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Ehler Danlos Syndrome: An Overview

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ABSTRACT

Ehler Danlos Syndrome is characterized in its most common form by hyperextensibility of the skin, hypermobility of joints often resulting in dislocations, and tissue fragility exemplified by easy bruising, atrophic scars following superficial injury, and premature rupture of membranes during pregnancy. Heterogeneity between the several clinical syndromes both complicates the diagnosis of EDS and makes accurate diagnosis imperative. It is caused by various abnormalities in the synthesis and metabolism of collagen (a component of the matrix) and other connective tissue proteins and its Signs vary widely based on which type of EDS the patient has. There is no cure for Ehlers Danlos Syndrome. The treatment is supportive and close monitoring of the cardiovascular system, physical therapy, occupational therapy, and orthopedic instruments (e.g., wheelchairs, bracing) may be helpful.

Key Words: Ehler danlos syndrome, hyperextensibility, Collagen.

INTRODUCTION

The Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder affecting as many as 1 in 5,000 individuals [1]. EDS is characterized in its most common form by hyperextensibility of the skin, hypermobility of joints often resulting in dislocations, and tissue fragility exemplified by easy bruising, atrophic scars following superficial injury, and premature rupture of membranes during pregnancy. The recognition of frequent ultrastructural abnormalities of collagen fibrils in EDS patients led to the concept that EDS is a disorder of fibrillar collagen metabolism [2]. Following the identification of specific mutations in the genes encoding collagen types I, III, and V, as well as several collagen processing enzymes, the EDS classification scheme was collapsed into six distinct clinical syndromes [3], emphasizing the molecular basis of each form (Table 1).

CLASSIFICATION OF EHLER DANLOS SYNDROME

At least 6 discernible phenotypes of Ehlers-Danlos syndrome are recognized, however, a great deal of overlap among the phenotypes is observed, making absolute clinical diagnosis difficult, if not impossible, at times. As many as 50% of patients with Ehlers-Danlos syndrome do not have a type or form that can be classified easily on clinical basis alone. This complicates the diagnostic process, because specific molecular diagnosis or confirmation (if available) may not be possible until a clinical subtype has been defined.

The table below lists the identifiable forms of Ehlers-Danlos syndrome proposed by a group of clinical experts from the medical advisory board of the Ehlers-Danlos National Foundation (EDNF) in 1997 [4]. This nosology is currently used in the clinical setting.

TABLE: 1 THE VILLEFRANCHE CLASSIFICATION OF EDS [3]

Type	Inheritance	Previous Nomenclature	Major Diagnostic Criteria	Minor Diagnostic Criteria
Classic	Autosomal dominant	Types I and II	Skin hyperextensibility, wide atrophic scars, joint hypermobility	Smooth, velvety skin, easy bruising, molluscoid pseudotumors, subcutaneous spheroids, joint hypermobility, muscle hypotonia, postoperative complication (eg, hernia), positive family history, manifestations of tissue fragility (eg, hernia, prolapse)
Hypermobility	Autosomal dominant	Type III	Skin involvement (soft, smooth and velvety), joint hypermobility	Recurrent joint dislocation, chronic joint pain, limb pain, or both, positive family history
Vascular	Autosomal dominant	Type IV	Thin, translucent skin, arterial/intestinal fragility or rupture, extensive bruising, characteristic facial appearance	Acrogeria, hypermobile small joints, tendon/muscle rupture, clubfoot, early onset varicose veins, arteriovenous, carotid-cavernous sinus fistula, pneumothorax, gingival recession, positive family history, sudden death in close relative
Kyphoscoliosis	Autosomal recessive	Type VI – lysyl hydroxylase deficiency	Joint laxity, severe hypotonia at birth, scoliosis, progressive scleral fragility or rupture of globe	Tissue fragility, easy bruising, arterial rupture, marfanoid, microcornea, osteopenia, positive family history (affected sibling)
Arthrochalasia	Autosomal dominant	Type VII A, B	Congenital bilateral dislocated hips, severe joint hypermobility, recurrent subluxations	Skin hyperextensibility, tissue fragility with atrophic scars, muscle hypotonia, easy bruising, kyphoscoliosis, mild osteopenia
Dermatosparaxis	Autosomal recessive	Type VII C	Severe skin fragility, saggy, redundant skin	Soft, doughy skin, easy bruising, premature rupture of membranes, hernias (umbilical and inguinal)

