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Ehlers-Danlos Syndrome: Immunologic contrasts and connective tissue comparisons

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ABSTRACT

Ehlers-Danlos Syndrome (EDS) is a family of multisystemic hereditary connective tissue disorders now comprised of 13 recognized subtypes, classical, classical-like, cardiac-valvular, vascular, hypermobile, arthrochlasia, dermosparaxis, kyphoscoliotic, brittle cornea syndrome, spondylodysplastic, musculocontractural, myopathic, and periodontal, as designated by the most recent 2017 International classification system. Clinical presentation of this disease can range from mild manifestations including skin hyperextensibility and joint hypermobility, to more severe complications such as vascular and organ rupture. While there may be accompanying inflammation in some of the subtypes of EDS, the pathogenic mechanisms have not been clearly defined. Thorough evaluation incorporates clinical examination, family history, laboratory testing, and imaging. In recent years, studies have identified multiple gene variants involved in the pathogenesis of specific EDS subtypes as well as elaborate clinical diagnostic criteria and classification models used to differentiate overlapping conditions. The differential diagnosis of EDS includes hypermobility spectrum disorders, Marfan syndrome, Loey-Dietz syndrome, Cutis laxa syndromes, autosomal dominant polycystic kidney disease, osteogenesis Imperfecta Type 1, fibromyalgia, depression, and chronic fatigue syndrome. Surgical treatment is reserved for complications, or emergencies involving vascular or orthopedic injury because of the risk of poor wound healing. Management techniques each have their own consequences and benefits, which will also be discussed in this review article. Patients affected by this spectrum of disorders are impacted both phenotypically and psychosocially, diminishing their quality of life.

1. Introduction

Ehlers-Danlos syndrome (EDS) is comprised of a family of heritable connective tissue disorders (HCTD) involving multiple anatomical structures and organ systems including integumentary, musculoskeletal, cardiovascular, and gastrointestinal systems. Many of its subtypes have overlapping hallmark features including skin hyperextensibility, joint hypermobility, easy bruising, and organ rupture. EDS was first documented in 1898 b y Danish physician Edvard Ehlers and later by French physician Henri-Alexandre Danlos in 1908. In 1988, 11 subtypes of this challenging disorder were recognized by the Berlin Nosology through the evaluation of clinical presentation and inheritance patterns. Due to the similarities shared between different forms of EDS, however, proper diagnosing became increasingly complex and contradictory with the use of this classification system. This gave rise to the Villefranche Nosology in 1998, which identified six EDS subtypes and included the molecular basis, and major and minor criteria, for each. Although this nosology model has proven to be significant in finding and characterizing EDS, new variants and genetic testing techniques have been discovered since then, and the Villefranche Nosology has become outdated. The International EDS Consortium constructed an updated EDS classification system in 2017 that is now widely used and encompasses many aspects of both the clinically and genetically varied subtypes. This 2017 international classification recognizes 13 forms of EDS and provides detailed classification, clinical diagnosis, and molecular basis (Table 1). This rare spectrum of diseases is challenging to understand, yet with the proper clinical evaluation, management strategies, and education, this seemingly misunderstood disorder can become more tangible.

2. Natural history/clinical features of EDS subtypes

EDS is characterized by 13 major subtypes: classical, classical-like,

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Table 1
EDS subtypes based on 2017 International Classification.

