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A "Hyperextensive" Review of Ehlers-Danlos Syndrome

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Ehlers-Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders characterized by hyperextensibility, delayed wound healing, joint hypermobility, thin skin, easy bruising, tissue fragility, "cigarette-paper" scarring over bony prominences, mitral valve prolapse, and other findings. There are 6 main types of EDS. Regardless of presentation as a chief concern or an incidental finding, physicians should be aware that the prominent skin findings of EDS are cutaneous signs of an important systemic disorder.

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Ehlers-Danlos syndrome (EDS) is a genetic disease first described by the Danish dermatologist Edvard Ehlers[1] in 1901 as a state of hyperelasticity of the skin whereby the patient is prone to excessive bruising. The French dermatologist Henri Alexander Danlos[2] reported on molluscoid or fibrous pseudotumors involved in the syndrome in 1908. In 1934, the condition was named *Ehlers-Danlos syndrome* by Pomeau-Delille and Soulie.[3] Ehlers-Danlos syndrome was further described by Parkes Weber[4] in 1936 as having the following 3 cardinal features: hyperextensibility of the skin, looseness of the joints, and friability of the skin and blood vessels. Its prominent skin findings should be recognized, as they are cutaneous signs of an important systemic disorder.

Epidemiology and Etiology

Ehlers-Danlos syndrome is a rare spectrum of inherited skin disorders with a prevalence commonly estimated to be between 1 in 10,000 to 1 in 20,000 live births worldwide.[5] It may affect as many as 1 in 5000 individuals, as it is underdiagnosed because of variability of clinical expression among individuals, even within families. There appears to be no racial predisposition to this syndrome, which is found worldwide.[6]

Ehlers-Danlos syndrome is attributed to specific mutations in the genes coding collagen types I, III, and V, as well as genes for enzymes responsible for collagen synthesis and processing.[7] In 1998, EDS was divided into 6 major subtypes with various modes of inheritance.[8] The specific categories according to the Villefranche classification system are classical (types I and II), hypermobility (type III), vascular (type IV), kyphoscoliosis (type VI), arthrochalasia (types VIIa and VIIb), and dermatosparaxis (type VIIc)(Table 1). Autosomal dominant inheritance accounts for the incidence of the classical, hypermobility, vascular, and arthrochalasia subtypes. The kyphoscoliosis and dermatosparaxis groups are inherited in an autosomal recessive fashion. Approximately 90% of patients with EDS have either the classical or hypermobility subtype.[9] Less than 10% of patients with EDS have the vascular subtype, and the other 3 subtypes make up a very small percentage of total EDS prevalence.[10]

The spectrum of EDS diseases is a consequence of an underlying defect in fibrillar collagen metabolism.[7] Several mutations in different types of collagen and related processing enzymes have been identified and established as clear causes of EDS. Specific gene mutations include collagen V alpha-1 gene, *COL5A1;* collagen V alpha-2 gene, *COL5A2;* collagen III alpha-1 gene, *COL3A1;* collagen I alpha-1 gene, *COL1A1;* and collagen I alpha-2 gene, *COL1A2,* as well as mutations in lysyl hydroxylase and procollagen N-peptidase, enzymes responsible for collagen synthesis and processing.[7] Collagen provides support and elasticity for movement of the body, and a defect in the synthesis of

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Table 1.

Villefranche Classification System of 6 Major Subtypes of EDS

Villefranche Name	EDS Type	Inheritance	Genetic Defect
Classical	Gravis (I), mitis (II)	AD	*COL5A1/COL5A2*
Hypermobility	III	AD	Unknown
Vascular	IV	AD	*COL3A1*
Kyphoscoliosis	VI	AR	Lysyl hydroxylase
Arthrochalasia	VIIa/VIIb	AD	*COL1A1/COL1A2*
Dermatosparaxis	VIIc	AR	Procollagen N-peptidase

Abbreviations: EDS, Ehlers-Danlos syndrome; AD, autosomal dominant; *COL5A1,* collagen V alpha-1 gene; *COL5A2,* collagen V alpha-2 gene; *COL3A1,* collagen III alpha-1 gene; AR, autosomal recessive; *COL1A1,* collagen I alpha-1 gene; *COL1A2,* collagen I alpha-2 gene.

Data from Beighton et al.[8]

this connective tissue can affect the mechanical properties of skin, joints, ligaments, and blood vessels.[11] The specific gene involved determines the subtype of EDS and ultimately the actual clinical manifestations of the disease.