The major diagnostic criteria are highly specific. The presence of one or more major criteria is necessary for clinical diagnosis and is highly indicative and warrants laboratory confirmation whenever possible. One or more minor diagnostic criteria aid in clinical diagnosis but are not sufficient. Other forms of the syndrome have been reported. Type V Ehlers-Danlos syndrome was described in a single family. Type VIII is similar to classic Ehlers-Danlos syndrome but is also associated with periodontal disease, it is not a clearly distinct clinical entity. Type IX has been reclassified as an allelic form of Menkes disease. Type X was described in one family. Type XI was described as familial hypermobility syndrome and was previously removed from classifications. Ehlers-Danlos-like syndrome from tenascin-X deficiency has recently been described. Type I collagen mutations can cause an arthrochalasia-type syndrome with predisposition to arterial rupture in early adulthood.

The Online Mendelian Inheritance in Man (OMIM) database provides updated information on the clinical and molecular understanding of single gene (monogenic) disorders. The inheritance pattern, OMIM number, and original clinical descriptions of 10 major types of Ehlers-Danlos syndrome are listed below. The OMIM entries were reviewed in developing the Villefranche classification and include the following,

- Ehlers-Danlos syndrome type I (OMIM #130000, autosomal dominant), Distinguishing features include easy bruising, mitral valve prolapse, premature rupture of the fetal membranes, and premature birth.
- Ehlers-Danlos syndrome type II (OMIM #130010, autosomal dominant), This phenotype is similar to type 1, but the effects are milder.
- Ehlers-Danlos syndrome type III (OMIM #130020, autosomal dominant), Features include striking joint hypermobility and minimal skin changes.
- Ehlers-Danlos syndrome type IV (OMIM #130050, autosomal dominant), Type IV is the vascular/ecchymotic form. Patients with type IV Ehlers-Danlos syndrome have prominent venous markings, which are readily visible through the skin. Diagnostically, this type is most important because patients are subject to spontaneous rupture of the bowel, medium-sized arteries, or both. Often, rupture leads to early death. Median life expectancy in these patients is 45-50 years.
- Ehlers-Danlos syndrome type V (OMIM #305200, X-linked recessive), This phenotype is similar to, if not indistinguishable from, type 2, however, in familial cases, type V exhibits X-linked recessive inheritance.
- Ehlers-Danlos syndrome type VI (OMIM #225400, autosomal recessive), Patients may present with retinal detachments, microcornea, myopia, and scoliosis. Differentiating hypermobility from neuromuscular hypotonia in these patients may be difficult. [4]
- Ehlers-Danlos syndrome type VII (OMIM #130060, types VIIA and VIIB, autosomal dominant, OMIM #225410, type VIIC, autosomal recessive), Patients exhibit arthrochalasia multiplex congenita (hyperflaccidity of the joints without hyperelasticity of the skin), short stature, and micrognathia. Multiple congenital skull fractures have been reported in Ehlers-Danlos syndrome type VIIC. [5]
- Ehlers-Danlos syndrome type VIII (OMIM #130080, autosomal dominant), In addition to the other notable features, patients with type VIII Ehlers-Danlos syndrome have multiple skin striae and significant dental problems, including early tooth loss, periodontitis, and alveolar bone loss.
- Ehlers-Danlos syndrome type IX (OMIM #304150, X-linked recessive), Features include occipital exostoses, bladder diverticula or rupture, bony dysplasias, and decreased copper and ceruloplasmin. Ehlers-Danlos syndrome type IX is no longer a subtype.

- Ehlers-Danlos syndrome type X (OMIM #225310, autosomal recessive), Patients exhibit poor wound healing, petechiae, and a platelet aggregation defect, which can be corrected with fibronectin supplementation.