Subtypes	Notable cclinical features	Inheritance pattern	Gene(s) involved	Structural effect of disorder
1. Classical EDS	•Skin fragility •Skin hyperextensibility •Atrophic scarring •Joint hypermobility •Common joint dislocations •Easy bruising •Hernia	Autosomal dominant	•COL5A1 •COL5A2 •Rarely COL1A1	Affects primary structure and processing of collagen
2. Classical-like EDS	•Skin fragility •Skin hyperextensibility •Joint hypermobility (affecting shoulder and ankle) •Common joint dislocations •Easy bruising •Foot deformities •Peripheral edema •Mild muscle weakness and atrophy •Polyneuropathy •Organ prolapse	Autosomal recessive	•TNXB	Affects myomatrix structure and function
3. Cardiac-valvular EDS	•Joint hypermobility •Skin hyperextensibility •Severe defects of cardiac valves •Hernia •Pectus deformity	Autosomal recessive	•COL1A2	Affects primary structure and processing of collagen
4. Vascular EDS	•Aneurysm, dissection, or rupture of arteries •Perforation or rupture of gastrointestinal organs •Rupture of uterus during pregnancy •Skin translucency •Easy bruising •Distinctive facial features	Autosomal dominant	•COL3A1 •Rarely COL1A1	Affects primary structure and processing of collagen
5. Hypermobile EDS	•Joint hypermobility •Velvety/soft skin •Slightly hyperextensive skin •Common joint dislocations and subluxations •Chronic pain	Autosomal dominant	•Causative gene unidentified in most cases •TNXB gene and COL3A1 gene in minority of cases	
6. Arthrochalasia EDS	•Severe joint hypermobility at birth •Congenital dislocation of bilateral hips •Skin hyperextensibility •Atrophic scarring	Autosomal dominant	•COL1A1 •COL1A2	Affects primary structure and processing of collagen
7. Dermatosparaxis EDS	•Extreme skin fragility and laxity •Delayed closures of fontanels •Distinctive facial features •Blue discoloration of sclera •Short fingers and stature	Autosomal recessive	•ADAMTS2	Affects primary structure and processing of collagen
8. Kyphoscoliotic EDS	•Kyphoscoliosis •Joint hyperflexibility •Muscle hypotonia •Ocular fragility •Skin hyperextensibility •Atrophic scarring •Arterial rupture •Respiratory compromise in severe cases	Autosomal recessive	•PLOD1 •FKBP14	Affects folding and cross-linking of collagen
9. Brittle cornea Syndrome	•Fragile cornea with risk of rupture •Blue sclerae •Early keratoconus and keratoglobus •Severe myopia •Detachment of retina •Deafness •Mild contractures of fingers •Distal joint hypermobility	Autosomal recessive	•ZNF469 •PRDM5	Affects intracellular processes
10. Spondylodysplastic EDS	•Hypotonia of muscles •Short stature and bowing of limbs •Skin hyperextensibility •Delayed cognitive and motor development	Autosomal recessive	•B4GALT7 •B3GALT6 •SLC39A13	Affects biosynthesis of glycosaminoglycan and intracellular processes

(*continued on next page*)

Table 1 (*continued*)

Subtypes	Notable cclinical features	Inheritance pattern	Gene(s) involved	Structural effect of disorder
11. Musculocontractural EDS	•Multiple contractures •Club foot •Early craniofacial abnormalities •Skin hyperextensibility • Increased wrinkling of palms •Kidney stones	Autosomal recessive	•CHST14 •DSE	Affects biosynthesis of glycosaminoglycan
12. Myopathic EDS	•Congenital muscle weakness and atrophy, lessening with age •Contractures of proximal joints •Joint hypermobility •Developmental motor delay	Autosomal dominant or autosomal recessive	•COL12A1	Affects myomatrix structure and function
13. Periodontal EDS	•Early, severe periodontitis •Detachment of gingiva •Pretibial plaques •Easy bruising •Joint hypermobility •Higher risk of infection	Autosomal dominant	•C1R •C1S	Affects complement pathways

cardiac-valvular, vascular, hypermobile, arthrochlasia, dermosparaxis, kyphoscoliotic, brittle cornea syndrome, spondylodysplastic, musculocontractural, myopathic, and periodontal. The natural history and clinical features of each form, although similar in certain regards, can be vastly different, ensuring the distinguishability and individuality of each.