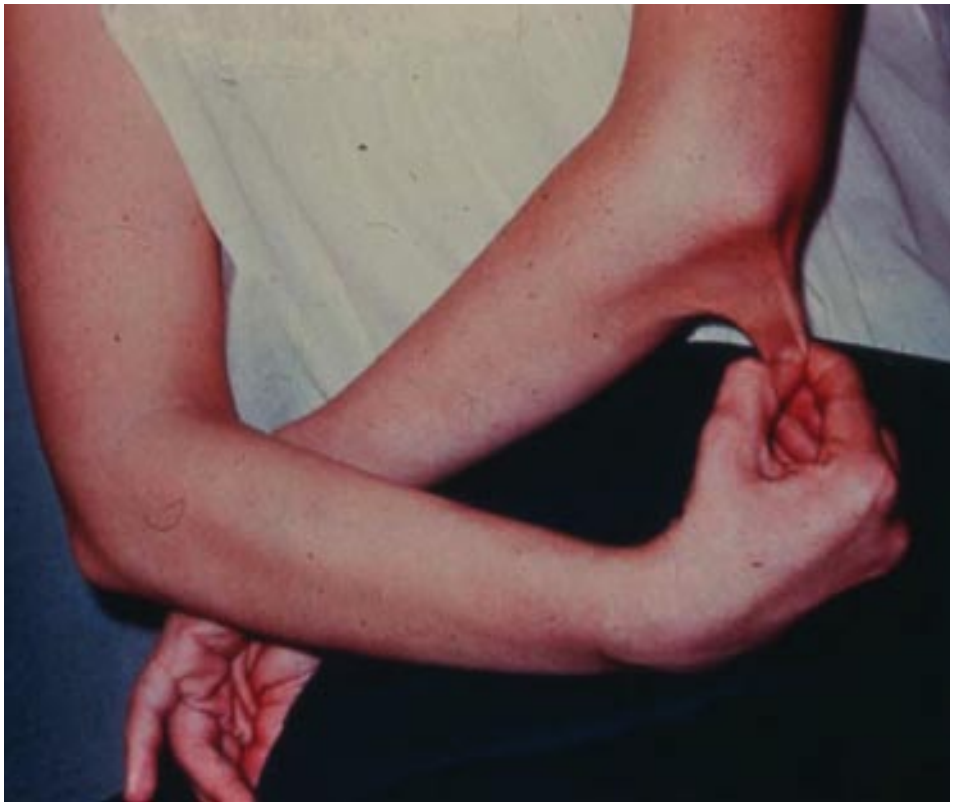
Clinical Features

The clinical manifestations of EDS largely depend on its specific subtype. However, skin hyperextensibility, delayed wound healing with atrophic scarring, joint hypermobility, bruising easily, and generalized connective tissue fragility are present to varying degrees in each subtype (Figure).[11] These classic signs of EDS frequently appear in patients aged 4 to 6 years.[12] Hence, many of these findings are dermatologic in nature and tend to be first evident in the pediatric population. Specifically, skin tends to be hyperextensible with preserved elastic recoil.[13] Redundant skin tends to develop over elbows and knees, and atrophic scars resembling cigarette paper may form over these trauma-prone regions as the child begins to crawl or walk. Molluscoid pseudotumors (fibrous lumps measuring 2–3 cm) also commonly develop at trauma-prone sites. In addition, subcutaneous, firm, cystlike, calcified spheroids may appear along the forearms or shins.[13]

Excessive bruising, a manifestation of fragility of the capillaries and perivascular connective tissues, often is the chief concern.[14] This finding may understandably lead the clinician to suspect child abuse; special attention to the other cutaneous signs must be given to avoid this misdiagnosis.[15] Periodontal disease with early loss of teeth and hernias of all types are common with each of the subtypes of EDS.[10] Joint pain also is a frequent finding in patients with EDS, often secondary to joint dislocation.[6]

Classical EDS (types I and II) tends to be the easiest to recognize, with moderate to severe skin hyperelasticity and joint hypermobility and dislocation.[6] Epicanthal folds also are most commonly found in EDS type I.[13] Patients with EDS type I may present with complications such as hernias, pelvic organ prolapse, premature arthritis, and cervical insufficiency.[16] Ehlers-Danlos syndrome type II, the mitis form, is clinically similar to EDS type I, the gravis form, but the features are less severe in the mitis form.[3] In particular, these patients tend to lack the broad atrophic scars seen in EDS type I.[16] Ehlers-Danlos syndrome type III is the most frequent form, causing recurrent joint dislocations often leaving a patient unable to walk.[6] Skin involvement tends to be less prominent than in the classical forms of EDS. Chronic limb/joint pain is a prominent feature of EDS type III.[16]

