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Review Article

A Review on Ehlers-Danlos Syndrome

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ABSTRACT

Ehlers-Danlos syndrome (EDS) is a group of inherited disorders that affect the connective tissues primarily skin, joints**,** and blood vessel walls**.** Connective tissue is a complex mixture of proteins and other substances that provides strength and elasticity to the underlying structures in the body. People who have Ehlers-Danlos syndrome usually have overly flexible joints and stretchy, fragile skin. This can become a problem if a person has a wound that requires stitches, because the skin often is not strong enough to hold them. A more severe form of the disorder, called vascular Ehlers-Danlos syndrome, can cause the walls of the blood vessels, intestines or uterus to rupture. If a person has a vascular Ehlers-Danlos syndrome, he/she may want to talk to a genetic counselor before starting a family. EDS is typically classified into six types like The Classical type (formerly types I and II), The Hyper mobility type (type III), The Vascular type (type IV), The Kyphoscoliosis type (type VI), The Arthrochalasial type (type VIIA and VIIB), The Dermatosparaxis type (type VIIC). The combined frequency of EDS is 1 in 5000 individuals worldwide. Major mutations in COL5A1 gene and COL5A2 genes are responsible for EDS. There is more chance to autosomal inheritance of EDS. There is no specific therapy to cure Ehlers-Danlos syndrome. Physical therapy is often needed. Some of the other medications are under different phases of clinical trials.

Key words: Ehlers – Danlos syndrome, connective tissues, mutations, autosomal inheritance.

INTRODUCTION

EHLERS-DANLOS SYNDROME (EDS) is a group of disorders that affect the connective tissues that support the **s**kin, bones, blood vessels and many other organs and tissues. Defects in connective tissues cause the signs and symptoms of EDS, which vary from mildly loose joints to life threatening complications. [1]

Classification

Previously, there were more than 10 recognized types of EDS, differentiated by roman numerical. In 1997, researchers proposed a simpler classification that reduced the number of major types to six and gave them descriptive names

- The classical type (formerly types I and II)
- The hyper mobility type (type III)
- The vascular type (type IV)
- The kyphoscoliosis type (type VI)
- The arthrochalasia type (type VIIA and VIIB)
- The dermatosparaxis type (type VIIC)

This six-type classification, known as the villefranche nomenclature, is still commonly used. The types are distinguished by their signs and symptoms, their underlying genetic causes, their patterns, of inheritance. [1] Sine 1997, several additional forms of the condition have been described. These additional forms appear to be rare,

affecting a small numbers of families, and most have not been well characterized. Although all types of EDS affects the joints and skin, additional features vary by type. A usually large range of joint movement (hyper mobility) occurs with most forms of EDS, particularly the hyper mobility type. [2]

Infants with hyper mobile joints often have weak muscle tone, which can delay the development of motor skills such as sitting, standing and walking. The loose joints are unstable and prone to dislocation, chronic pain. Hyper mobility and dislocations of both hips at birth are characteristic features in infants with arthrochalasia type of EDS. Many people with EDS have soft, velvety skin that is highly stretchy (elastic) and fragile. Affected individuals tend to bruise easily, and some type of the condition also causes abnormal scarring. [3]

People with classical form of EDS experience wounds that split open with little bleeding and leave scars that widen over time to create characteristic "cigarette paper" scars. The dermatosparaxis type of the disorder is characterized by skin that sags and wrinkles. Extra (redundant) folds of skin may be present as affected children get older. [3]

Some forms EDS, notably the vascular type and to a lesser extent the kyphoscoliosis and classical types, can involve serious and potentially life-threatening complication due to unpredictable tearing (rupture) of blood vessels. The rupture can cause internal bleeding, stroke, and shock.

The vascular type of EDS is also associated with an increased risk of organ rupture, including tearing of the intestine and rupture of the uterus (womb) during pregnancy. People with the kyphoscoliosis form of EDS experience severe, progressive curvature of the spine that can interfere with breathing. [3]

Frequency [4]

Although it is difficult to estimate the overall frequency of EDS, the combined prevalence of all types of this condition may be about in 1 in 5,000 individual worldwide. The hyper mobility and classical forms are most common; the hyper mobility type may affect as many as 1 in 10,000 to 15,000 people, while the classical type probably occurs in 1 in 20,000 to 40,000 people.