Classical EDS, comprised of former EDS type 1 and EDS type 2, is a hereditary autosomal dominant connective tissue disorder that is most commonly associated with symptoms of skin fragility, skin hyperextensibility, joint hypermobility, atrophic scarring, and easy bruising. Patients who have been previously diagnosed with EDS type I or EDS type II are now characterized under the same classification of classical EDS as both types form a clinical continuum [1] (Table 2). Developed in 2017, the diagnostic criteria used to identify classical EDS consists of components of medical examination, accomplished through a major and minor diagnostic criterion, and consideration of family history. One of the singular most common clinical features of classical EDS is cutaneous manifestations. More specifically, skin hyperextensibility, in which skin is easily extended and maintains a smooth, velvety texture, can lead to atrophic scarring and/or delayed wound healing. Chilblains and acrocyanosis are present in a minority of classical EDS cases. Joint hypermobility, shown through hyperextensibility of small and large joints, is also a common clinical feature of classical EDS that can trigger additional complications such as joint dislocations and subluxations. Easy bruising presents itself through a brown discoloration of the skin and is commonly found to reoccur in the same cutaneous regions. Patients may also experience pelvic prolapse and problems involving the gastrointestinal, dental, and cardiovascular systems [2,3].

Classical-like EDS, an autosomal recessive disorder, also presents with skin fragility, skin hyperextensibility, and easy bruising. Unlike classical EDS, atrophic scarring is not present in classical-like EDS. This EDS subtype also greatly affects the joints, causing joint hypermobility, most commonly affecting the shoulders and ankles, and recurrent joint dislocations. Foot and hand deformities, peripheral edema, polyneuropathy, and mild myopathy can be noted as well. In severe cases, patients may experience uterine or rectal prolapse [4].

Table 2
Diagnostic criteria of classical EDS.

Diagnostic criteria	Findings
Major criteria	•Skin hyperextensibility o Tested by pulling up skin on volar surface of forearm until skin resists •Atrophic scarring •Joint hypermobility o Tested by Beighton scale •Family history of EDS
Minor criteria	•Velvety, smooth skin •Molluscoid pseudotumors •Subcutaneous spheroids •Joint hypermobility complications •Signs of tissue fragility and extensibility •Easy bruising •Muscle hypotonia •Surgical complications

Cardiac-valvular EDS, is associated with joint hypermobility, skin hyperextensibility, variable atrophic scarring, and defects of the cardiac valves [1,5]. It is inherited through an autosomal recessive gene. Furthermore, severe valvular abnormalities involve the mitral and aortic valves. Individuals diagnosed with cardiac-valvular EDS also exhibit signs of joint dislocations, foot and chest deformities, and inguinal hernia [4].

Arguably, the most critical and dangerous form of EDS is autosomal dominant vascular EDS, formerly EDS type IV, which accounts for about 4–5% of all cases [6,7]. Although characteristics of easy bruising, skin translucency, small joint hypermobility, congenital hip dislocation, and distinct facial features are found in this type of EDS, the most consequential features are the high risks for vascular fragility and arterial aneurysms, dissections, or ruptures [2]. Patients may also have facial features such as proptotic eyes, narrow nose, and thin lips [8,9]. In addition, unlike other forms of EDS, vascular EDS does not present characteristics of skin hyperextensibility. Spontaneous organ rupture or perforation in the gastrointestinal system, specifically the sigmoid colon, is common as well [5]. Rupture of the spleen and liver, and unprovoked pneumothorax may occur in few cases of Vascular EDS [10,11]. Pregnant patients suffering from this disorder face additional challenges, especially during the third trimester, due to the high risk of uterine rupture. Such a condition can lead to severe postpartum hemorrhage, often requiring hysterectomy [12]. Reoccurring umbilical, inguinal, incisional, and hiatal hernias have also been noted symptoms of this disease. Due to anatomical and pathophysiological attributes, certain blood vessels are more prone to arterial complications which can further lead to spontaneous hemorrhage. For example, the hepatic arteries, renal arteries, splenic arteries, and internal carotid arteries are most commonly associated with arterial aneurysms [6,13,14]. Varicose veins can also be associated with vascular EDS [15]. Patients often present with these clinical features at a young age. Family history plays an important role in the diagnosis of this disease as about 60% of individuals found to have vascular EDS during childhood have positive family history. Without known family history, 50% of children diagnosed with vascular EDS often experience major complications by a mean age of 11 years.