Ehlers-Danlos syndrome type IV, often referred to as vascular EDS, is usually not diagnosed until adulthood but can present in infancy or childhood with low birth weight, prematurity, congenital dislocation of the hips, and easy bruising.[17] Although skin hyperextensibility tends to be much less noticeable, skin lucency and bruising are more prominent in this subtype.[13] Cardinal features include distinctive facial features; thin translucent skin; excessive bruising/hematomas; and fragility or rupture of vessels and/or viscera including arterial, intestinal, and uterine walls.[10] Typical facial appearance includes



Child with Ehlers-Danlos syndrome with hyperelastic skin.

thin nose, thin lips, tight skin, hollow cheeks, staring eyes, and lobeless ears, but these features often are not prominent in children.[8] The diagnosis of EDS type IV should be considered in any patient aged 45 years or younger presenting with arterial tearing or dissection, colonic perforation, or visceral rupture.[18]

Ehlers-Danlos syndrome type V is X linked recessive with skin fragility similar to classical EDS but with much less joint hypermobility and bruising (Table 2).[19] Kyphoscoliotic EDS, type VI, is rare. It is first apparent with marked muscular hypotonia, kyphoscoliosis, marfanoid habitus, fragile ocular globe, osteopenia, and occasionally vascular fragility.[20] Arthrochalasis EDS, types VIIa/VIIb, presents with marked joint laxity, soft skin, mild skin hyperextensibility, and congenital bilateral hip dislocations.[19] Ehlers-Danlos syndrome type VIII manifests with early-onset periodontitis beginning at puberty and resulting in loss of teeth by 30 years of age. Hyperelasticity of the skin and hypermobility of joints are moderate in EDS type VIII. [3]

Diagnosis

Diagnosis of EDS is clinical, based on established major and minor criteria for the disease (Table 3). Each subtype of EDS has specific major and minor criteria. The presence of one or more major criteria is necessary for making the diagnosis or at least highly indicative of EDS and suggests the need for further laboratory investigation.[8] Minor criteria have less diagnostic specificity and cannot be used to diagnose a particular subtype of EDS in the absence of major criteria. Minor criteria alone often suggest the presence of an EDS-like condition if major criteria are not present.[8]

Histologic and laboratory findings also can be used to aid in the diagnosis of EDS if clinical criteria are unclear. These tests usually are specific to the subtype of EDS suspected on clinical grounds. Biochemical analysis of type III collagen in skin fibroblasts can be performed to verify a diagnosis of EDS type IV, revealing decreased amounts or even absence of type III collagen.[14] Tests to verify a mutation in the *COL3A1* gene may be performed in a patient with suspected EDS type IV to confirm the diagnosis, but this method carries only a 61% sensitivity.[21] In classical EDS (types I and II), biopsy specimens often reveal rare and thin collagen bundles in the dermis, which are less refringent than healthy skin.[22] Electron microscopy, however, is required to observe miniscule details in collagen distribution and arrangement.

Differential Diagnosis

Joint hypermobility is seen in approximately 10% of the population in the Western world and as much as 25% of individuals in certain populations.[23] It is important to remember that not all cases of skin

Table 2.

Other Subtypes of EDS Not Classified by Villefranche

Other Subtypes	EDS Type	Inheritance
X linked	V	X linked recessive
Periodontitis	VIII	AD
Fibronectin deficient	X	
Familiar hypermobility syndrome	XI	AD

Abbreviations: EDS, Ehlers-Danlos syndrome; AD, autosomal dominant.

Data from Beighton et al.[8]

elasticity and joint hypermobility are because of EDS.[24] Lesser degrees of skin elasticity and/or joint hypermobility also may be present in individuals without EDS. Symptomatic hypermobility often is caused by joint hypermobility syndrome, a benign condition in patients with a certain degree of joint hypermobility as measured by the Beighton scoring system.[25] Traditionally, this disorder was described as occurring in patients with a genetic background distinct from EDS.[26] However, some experts believe benign joint hypermobility syndrome may be the same as EDS type III because the clinical criteria required for diagnosis are nearly identical.[23]

Joint hypermobility also may be caused by other pathologic conditions, such as Marfan syndrome or cutis laxa. Osteogenesis imperfecta is another collection of genetic disorders whereby the primary manifestation may be joint hypermobility and chronic dislocations.[27] Generalized joint laxity also may be secondary to diseases such as acromegaly, hyperparathyroidism, chronic alcoholism, and rheumatic fever.[23] If the chief concern is excessive bruising, various hematologic tests can be ordered to further investigate blood disorders. Clotting factors, platelet aggregation, and bleeding time usually are unremarkable in patients with bruising caused by EDS.[14]