Other forms of EDS are very rare. About 30 cases of arthrochalasia type and about 60 cases of the kyphoscoliosis type have been described. The vascular type is also rare, estimates vary widely, but the condition may affect about 1 in 250,000 people.

Genetic Changes [5]

Mutations in more than a dozen genes have been found to cause EDS. The classical type results more often from mutations in either the COL5A1 gene or the COL5A2 gene. Mutations in the TNXB gene have been found in a very small percentage of cases of the hypermobility type (although in most cases, the cause of this type is unknown). The vascular type results from mutations in the COL3A1 gene. PLOD1 gene mutations cause the kyphoscoliosis type. Mutations in the COL1A1 gene or the COL1A2 result in the arthrochalasia type. The dermatosparaxis type is caused by mutations in the ADAMTS2 gene. The other, less well characterized forms of EDS result from mutations in the other genes, some of which have not been identified.

Some of the genes associated with EDS, including COL1A1, COL1A2, COL3A1, COL5A1 and COL5A2, provide instructions for making pieces of several different types of collagen. These pieces assemble to form mature collagen molecules that give structure and strength to connective tissues throught the body. Other genes, including ADAMTS2, PLOD1 and TNXB, provide instructions for making proteins that process are interact with collagen. Mutations that cause the different forms of EDS disrupt the production or processing of collagen, preventing these molecules from being assembled properly. These defects weaken connective tissues in the skin, bones, and other parts of the body,

resulting in the characteristic features of this condition.

Inheritance Pattern

The inheritance pattern of EDS varies by type. The arthrochalasia, classical, hypermobility, and vascular forms of the disorder have an autosomal dominant pattern of inheritance. Autosomal dominant inheritance means that one copy of the altered gene in each cell is sufficient to cause the disorder. In some cases, an affected person inherits the mutation from one affected parent. Other cases result from new (sporadic) gene mutations and occur in people with no history of the disorder in their family.

The dermatosparaxis and kyphoscoliosis types of EDS, as well as some of the rare, less well characterized types the disorder, are inherited in an autosomal recessive pattern. In autosomal recessive inheritance, two copies of the gene in each cell are altered. Most often, the parents of an individual with an autosomal recessive disorder are carriers of one copy of the altered gene but don't show signs and symptoms of the disorder. [6]

Symptoms

Symptoms of EDS include [6]

- Back pain
- Double-jointedness
- Easily damaged, bruised, and poor wound healing
- Flat feet
- Increased joint mobility, joints popping, early arthritis
- Joint dislocation
- Joint pain
- Premature rupture of membranes during pregnancy
- Very soft and velvety skin
- Vision problems

Table. No.1: Clinical manifestations and gene mutations in EDS

Type	Clinical manifestations		Protein	Gene mutation
	Major criteria	Minor criteria		
Classic (type I/II)	• Skin hyper extensibility • Widened atrophic scarring • Joint hyper mobility	• Easy bruising • Smooth and velvety skin • Molluscoid pseudo tumours • Subcutaneous spheroids • Muscular hypotonic • Complications of joint hyper mobility • Surgical complications • Positive family history	Type V procollagen (nearly 50%)	***COL5A1 COL5A2***
Hyper mobility (type III)	• Generalized joint hyper mobility • Mild skin involvement	• Recurring joint dislocations • Chronic joint pain • Positive family history	Tenascin X (< 10%)	***TNX-B***
Vascular (type IV)	• Excessive bruising • Thin, translucent skin • Arterial/intestinal/uterine fragility or rupture • Characteristic facial appearance	• Acrogeria • Early onset varicose veins • Hyper mobility of small joints • Tendon and muscle rupture • Arteriovenous or carotid-cavernous sinus fistula • Pneumo(heamo) thorax • Positive family history, sudden death in close relatives	Type III procollagen	***COL3A1***
Kyphoscoliosis (type VI)	• Severe muscular hypotonic at birth • Generalized joint laxity • Kyphoscoliosis at birth • Scelral fragility and rupture of the globe	• Tissue fragility, including atrophic scars • Easy bruising • Arterial rupture • Marfanoid habitus • Micro cornea • Osteopenia	Type VIA: Lysyl hydroxylase 1 Type VIB: not known	***LH-1 (PLOD1)***
Arthrochalasia (type VIIA & B)	• Severe generalized joint Hyper mobility with recurrent subluxations • Congenital bilateral hip dislocation	• Skin hyper extensibility • Tissue fragility, including atrophic scars • Easy bruising • Muscular hypotonic • Kyohoscoliosis • Mild osteopenia	Type 1 Procollagen	***COL1A1 COL1A2***
Dermatosparaxis(type VIIC)	• Severe skin fragility • Sagging, redundant skin • Excessive bruising	• Soft, doughy skin texture • Premature rupture of membranes • Large hernia	Procollagen-N-proteinase	***ADAMTS-2***