Unlike vascular EDS, hypermobile EDS, formerly known as EDS type III, is believed to be the most common and least severe subtype of EDS [16]. This condition most frequently presents itself with symptoms of joint hypermobility. Experts today still face challenges distinguishing hypermobile EDS and hypermobility Spectrum Disorders (HSD). Joint

hypermobility often leads to joint dislocations and subluxations of peripheral and axial joints. Non-inflammatory joint pain is also a hallmark of this EDS subtype. Patients experience chronic pain which can begin anytime between the ages of 15 and 60 years [16]. Myalgia, fatigue, and difficulty sleeping are also common in hypermobile EDS [17]. In addition, psychiatric and psychological symptoms, such as anxiety, depression, eating disorders, and drug abuse, are more prevalent in hypermobile EDS in comparison to other forms of EDS [18]. Cutaneous manifestations are occasionally seen in hypermobile EDS, including skin hyperextensibility and softness. Literature shows discrepancies regarding the presence of large atrophic scarring in this type of EDS [1,15]. Systemic features, though uncommon, can also be noted, including cardiovascular, neurologic (headaches), gastrointestinal, and ocular manifestations. Although the gene for hypermobile EDS has not been identified, there are a minority of cases which have been attributed to variants in TNXB and COL3A1 and have been associated with an autosomal dominant inheritance pattern [19].

Arthrochalasia EDS, formerly known as EDS type VIIA and VIIB, is inherited through an autosomal dominant inheritance pattern and is most commonly characterized by severe congenital joint hypermobility with dislocation of bilateral hips. Skin hyperextensibility, easy bruising, and atrophic scarring are also often found in patients affected by this EDS subtype [1,20,21]. Although some characteristics are shared with other EDS subtypes, the most distinguishing features of dermatosparaxis EDS, or former EDS type VIIC, are extreme skin fragility and laxity, delayed closures of fontanels, distinctive facial features, blue discoloration of the sclera, stunted growth of hands, and short stature. Patients may also show mild symptoms of joint hypermobility [20,21]. Dermatosparaxis EDS is inherited through an autosomal recessive gene.

Formerly known as EDS type VI, kyphoscoliotic EDS is distinguished by the presence of congenital hypotonia and muscle weakness, joint hyperflexibility, worsening scoliosis, hearing impairment, skin hyperextensibility, and atrophic scarring. This EDS subtype is inherited through an autosomal recessive gene. Affected children have delayed development of motor function, which typically improves during childhood. Although some adults still struggle with muscle weakness, they are generally independent with regards to their daily activities [22]. On occasion, clinical features can include rupture and dissection of arteries, blue sclerae, ocular fragility, and complications during pregnancy. In extreme cases, patients may experience respiratory compromise [1].

Brittle cornea syndrome is a unique subtype of EDS that is inherited through an autosomal recessive pattern and is most notable for its ocular manifestations. For example, a fragile, thin cornea (often with a central thickness less than 400 μm) with a risk of rupture is a hallmark. Other common conditions include, but are not limited to, blue coloring of the sclerae, severe myopia, detachment of the retina, and early keratoconus or keratoglobus. Keratoconus is characterized as worsening thinning of the cornea, which may lead to blurry or double vision, astigmatism, and sensitivity to light. Similarly, keratoglobus is the thinning of the cornea, often resulting in a change of morphology of the cornea from a smooth curve to a more globular shape. Apart from these serious ocular manifestations, Brittle Cornea Syndrome can also be associated with deafness and abnormalities of the tympanic membrane. Musculoskeletal and cutaneous features including joint hypermobility, hip dysplasia, scoliosis, mild contractures of fingers, and skin translucency can also be seen [4].