Since the classification scheme was accepted, a possibly new form has been described. Six patients from 2 consanguineous families were reported to have Ehlers-Danlos syndrome-like features and radiological findings of a skeletal dysplasia [6]. Findings included hyperelastic, thin, and bruisable skin, hypermobile small joints with a tendency to contractures, and protuberant eyes with bluish sclerae. The affected individuals had platyspondyly with moderate short stature, osteopenia, and widened metaphyses. All patients in the initial report had a homozygous c.483_491 del9 SLC39A13 mutation that encodes for a membrane-bound zinc transporter SLC39A13. The existence and classification of type VIII is under debate. [7] Hypermobility can be objectively determined. [8] A galactosyltransferase I deficiency form of progeroid Ehlers-Danlos syndrome has been described. [9]

GENETICS OF EDS

Recently, the progress of the Human Genome Project and other advances in molecular genetics have provided much information regarding the molecular basis of Ehlers-Danlos syndrome. Physical positions of involved genes and their locations on chromosomal maps are provided in the table below.

TABLE: 2 MOLECULAR BASES OF EDS

Type	Old Nomenclature	Protein Abnormality	Gene Abnormality	Chromosome Locus
Classic	Type I/II	Type V collagen	COL5A1, COL5A2	9q34.2-34.3 2q31
Hypermobility	Type III	Unknown	Unknown	Unknown
Vascular	Type IV	Type III collagen	COL3A1	2q31
Kyphoscoliosis	Type VI	Lysyl hydroxylase deficiency (some)	PLOD1	1p36.3-36.2
Arthrochalasia	Type VII A/B	Type I collagen	COL1A1 COL1A2	17q31-22.5 7q22.1
Dermatosparaxis	Type VIIC	N-proteinase	ADAMST2	5q23-24

PATHOPHYSIOLOGY

Individuals with Ehlers-Danlos syndrome demonstrate connective tissue abnormalities as a result of defects in the inherent strength, elasticity, integrity, and healing properties of the tissues. [10] The specific characteristics of a particular form of Ehlers-Danlos syndrome stem from the tissue-specific distribution of various components of the extracellular matrix. Each tissue and organ system expresses an array of connective proteins. The means of production and relative proportion and distribution of each protein array are unique. In addition, the specific interactions of various components of the matrix are tissue specific.

Major constituents of the extracellular matrix

Ehlers-Danlos syndrome is caused by various abnormalities in the synthesis and metabolism of collagen (a component of the matrix) and other connective tissue proteins.

Collagen comprises the most abundant proteins in the body. Collagen proteins are multimeric, occurring in trimers with a central triple helical region. A minimum of 29 genes contribute to the

collagen protein structure, and the genes are located on 15 of the 24 human chromosomes and form at least 19 identifiable forms of collagen molecules.

Elastic fibers are created by the association of elastin with an underlying microfibrillar array. The underlying basis of all connective tissue matrices is the microfibrillar array. An example of a microfibrillar protein is fibrillin, which is the abnormal protein found in patients with Marfan syndrome. Elastin and other structural proteins are woven onto the microfibrillar array to provide the basic meshwork for the connective tissue matrix. Abnormalities of elastin have been associated with other connective tissue disorders, such as cutis laxa. Deletion of the elastin gene is involved in many of the pathophysiologic processes seen in Williams syndrome.

Proteoglycans are core proteins that are bound to glycosaminoglycans (also commonly termed mucopolysaccharides). Essentially, proteoglycans are the glue of the connective tissue protein that seal and cement the underlying connective tissue matrix. Macromolecular proteins include the glycoproteins of the basement membrane (type IV collagen, laminin, nidogen) and the extracellular matrix (fibronectin, tenascin). Fig 1. And Fig 2. Explain the detail mechanism of Ehler Danlos Syndrome. [11]

