting, tingling, electrical-type pain often described.[25] Migraine headaches, caused by cervical muscle tension and temporomandibular dysfunction, are also common.[25] Osteoarthritis or degenerative joint disease presents earlier in those with EDS and compounds the chronic pain.[25] Treatment involves the use of analgesics and nonsteroidal anti-inflammatory drugs.[6,25] Topical anesthetics such as lidocaine may be useful for localized pain as well.[25]

Conclusions

Ehlers-Danlos syndrome can present in the newborn period. The 6 major types of EDS explain the wide variation in presentation and clinical findings. Early genetic counseling will help couples make the appropriate reproductive decisions. If an infant presents with suspicious clinical findings, classification of his or her symptoms based on the major and minor diagnostic criteria should be attempted. If the family history is positive, the EDS type will be useful in further focusing the evaluation. Whenever possible, laboratory confirmation of the diagnosis is recommended. Understanding each type of EDS and the type-specific problems will help the multidisciplinary healthcare team meet the infant's needs and provide anticipatory guidance and support for the family. The ultimate goal is to preserve and optimize quality of life for the individual with EDS.

Table 1. Comparing and Contrasting Types of Ehlers-Danlos Syndrome[1-7,9-47]

Current Classification EDS Type	Prevalence	Inheritance Pattern	Gene(s) Mutation Responsible	Gene Function	Diagnosis Confirmed By	Clinical Features	Maternal/Pregnancy Complications
Classical (Formerly known as Type I Severe classic type, gravis type Type II Mild classic type, mitis type)	Affects 20,000 to 40,000 people	Autosomal dominant	Chromosome 17 COL1A1 (collagen, type 1, alpha 1)	Provides the genetic instructions to make collagen	Family history and clinical examination Targeted mutation analysis for a specific mutation, available only in research labs	• Skin hyperextensibility • Intrauterine growth restriction • Joint hypermobility • Redundant skin folds, eyelids • Skin scarring (fish mouth or cigarette paper scars) • Congenital diverticula of the bladder (typically males; rare but reported in females) • Inguinal hernias (males)	• Preterm labor • Scoliosis (problems with anesthesia) • PROM • Atonic uterus at cesarean birth
			Chromosome 7 COL1A2 (collagen, type 2, alpha 2)	Same			
			Chromosome 9 COL5A1 (collagen, type 5 alpha 1)	Same			
			Chromosome 2 COL5A2 (collagen, type 5, alpha 2)	Same			
Hypermobility (Formerly known as Type III)	Most common type Affects 1 in	Autosomal dominant	No known gene Diagnosis is by clinical	Same as above Provides	Family history and clinical examination and presenting	• Smooth, velvety skin • Easy bruising • Joint	• Preterm labor • Postpartum hemorrhage