Management

Unfortunately, there is no cure for EDS. No specific disease-modifying modality exists either. Pharmacologic options include the use of nonsteroidal anti-inflammatory agents or rarely opioids for joint pain.[6] Consulting a pain management specialist should be considered, as patients with EDS may have comorbid complex regional pain syndrome type I, a disease that presents with chronic pain and vasodysregulation following limb trauma healing.[16] In addition, many patients benefit from physical and occupational therapy to strengthen muscles and reduce repetitive joint trauma. Management of a patient with EDS often calls for a multidisciplinary approach involving multiple specialists. Routine evaluation of the patient's nutrition, growth, eyes, heart, skin, and joints is recommended.[28]

The primary form of care ultimately administered to patients with EDS is preventative in nature. Children should be taught to avoid high-impact sports and refrain from exhibiting the hypermobility of their joints to their peers for entertainment purposes, as they are often known to do.[28] Even minor trauma and small joint dislocations in these patients can be problematic because EDS causes poor wound healing due to defective collagen synthesis. Special attention should be paid to skin care, given the evident dermatologic manifestations of EDS. Avoiding skin damage by using mild soaps, avoiding adhesive bandages, refraining from excessive sun exposure, and wearing sunscreen is advisable.[28]

Vascular EDS (type IV) requires special consideration given that it may lead to premature death from spontaneous arterial rupture.[29] Other serious complications include spontaneous pneumothorax, rupture of the colon, and rupture of the gravid uterus.[30] It is the only lethal form of EDS, and its prevalence is approximately 1 in 250,000 individuals.[31] Complications typically do not occur during childhood, so patients may not know that they have EDS type IV specifically until adulthood, at which point the disease may become evident with spontaneous aneurysm, rupture, or arterial dissection.[29] Other vascular abnormalities include vascular fistulas and mitral valve prolapse. Spontaneous rupture of vessels and visceral structures is known to complicate surgical procedures, which must be kept in mind when utilizing surgical interventions for any reason in these patients.

Table 3.

Diagnostic Criteria for Subtypes of EDS

Classification	Major Criteria	Minor Criteria
Classical (types I and II)	Moderate to severe skin hyperelasticity	Smooth velvety skin
		Molluscoid pseudotumors
	Widened atrophic scars (for type I)	Subcutaneous spheroids
		Complications of joint hypermobility
	Joint hypermobility and dislocation	Muscle hypotonia
		Easy bruising
		Manifestations of tissue extensibility and fragility
		Surgical complications
		Positive family history
		Hernias
		Pelvic organ prolapse
		Premature arthritis
		Cervical insufficiency
Hypermobility (type III)	Skin hyperextensibility	Recurrent joint dislocations
	Widened atrophic scars	Chronic limb/joint pain
	Generalized joint hypermobility	Positive family history
Vascular (type IV)	Thin translucent skin	Acrogeria
	Arterial, intestinal, and uterine fragility or rupture	Hypermobility of small joints
		Tendon and muscle rupture
	Extensive bruising/hematomas	Talipes equinovarus (clubfoot)
	Characteristic facial appearance	Early-onset varicose veins
		Arteriovenous, carotid-cavernous fistula
		Pneumothorax/pneumohemothorax
		Gingival recession
		Positive family history with sudden death in close relatives
Kyphoscoliosis (type VI)	Generalized joint laxity	Tissue fragility with atrophic scars
	Severe muscle hypotonia at birth	Easy bruising

Classification	Major Criteria	Minor Criteria
Kyphoscoliosis (type VI) (continued)	Scoliosis at birth that is progressive	Arterial rupture
		Marfanoid habitus
	Scleral fragility and rupture of ocular globe	Microcornea
		Considerable osteopenia
		Positive family history
Arthrochalasia (types VIIa/VIIb)	Severe generalized joint hypermobility with recurrent subluxations	Skin hyperextensibility
		Tissue fragility with atrophic scars
		Easy bruising
	Congenital bilateral hip dislocations	Muscle hypotonia
		Kyphoscoliosis
		Mild osteopenia
Dermatosparaxis (type VIIc)	Severe skin fragility	Soft doughy skin texture
	Sagging redundant skin	Easy bruising
		Premature rupture of fetal membranes
		Large umbilical/inguinal hernias

Abbreviation: EDS, Ehlers-Danlos syndrome.

Data from Beighton et al.[8]

A pediatrician or dermatologist may be the first to recognize EDS in a child. However, management of EDS often requires a team approach, including evaluation by a cardiologist, orthopedist, and gynecologist.[19] Complications during pregnancy, such as uterine rupture, are common in EDS, which must be discussed as female patients reach childbearing age. Pain management and psychiatric evaluation for depression also should be considered given that patients with EDS have a high rate of pain and subsequent psychological distress.[32] Referral to a geneticist for counseling and classification of the specific EDS subtype involved is advised.[19]

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