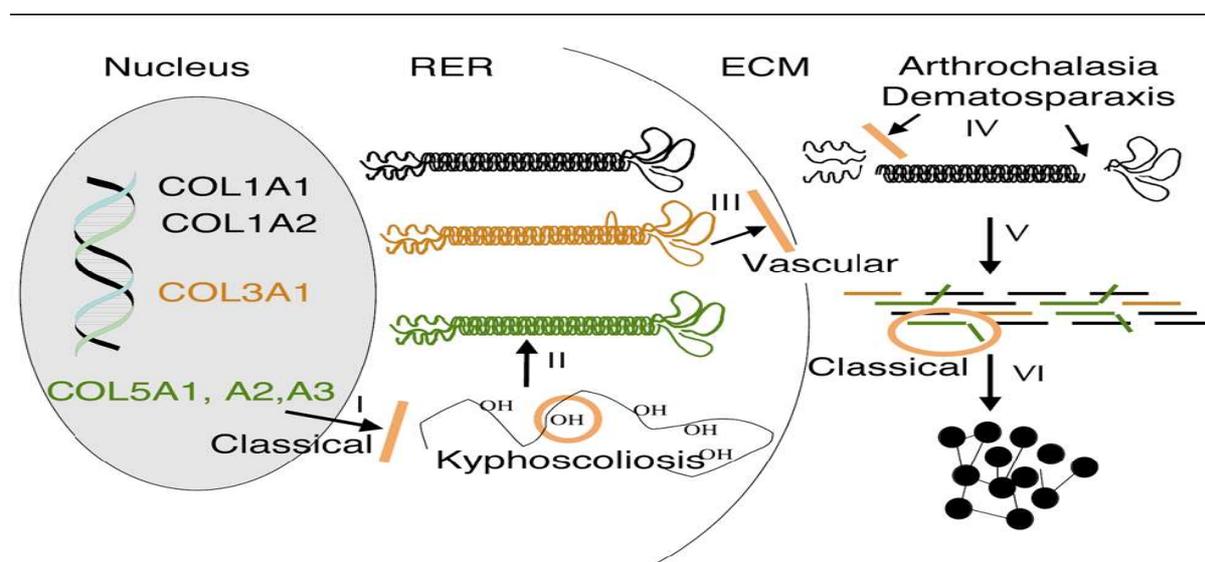


Fig 1. The biosynthetic pathway for the fibrillar collagens expressed in skin, identifying steps that are affected in different forms of EDS.

(I) Collagen gene transcription is highly regulated, but haploinsufficiency for COL5A1 is uncompensated and leads to a reduction in COL5A1 mRNA and $\alpha 1(V)$ procollagen chains. This accounts for 30–50% of classical EDS cases. (II) Many proline and lysine residues in the translated procollagen chains are hydroxylated by lysyl- and proline hydroxylases. Hydroxylation is essential for subsequent crosslinking and lysyl-hydroxylase deficiency causes the kyphoscoliosis form of EDS. (III) Procollagen α -chains are assembled into trimers within the rough endoplasmic reticulum (RER). Mutations in COL3A1 that interrupt the triple helical structure prevent normal processing and secretion of collagen III, causing the vascular form of EDS. (IV) In the ECM, the NH₂- and COOH-terminal propeptides are cleaved by specific peptidases. Dominant mutations in COL1A1 and COL1A2 can prevent cleavage and cause arthrochalasia, while recessive loss of the N-procollagen peptidase cause dermatosparaxis. (V) Collagen molecules self-assemble into heterotypic fibrils. Dominant-negative mutations in COL5A1 and COL5A2 alter fibril assembly and cause some cases of classical EDS. (VI) Collagen fibrils are deposited in tissue-specific arrangements in close association with many fibril-associated proteins and proteoglycans. Because new fibrils are laid down in close association with the fibroblast cell membrane, interactions between the fibril and the cell are important and may involve direct interaction with collagens and/or matricellular proteins, including tenascin-X (TNX).