	10,000 to 15,000 people		examination only A small subgroup of individuals have been found with TNCB (tenascin XB) located on chromosome 6	the instructions for making the protein tenascin-X	symptoms such as recurrent joint dislocations, chronic joint and limb pain	hypermobility with unusual range of motion • Inguinal hernias (males)	
Vascular (Formerly known as Type IV Ecchymotic type, arterial type)	Affects 1 in 100,000 to 200,000 people Most serious form of EDS due to arterial or major organ rupture. Risk of sudden death in the 3rd or 4th decade of life	Autosomal dominant	Chromosome 2 COL3A1 (collagen, type 3, alpha 1) 320 mutations of this gene have been identified	Creating procollagen for strength in the connective tissues of skin, lungs, intestinal walls, and blood vessel walls	Skin biopsy for collagen analysis for abnormal electrophoretic mobility Sequence analysis testing to identify mutations available for genetic counseling	• Distinctive facial features • Thin translucent skin over the chest and abdomen • Acrogeria • Lobeless ears • Respiratory distress suggestive of pneumothorax • Short stature	• Uterine fragility or rupture • Postpartum arterial bleeding • Vaginal or perineal tears during delivery • Wound dehiscence possible after a cesarean birth • High maternal mortality (25%) • Pneumothorax
Kyphoscoliosis (Formerly known as Type VI Ocular-scoliotic)	<60 cases reported worldwide	Autosomal recessive	Chromosome 1 PLOD (procollagen-lysine, -2-oxoglutarate 5-dioxygenase)	Lysyl hydroxylase adds hydroxyl groups to lysines (amino acids) in collagen	Urine test to detect increased ratio of deoxypyridinoline to pyridinoline cross-links	• Joint laxity and severe muscle hypotonia at birth • Kyphoscoliosis is present at birth • Scleral fragility and rupture of the ocular globe • Marfan-like appearance	• Scoliosis • Measurement of lysyl hyroxylase in the amniotic fluid may predict the outcome of an infant
Arthrochalasia (Formerly known as Type VIIA Type VIIB)	30 cases reported worldwide	Autosomal dominant	Chromosome 17 COL1A1 Chromosome 7 COL1A2 Most cases occur with no family history (spontaneous mutations)	Genetic instructions to make collagen	Electrophoresis and mutation analysis	• Congenital bilateral hip dislocation • Severe generalized joint hypermobility with recurrent subluxations	
Dermatosparaxis (Formerly known as Type VIIC)	Rarest form; only 10 cases reported worldwide	Autosomal recessive	Chromosome 5 ADAMTS-2 (a disintegrin-like and metalloprotease reprolysin type with thrombospondin type 1 motif, 2)	Initiates the production of several procollagen proteins	Electrophoresis	• Severe skin fragility and bruising • Doughy, sagging, redundant skin (especially facial) • Large umbilical hernia • Blue sclera • Short stature, dwarfism	• PROM
Other (Formerly known as Type V)	Rare, only described in 1 family	X-linked recessive	Unknown	Unknown	Family history		• Tissue fragility • Scoliosis
Type VIII	Rare	Autosomal dominant	Similar to classical type	Unknown	Uncertain	• Periodontal friability, loss of teeth by age 30	
Type IX (occipital horn syndrome)	Rare	X-linked recessive allelic to Menkes syndrome	Unknown	Abnormal copper utilization	Decreased copper and ceruloplasmin levels	• Mildly extensive skin, occipital horn-like exostosis short humeri, short clavicles, bowed long bones, chronic diarrhea, bladder diverticulae	
Type X	Rare, only described in 1 family	Autosomal recessive	Unknown	Unknown	Family history	• Joint hypermobility • Poor wound healing • Platelet aggregation defect	

PROM, premature rupture of membranes.

Table 2. Comparing and Contrasting the Major and Minor Diagnostic Criteria for Ehlers Danlos Syndrome By Type [1,2,10,25,28,35]

EDS Type	Major Diagnostic Criteria	Minor Diagnostic Criteria
Classical	Skin hyperextensibility, widened atrophic scars, joint hypermobility	• Positive family history
		• Physical findings include smooth velvety skin, mulluscoid pseudotumors, subcutaneous spheroids, complications of joint hypermobility (sprains, dislocations/subluxations), muscle hypotonia, delayed gross motor development, easy bruising, tissue extensibility, fragility, surgical complications
Hypermobility	Skin involvement (either smooth/velvety skin or hyperextensibility), generalized joint hypermobility	• Positive family history
		• Physical findings include recurring joint dislocations, chronic joint/limb pain
Vascular	Thin translucent skin, arterial/intestinal/uterine fragility or rupture, extensive bruising, characteristic facial appearance	• Positive family history, specifically sudden death of a close relative(s)
		• Physical findings include acrogeria, hypermobility of small joints, tendon and muscle rupture, clubfoot, early onset varicose veins, arteriovenous, carotid-cavernous sinus fistula, pneumothorax/pneumohemothorax, gingival recession
Kyphoscoliosis	Generalized joint laxity, severe muscle hypotonia at birth, scoliosis at birth, scleral fragility, rupture of the ocular globe	• Positive family history (e.g., affected siblings)
		• Physical findings include tissue fragility, atrophic scars, easy bruising, arterial rupture, marfanoid habitus (Marfan-like), microcornea, osteopenia on radiograph
Arthrochalasis	Severe generalized joint hypermobility with recurrent subluxations, congenital bilateral hip dislocation	• Physical findings include skin hyperextensibility, tissue fragility, atrophic scars, easy bruising, muscle hypotonia, kyphoscoliosis, osteopenia on radiograph
Dermatosparaxis	Severe skin fragility, sagging redundant skin	• Physical findings include soft, doughy skin, easy bruising, premature rupture of fetal membranes, large hernias (umbilical or inguinal)