Spondylodysplastic EDS is characterized by joint hypermobility, hypotonia of muscles, short stature, and bowing of limbs [20]. In addition, individuals diagnosed with this EDS subtype may experience skin hyperextensibility, osteopenia, flat feet, and delayed motor as well as impaired cognitive development. The musculoskeletal abnormalities can often be identified through characteristic findings on imaging studies. This disorder has an autosomal recessive inheritance pattern, involving the B4GALT7, B3GALT6, and SCL39A13 genes [4]. Interestingly, variants of each gene results in unique clinical features. For instance, variants in the B4GALT7 gene presents with contractures of the elbows, presence of only one transverse palmar crease, distinct craniofacial features, clouded cornea, and significant hypermetropia. B3GALT6 gene variants lead to kyphoscoliosis, hand joint contractures, abnormal finger structure, club foot, distinct craniofacial features, dental manifestations, spontaneous fractures secondary to osteoporosis, aneurysm of the ascending aorta, and restrictive lung disease. Lastly, blue discoloration of the sclerae, ocular protuberance, and hand deformities with fine wrinkling of palms and wasting of the thenar muscle are associated with variants of the SCL39A13 gene.

As the name implies, musculocontractural EDS, an autosomal recessive disorder, presents with multiple congenital contractures as well as club foot deformities [19]. Early craniofacial abnormalities, skin hyperextensibility and fragility, atrophic scarring, easy bruising, and prominent wrinkling of the palms are common findings. Significant, yet less frequent clinical features of musculocontractural EDS include joint dislocations, deformities of the spine, chest wall, hands, and feet, bladder/kidney stones, diverticulosis of the colon, and ocular abnormalities such as myopia, astigmatism, and glaucoma [4].

Unlike other recognized EDS subtypes, myopathic EDS can be inherited through either an autosomal dominant or autosomal recessive pattern [20]. Joint hypermobility, developmental motor delay, contractures of the proximal joints, muscle atrophy, and congenital muscle weakness that lessens with age, are seen in individuals with myopathic EDS [4]. Atrophic scarring and soft skin are also common features of this disorder.

Lastly, periodontal EDS, an autosomal dominant condition, is associated with extreme periodontitis, or the inflammation and infection of the gums, that often leads to the destruction of the jaw bone and detachment of the gingiva. Pretibial plaques (brownish discoloration of the shins), joint hypermobility, easy bruising, skin hyperextensibility, and atrophic scarring are noted manifestations of this EDS subtype. In addition, patients with Periodontal EDS are found to be at a higher risk of infections [4].

The information discussed above reviews both the similarities and variations in the phenotypic features of EDS. Although more thorough research is still needed, identification of these pertinent and critical characteristics is important in managing and preventing complications, which may often prove lifesaving.

3. Epidemiology

EDS is a relatively rare disease affecting anywhere between 1 in every 5000 to 250,000 individuals. Multiple sources state varying prevalence of this disease as it is still a fairly unfamiliar condition [8,11,21,23]. Much of EDS's epidemiology is unknown as thorough studies have not been conducted. However, there seems to be no significant racial or geographical factors that influence susceptibility to EDS. Classical EDS is present in about 1 in every 20,000 individuals [1]. Those with parents affected by Classical EDS have a 50% likelihood of developing the disease [21]. Vascular EDS accounts for a relatively small percentage of all EDS cases (about 4–5%) and affects approximately 1 in every 50,000 to 250,000 individuals [8]. Pregnant patients diagnosed with Vascular EDS are at a higher risk than their nonpregnant counterparts as they face a 5% chance of mortality during each pregnancy [9]. In addition, children of individuals with this disease have a 50% chance of inheriting the disorder as vascular EDS is almost always passed on through an autosomal dominant gene. Hypermobility, a hallmark feature of hypermobile EDS, is more common in females than in males [24,25].

4. Diagnostic criteria

The clinical diagnosis of EDS and its subtypes is a complex process as it involves consideration of family history, clinical features, and laboratory testing. In addition to identifying clinical features, proper diagnosis can be confirmed through molecular and genetic testing, targeting the responsible genes. In this literature review, we will highlight the diagnostic criteria for three forms of EDS: classical, hypermobile, and

Table 3
Beighton Scale. Points are given for each joint examination below; a minimum of 5 out of 9 points are needed for joint hypermobility diagnosis.