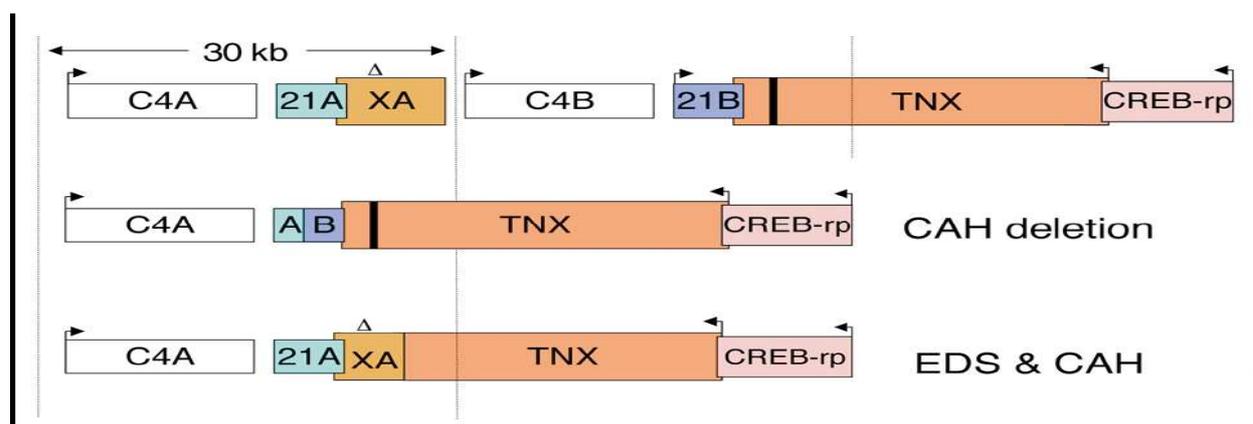


Fig 2. A novel deletion in the C4/CYP21/TNX/CREB-rp locus is associated with EDS.

The C4 genes, the CYP21 genes and part of TNX are duplicated on chromosome 6. Dashed lines indicate the limits of the duplication event. The normal locus is shown in the top panel. Arrows indicate direction of transcription. TNX is overlapped at its 3' end by the CYP21B (21B) gene encoding steroid 21-hydroxylase and, at its 5' end, by CREB-related protein (CREB-rp). XA is a partial duplicate of TNX that is a pseudogene transcribed but not translated in the human adrenal. XA contains a 121 bp deletion (α) that truncates the open reading frame corresponding to TNX. CYP21A (21A) is a pseudogene. One-quarter of CYP21B-deficient alleles carry a 30 kb deletion extending from CYP21A to CYP21B (middle panel). This creates a nonfunctional CYP21AB fusion gene and deletes XA, but does not alter TNX. We described a similar deletion (lower panel) extending from XA to TNX that completely deletes CYP21B and creates a TNX/XA fusion gene. This deletion is associated with a new contiguous gene syndrome consisting of congenital adrenal hyperplasia, due to CYP21B deficiency, and EDS, due to TNX deficiency.

SIGNS AND SYMPTOMS

Signs vary widely based on which type of EDS the patient has. In each case, however, the signs are ultimately due to faulty or reduced amounts of collagen. EDS most typically affects the joints, skin, and blood vessels, the major signs and symptoms are shown in table: 3

TABLE: 3 MAJOR SYMPTOMS OF EDS

Highly flexible fingers and toes	Flat feet
Loose, unstable joints that are prone to, sprain, dislocation, subluxation (partial dislocation) and hyperextension (double jointedness) [12]	Fragile blood vessels resulting from cystic medial necrosis with tendency towards aneurysm (even abdominal aortic aneurysm)
Fatigue, which can be debilitating	Easy bruising
High and narrow palate, resulting in dental crowding	Low muscle tone and Muscle weakness
Vulnerability to chest and sinus infections	Joint pain without inflammation
Difficulty regulating own body temperature, resulting in a vulnerability to the cold and heat. Many patients suffer fatigue and dizziness when exposed to hot conditions, eg. having to sit outside on a hot day	Cardiac effects, typically accompanied by Valvular heart disease (such as mitral valve prolapse, which create an increased risk for infective endocarditis during surgery, as well as possibly progressing to a life-threatening degree of severity of the prognosis of mitral valve prolapse)
Severe mouth ulcers. Many patients complain of having several mouth ulcers at any one time. This is believed to be due to tissue fragility and vulnerability to infection	Sensitivity to medications. One of the cruelest aspects of EDS is that many patients experience bad reactions to medications, such as pain killers, making it very difficult to find safe, effective pain management[citation needed]
Nerve compression disorders (carpal tunnel syndrome, acroparesthesia, neuropathy)	Early onset of osteoarthritis
Unexplained "pins and needles" or numbness in extremities	Abnormal wound healing and scar formation (scars may appear like cigarette burns)
Food allergies and intolerances are very common	Swan neck deformity of the fingers
Infants with hypermobile joints often appear to have weak	Deformities of the spine, such as, Scoliosis (curvature

muscle tone (hypotonia), which can delay the development of motor skills such as sitting, standing, and walking	of the spine), Kyphosis (a thoracic hump), Tethered spinal cord syndrome, Occipitoatlantoaxial hypermobility, Arnold-Chiari malformation (brain disorder)
Fibromyalgia symptoms, Myalgia and arthralgia	Osteopenia (low bone density)
Talipes equinovarus (club foot), especially in the Vascular type	Functional bowel disorders (functional gastritis, irritable bowel syndrome)
Velvety-smooth skin which may be stretchy and is often translucent, with blue veins clearly visible on limbs and particularly in the hands	Migraines and headaches, including postural headaches from spontaneous intracranial hypotension
Premature rupture of membranes during pregnancy	Arterial/intestinal/uterine fragility or rupture
Blue sclera	Otosclerosis (hearing loss)
Platelet aggregation failure (platelets do not clump together properly)	Vascular skin conditions, Raynaud's phenomenon, Livedo reticularis