Exams and Tests

Examination by a health care provider may show [7]

- Deformed surface of the eye (cornea)
- Excess joint looseness and joint hypermobility
- Mitral valve in the heart does not close tightly (mitral valve prolapsed)
- Rupture of the intestines, uterus, or eyeball (seen only in vascular **EDS**, which is rare)
- Soft, thin, or very stretchy skin

Tests to diagnose **EDS** include:

- Collagen typing (performed on a skin biopsy sample)
- Collagen gene mutation testing
- Echocardiogram (heart ultrasound)
- Lysyl hydroxylase or oxidase activity (to check collagen formation)

EDSer Pain scale

Score	**0-3**	**4-6**	**7-10**	**11-13**	**14+**
Indication	Non existent VERY rare	This is how we feel every day. This is our 'normal'. Because of this we are really good at hiding it	This is when our pain is 'hightened' above the usual. Here the pain may be apparent to others but still easily hidden with a smile	This is when pain is more widespread. It is apparent to others. We may be quiet, set back, and moody	This pain is UNBEARABLE overwhelming. We will not want to move. We will be in tears this is our breaking point.

SUGGESTED EVALUATIONS FOR THE PRIMARY CARE GIVER FOLLOWING EDS [8, 9]

Tier I:

1. Assess musculoskeletal pain and joint stability
   - Gait abnormalities (many well benefit from shoe orthotics).
   - Temporomandibular joint dysfunction.
     - If present, craniofacial pain specialist referral recommended
   - Physical therapy referral.
   - Orthopedic referral if indicated for recurrent instability.
   - Pain management is often best tiered using physical therapy, localized pain relief and behavioral therapy. For significant pain, consider referral to pain management specialist.
2. Evaluate for fainting or light-headedness especially due to low blood pressure/ orthostatic intolerance.
   - Consider tilt table testing and/or ECG if appropriate.
3. Assess for sleep disorders, excessive daytime sleepiness, and/or chronic fatigue
   - Administration of the Epworth Sleepiness scale (or similar questionnaire) may be of use.
   - Formal sleep study often not useful.
4. Evaluate for depression and/or anxiety.
   - Consider mental health referral especially for cognitive behavioral therapy.
5. Offer educational and support resources
   - Suggest use of patient advocate or case manager if applicable.
     - Patient Advocate Foundation, www.patientadvocate.org.

Tier II:

6. Assess activities of daily living and ergonomic habits.
   - Consider occupational therapy referral.
7. Address quality of life concerns.
8. Baseline echocardiogram for structural anomalies and possible aortic dilation
   - Refer as indicated
9. Evaluate for gastrointestinal signs/symptoms.
   - Constipation
   - Irritable bowel
   - Persistent heart burn including gastroparesis and/or hiatal hernia

10. Assess for pelvic floor insufficiency v. prolapsed.
    - If present, offer gynecologic or urologic referral.
11. Offer preconception counseling regarding genetic risks and pregnancy complications.
12. Consider genetic counseling referral.

Treatment [10]

There is no specific cure for Ehlers-Danlos Syndrome. Individual problems and symptoms are evaluated and cared for appropriately.

Physical therapy or evaluation by a doctor specializing in rehabilitation medicine is often needed. Some of the therapies are under clinical trials, they are

(1) Beta-blockers (celiprolo) are the drug used under the phase-IV clinical trials. Dose ranging from 100-400 mg BID

(2) Angiotensin-II receptor blockers like Irbesartan used under phase-III clinical trials. Apart from these therapies, mind-body therapy for pain in EDS is under phase-II clinical trials.

PATIENT EDUCATION PROGRAM AND EDS (PREDUSED)

The French association of the Ehlers-Danlos Syndromes and the rehabilitation center of the 'Croix-Rouge Francaise des Massues' propose a patient education program for the patients with a hyper mobility type SED (the PrEduSED program). This education program us open to patients and their caregivers located in France.

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