Joint examination	Left extremity (points)	Right extremity (points)	Bilateral extremities (points)	Spine (points)
•Extension of knees $\geq 190^{\circ}$	1	1	2	n/a
•Extension of elbows $\geq 190^{\circ}$	1	1	2	n/a
•Extension of thumbs to volar aspect of forearm	1	1	2	n/a
•Extension of fifth fingers $> 90^{\circ}$	1	1	2	n/a
•Forward flexion of trunk with palms flat on ground and knees fully extended	n/a	n/a	n/a	1

vascular, as these are the more commonly seen forms of EDS.

Diagnostic criteria are unique to each form of EDS, while some methods do overlap. For example, classical EDS can be identified through several prime criteria: major, minor, and Beighton. The major criteria tests skin hyperextensibility, by pulling up skin on volar surface of forearm until skin resists, presence of atrophic scarring, and joint hypermobility (using the Beighton criteria) [1,26]. The Beighton scale (Table 3) is comprised of five joint findings: extension of knees greater than 190°, extension of elbows greater than 190°, extension of thumbs to volar aspect of forearm, extension of fifth fingers greater than 90°, and forward flexion of the trunk with palms flat on the ground while knees are fully extended. A maximum of two points can be given for each joint finding, with the exception of forward flexion of the trunk for which only one point is available; a score of 5 out of 9 points is indicative of a joint hypermobility diagnosis.

In order to obtain a full comprehensive examination, presence of family history is also an important factor when diagnosing classical EDS. The minor diagnostic criteria encompasses the following: velvety skin, molluscoid pseudotumors, subcutaneous spheroids, joint hypermobility complications, tissue fragility or extensibility, easy bruising, muscle hypotonia, and surgical complications [1]. If at least one of these noted characteristics are present, it is taken into consideration, however, it is not independently diagnostic of classical EDS.

The diagnosis of hypermobile EDS formerly depends predominantly on the Brighton criteria. Since many consider hypermobile EDS to be nearly identical to hypermobility spectrum disorders, the same diagnostic guidelines are primarily used [17,27]. The Brighton criteria is comprised of a major and minor criteria [2,26,28] (Table 4). The major criterion consists of a Beighton score of 4 or greater and joint pain in 4 or more joints for longer than three years. The minor criterion includes a Beighton score of less than 3, joint pain in one to three joints for more than 3 months, back pain (e.g. spondylosis, spondylolisthesis) for at least 3 months, multiple subluxations/dislocations of 1 joint or single subluxation/dislocation of more than 1 joint, presence of 3 or more soft tissue injuries (e.g. bursitis, tenosynovitis), marfanoid habitus, skin manifestations (e.g. hyperelastic skin), ocular abnormalities (e.g. myopia, drooping of eyelids), varicosity of veins, hernia, and uterine or rectal prolapse [12].

Table 4
Brighton criteria.

Major
•Beighton score of 4 or greater
•Joint pain in 4 or more joints for longer than 3 months
Minor
•Beighton score less than 3
•Joint pain in up to 3 joints for more than 3 months
•Back pain for at least 3 months
•Multiple subluxations/dislocations of 1 joint or single subluxation/dislocation of more than 1 joint
•Presence of 3 or more soft tissue injuries
•Marfanoid habitus
•Skin manifestations
•Eye abnormalities
•Varicosity of veins
•Hernia
•Uterine or rectal prolapse

In 2017, the diagnostic criteria for Hypermobile EDS were revised by the International EDS Consortium. This updated three-criteria model based on clinical features and family history is currently used to diagnose hypermobile EDS (Table 5).

In this clinical diagnosis, Criterion 1 consists of the examination of joint hypermobility, determined by the Beighton score, explained above. Because joint hypermobility decreases with age, the Beighton score of 5 often leads to an overdiagnosis of joint hypermobility in children and its underdiagnosis in adults. To compensate for these discrepancies, many define joint hypermobility by a Beighton score of 6 or greater in prepubertal children and a score of 4 or greater in those above an age of 50 [2,4]. The following five-point questionnaire (5PQ), shown in Table 6, is used to determine any current or prior history of joint hypermobility. If the patient answers two or more of these questions positively, joint hypermobility may be diagnosed with a Beighton score of one point less that the specific point cutoff [29].