Because it is often undiagnosed or misdiagnosed in childhood, some instances of Ehlers–Danlos syndrome have been mischaracterized as child abuse. The pain associated with this condition is a serious complication.

DIFFERENTIAL DIAGNOSIS

There are several disorders that have some of the characteristics of Ehlers–Danlos syndrome. For example, in cutis laxa the skin is loose, hanging, and wrinkled. In EDS, the skin can be pulled away from the body but is elastic and returns to normal when let go. In Marfan syndrome, the joints are very mobile and similar cardiovascular complications occur. In the past, Menkes disease, a copper metabolism disorder, was thought to be a form of Ehlers–Danlos syndrome. Because of these similar disorders, a correct diagnosis is very important. [13]

Other Problems to Be Considered like Stickler syndrome, TGFBR -related phenotype, Ehlers-Danlos-like syndrome from tenascin-X deficiency (OMIM #606408), Ehlers- anlos/osteogenesis imperfecta overlap syndromes Vasculitis [14], Hypotonia , Loeys-Dietz Syndrome and Williams Syndrome

DIAGNOSIS

Laboratory Studies

The following laboratory studies may be indicated in patients with Ehlers-Danlos syndrome (EDS),

- To confirm the diagnosis of the vascular form (type IV) of Ehlers-Danlos syndrome and for arthrochalasia (Ehlers-Danlos syndrome type VIIA and VIIB) and dermatosparaxis (Ehlers-Danlos syndrome VIIC), biochemical studies can detect alterations in collagen molecules in cultured skin fibroblasts.
- Molecular (DNA-based) testing is available for Ehlers-Danlos syndrome types IV and VII as well.
- With the exception of kyphoscoliotic type (Ehlers-Danlos syndrome type VI), which can be identified by urinary analyte assay, the most common and remaining forms of Ehlers-Danlos syndrome are identified by clinical examination.

Imaging Studies

Zilocchi et al reviewed imaging findings in vascular Ehlers-Danlos syndrome. [15] Using CT scanning, MRI, ultrasonography, and angiography, the most common findings were arterial aneurysms and arterial dissections, followed by arterial ectasias and arterial occlusions.

Other Tests

Ultrastructural examination of collagen fibrils may be a useful additional diagnostic tool, for supporting the diagnosis of the classical form of Ehlers-Danlos syndrome but also for Ehlers-Danlos syndrome type VII and the differentiation into Ehlers-Danlos syndrome type VIIA and Ehlers-Danlos syndrome type VIIB. [16]

Procedures

Skin biopsy findings (performed for histopathologic analysis) are nondiagnostic.

CURRENT AND FUTURE TREATMENT ASPECT

There is no cure for Ehlers Danlos Syndrome. The treatment is supportive. Close monitoring of the cardiovascular system, physical therapy, occupational therapy, and orthopedic instruments (e.g., wheelchairs, bracing) may be helpful. One should avoid activities that cause the joint to lock or overextend.

A physician may prescribe bracing to stabilize joints. Surgical repair of joints may be necessary at some time. Physicians may also consult a physical and/or occupational therapist to help strengthen muscles and to teach people how to properly use and preserve their joints. To decrease bruising and improve wound healing, some patients have responded to ascorbic acid (vitamin C) by taking 1 to 4 grams daily.[citation needed]

In general, medical intervention is limited to symptomatic therapy. Prior to pregnancy, patients with EDS should have genetic counseling. Children with EDS should be provided with information about the disorder, so they can understand why contact sports and other physically stressful activities should be avoided. Children should be taught early on that demonstrating the unusual positions they can maintain due to loose joints should not be done as this may cause early degeneration of the joints. Family members, teachers and friends should be provided with information about EDS so they can accept and assist the child as necessary.