Table 3. Beighton's Criteria for Joint Hypermobility[1,2,46]

Joint Assessment	One Extremity	Both Extremities
Passive dorsiflexion of the little finger >90°	1	2
Passive flexion of thumbs to the forearm	1	2
Hyperextension of the elbows beyond 10°	1	2
Hyperextension of the knees beyond 10°	1	2
Forward flexion of the trunk with knees fully extended and palms resting on the floor	1	NA

NOTE. Beighton's Criteria is used in both children and adults to assess 5 different joint mobility performances with a maximum score of 9. A score of 5 is the minimum score suggestive of joint hypermobility.

Table 4. Ehlers-Danlos Syndrome Resource List for Parents and Professionals

Resource	Description of Contents
Canadian Ehlers-Danlos Association www.ehlersdanlos.ca 88 De Rose Ave Bolton, Ontario, Canada L7E 1A8 Phone: 905-951-7559 Fax: 905-761-7567	Information about EDS, list serves, personal web pages, links to other sites and a forum for posting questions.
Ehlers-Danlos National Foundation www.ednf.org 3200 Wilshire Blvd. Suite 1601, South Tower Los Angeles, Calif 90010 Phone: 800-956-2902 Fax: 213-427-0057	General information about EDS with a well-developed guide for educators and parents. Numerous links to other websites. Publishes a quarterly newsletter titled *Loose Connections* that provides current information on medical advances in EDS, updates on the activities of the Foundation, and valuable information on living with EDS.
Ehlers-Danlos Support Group www.ehlers-danlos.org PO Box 335 Farnham Surrey GU101XJ, England Phone: (44) 1252-690-940	A registered charity, run by volunteers, many of whom are affected by EDS. The website is designed to share medical information about EDS, to provide links to various support groups, and opportunities to share coping strategies and personal experiences. They also highlight the latest research and offer a variety of publications.
Online Mendelian Inheritance in Man www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM	Search for EDS: this site gives detailed and highly technical genetic descriptions for origins of various EDS types with an emphasis on the current progress related to gene mapping of these disorders.

EDS Today www.edstoday.org	A nonprofit organization that provides a wealth of information, article links, and support group information aimed at individuals and the medical community.
NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases www.niams.nih.gov/hi/topics/connective/connective.htm 1 AMS Circle Bethesda, Md 20892-3675 Phone: 301-496-8188 or 877-226-4267	Easy-to-read fact sheets written for consumers with detailed information about connective tissue diseases. A government publication, freely accessible and without copyright restrictions.
National Organization for Rare Diseases www.rarediseases.org 55 Kenosia Ave PO Box 1968 Danbury, Conn 06813-1968 Phone: 203-744-0100 Fax: 203-798-2291	Listings and descriptions of EDS of all types. Houses a database of >2000 organizations and sources of help for patients with rare diseases and searchable data base of >1150 rare diseases. Also accepts e-mail queries from patients who are having problems accessing services, or those who have questions related to genetic inheritance.
National Institutes of Health www.genetests.com or www.geneclinics.org	Contains the link to *GeneReviews*, which provides peer-reviewed information about all types of EDS as well as links to lab analysis through Gene tests.