Medical Care

A correct diagnosis in patients with Ehlers-Danlos syndrome (EDS) is critical and must be determined if possible.

- Confirmation using biochemical studies on collagen molecules is possible with cultured skin fibroblasts for the vascular form (Ehlers-Danlos syndrome type IV), for arthrochalasia (Ehlers-Danlos syndrome type VIIA and VIIB), and for dermatosparaxis (Ehlers-Danlos syndrome type VIIC). A diagnostic assay of urinary pyridinoline cross-links identifies the kyphoscoliosis type (Ehlers-Danlos syndrome type VI) Therefore, if the clinical diagnosis is type IV, type VI, and some of the forms of type VII Ehlers-Danlos syndrome, perform biochemical or molecular studies.
- Once a diagnosis of Ehlers-Danlos syndrome has been made, preventative measures should be undertaken. Wearing a MedicAlert bracelet may be helpful in case of life-threatening events.
- In the event of skin lacerations or other injuries, take extreme care with the use of sutures. Seriously consider alternatives to sutures, including adhesive strips and wound glues.
- Monitor patients for scoliosis and instruct them to avoid excessive or repetitive lifting and other activities that produce undue strain or stress on their already hypermobile joints.
- Pay careful attention to cardiac auscultation and evaluation. The murmur of mitral valve prolapse (particularly in classic and hypermobile Ehlers-Danlos syndrome) should be noted, if indicated, perform an echocardiography. In the presence of mitral valve prolapse, monitoring and screening are indicated, as is the use of subacute bacterial endocarditis (SBE) precautions.

- High-dose (1-4 g/d) ascorbic acid therapy has been tried and, in theory, has a potential effect. Clinical studies suggest that wound healing, even in patients not deficient in vitamin C, can be improved with supplementation above the recommended daily allowance. In patients with type VI Ehlers-Danlos syndrome, bleeding time, wound healing, and muscle strength seemed to improve after 1 year of high-dose vitamin C therapy, however, high-dose vitamin C therapy is not the standard of care.
- Recombinant factor VIIa has been used to help control surgical bleeding, but experience is limited and the usual surgical precautions for patients with Ehlers-Danlos syndrome should be followed.[17] Desmopressin may also be effective in reducing bleeding time, but the safety and efficacy of desmopressin in the prevention and treatment of bleeding in Ehlers-Danlos syndrome remains to be established. [18]

CONSULTATIONS

The following consultations may be indicated,

- Consultation with an ophthalmologist and dentist may be necessary. Recommend regular eye examinations.
- Accurate genetic counseling is one of the most critical issues in the treatment of patients with Ehlers-Danlos syndrome.
- Provide the family with detailed information regarding the inheritance pattern, recurrence risks, and identification of at-risk family members. Screen pertinent individuals in the family for subtle signs and symptoms of the condition regardless of whether signs or symptoms are suggested by the family history. Discuss the prognosis and natural history of the particular Ehlers-Danlos syndrome type in detail with the family.

Activity

Instruct patients with Ehlers-Danlos syndrome to avoid excessive or repetitive heavy lifting and other movements that produce undue strain or stress on the already hypermobile joints. [19] However, careful weight training with relatively low weight may be therapeutic. Advise patients to avoid (preventable) significant trauma.

Medication

High-dose ascorbic acid has been used, although it is not considered the standard of care (see Treatment). Desmopressin may normalize bleeding time in Ehlers-Danlos syndrome (EDS), but further studies are needed to establish safety and efficacy of this medication in treatment and/or prevention of bleeding in patients. [20]

MORTALITY/MORBIDITY

Reduced life expectancy is not generally a feature of Ehlers-Danlos syndrome, with the exception of the vascular form of Ehlers-Danlos syndrome (Ehlers-Danlos syndrome type IV). Median life expectancy for patients with type IV Ehlers-Danlos syndrome is 50 years because medium-sized arteries, the GI tract, and other organs tend to spontaneously rupture.

Morbidity in Ehlers-Danlos syndrome is related to the primary pathophysiology and includes dislocations, pain, or both from chronic joint laxity as well as aberrant scarring and wound healing from abnormal tensile strength of the skin [21] rectal prolapse can occur. [22]

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