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Sidebar 1: Putting a Face to Vascular Type EDS: A Mother's Story. By: Cathy Bowen

Editor's Note
The following story illustrates the importance of both taking a complete family history, and of really listening to the details of the story. David's pictures (Figs 7A-F) illustrate the changing face of EDS. David's history, as recounted by his mother, also provides some very important clues to the diagnosis of EDS. We thank this mother for her insights, and we heed her important reminder to look and listen ever so carefully to our patients and their parents.—MBF

David Daniel Bowen III was born March 31, 1982 after my water broke prematurely and I went into labor at 36 weeks gestation. He weighed 4 lbs 5 oz (1956 grams), was 17 ½ inches long, and his head measured 12 ¾ inches. The doctors evaluated David and decided that because of his head size he was actually small for gestational age and closer to 39 weeks. David was born with thin, translucent skin on his chest and abdomen that persisted throughout his life. He had bilateral inguinal hernias, cryptorchidism, bilateral hydroceles, and hypospadias. His hips were also rotated inward at birth later causing him to toe-in when he learned to walk. David also had a small mouth with a high arched palate, cross bite, and crowded teeth.

David was active in all sports; he especially loved hockey, karate, and basketball. However, he seemed to have a propensity for injuries. He had stitches in his scalp that would not hold. A dog bite under his right eye took 40 internal and external stitches. This wound healed without problems. Later an elbow wound developed into a deep cigarette paper scar. When he was 10 years old he tore his anterior cruciate ligament and had to wear a knee brace.

David had bowel problems. He could only stool every 2 to 3 days and would pass blood and mucous with large formed stools. At 13 ½ years of age he had a spontaneous sigmoid colon rupture and developed peritonitis and marked inflammation of the small bowel. This required a colostomy repair. His surgeon said this perforation was unusual; he had not seen it before and he did not understand the cause. Unfortunately, because of the perforation, the surgeon raised the question of abuse and a social worker conducted a child abuse investigation. Needless to say, no evidence was found. Although 5 different physicians were consulted no one gave David a diagnosis; he was treated like a normal healthy boy.

David recovered slowly after his surgery. On his eighth postoperative day when the intern was removing the staples from his incision, the skin spread apart and bled like a fresh wound. They placed adhesive strips on the wound edges and David was discharged home a day later. Postoperatively, David returned to the surgeon's office 3 times in the first 2 weeks because of complaints of extreme gas pain, loss of appetite, weight loss, pain under his right rib area, a pulling sensation, and right lower chest discomfort that interfered with taking a deep breath. The 5.5-inch vertical incision spread to 1.5 inches wide, and required recurrent cauterization to the wound edges. It took a long time to heal; however, these symptoms were not recognized as atypical. Four months later, David returned to surgery for an end-to-end reanastomosis that was complicated by multiple adhesions. The reanastomosis failed; David developed septic shock and was transferred to another facility for emergency surgery. On July 8, 1996, David died.

Shortly before his death David was first examined by a geneticist. She felt that he had a connective tissue disorder called Ehlers-Danlos syndrome type IV (now reclassified to EDS vascular type). David had a skin biopsy done confirming that this was a spontaneous "new" mutation of vascular-type EDS.

We remain completely devastated by David's loss even years later. Every day remains a struggle. No one can fathom the magnitude of these feelings unless they have lost a child this way. Our family tries to use our grief for David in a positive way, to bring education and awareness to others. Our hope is that we can prevent another family from having to endure what happened to us.

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The author gratefully thanks Mary Puchalski, RNC, MS, APN/CNS, for her assistance with the photographs for this article. This article is dedicated to Kali, Jo, and Cathy for sharing their pictorial definitions of EDS in the hopes of helping others. This article is also dedicated to Alberta Parish, RN, mother, and mentor. You always knew that I could accomplish any goal I strived for and you were right.

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