Criterion 2 incorporates three different subsections or features (A, B, and C) that cover syndromic features, skin manifestations, and family history. Two or more of these features must be prevalent in order for Criterion 2 to play a role in diagnosing hypermobile EDS. Feature A includes the presence of soft skin, inexplicable striae of skin surfaces, slight skin hyperextensibility, reoccurring hernias of the abdomen, piezogenic

Table 5
Three criteria model for diagnosis of hypermobile EDS.

Criterion 1
•Joint hypermobility
1. Beighton score of 6 or greater for prepubertal children
2. Beighton score of 4 or greater for adults above age of 50
•5PQ
1. Currently, or in the past, have you been able to place your palms flat against the ground while keeping your knees straight?
2. Currently, or in the past, have you been able to bend your thumb to the point where it touches the forearm?
3. During childhood, were you able to perform certain contortions or the splits?
4. As an adolescent, did you have more than one dislocation of the shoulder or knees?
5. Are you "double-jointed"?
Criterion 2
•Feature A
o Presence of soft skin
o Inexplicable striae of skin surfaces
o Slight skin hyperextensibility
o Reoccurring hernias of the abdomen
o Papules of the heels
o Atrophic scarring
o Aortic root dilation with a Z score of greater than 2
o Mitral valve prolapse
o Organ prolapse
o Crowding in the dental cavity
o Arachnodactyly
o Arm span to height ratio greater than or equal to 1.05
•Feature B
o At least one first-degree family member diagnosed with Hypermobile EDS using updated diagnostic criteria
•Feature C
o Musculoskeletal pain in at least two limbs daily for three or more months
o Chronic pain throughout body for three or more months
o Reoccurring joint dislocations or instability without the presence of trauma.
Criterion 3
•Absent skin fragility
•Absence of alternative connective tissue disorders

Table 6
Five-point questionnaire of the Beighton criteria.

1	. Currently, or in the past, have you been able to place your palms flat against the ground while keeping your knees straight?
2	. Currently, or in the past, have you been able to bend your thumb to the point where it touches the forearm?
3	During childhood, were you able to perform certain contortions such as the splits?
4rowhead	. As an adolescent, did you have more than one dislocation of the shoulders or knees?
5	Are you "double-jointed"?

papules of the heels, atrophic scarring, aortic root dilation with a Z score of greater than 2, prolapse of the mitral valve, organ prolapse (e.g. rectal, uterine, pelvic floor), crowding in the dental cavity, arachnodactyly, and arm span to height ratio of 1.05 or greater. If at least five of these mentioned clinical features are present, then feature A may be confirmed [2]. Feature B may be satisfied if the tested individual has a positive family history which is established if the patient has at least one first-degree family member diagnosed with hypermobile EDS, using the current diagnostic criteria. Feature C is defined by the presence of one of the following three musculoskeletal manifestations: musculoskeletal pain in at least two limbs daily for three or more months, chronic pain throughout the body for three or more months, and reoccurring non-traumatic joint dislocations or instability. Finally, Criterion 3 must satisfy certain prerequisite findings in order to rule out any alternative diagnoses. For example, skin fragility must be absent and other connective tissue disorders such as Marfan syndrome and hypermobility spectrum disorders must be eliminated [2].

Additionally, when diagnosing vascular EDS, family history is closely examined through pedigree information. Biochemical and molecular genetic testing are also often used during diagnosis to verify observed clinical features [8]. For example, biochemical evaluation such as electron microscopy, fibroblast culture, and histology can determine any abnormalities or deficiencies of the proteins responsible for vascular EDS [6,8,30]. Biochemical testing is a vital step in diagnosing this disease subtype as it can confirm collagen variants. Based on one study, a particular patient showed no positive family history, yet tested positive for vascular EDS through the usage of DNA testing [31].

Diagnosing EDS and its many subtypes remain a challenge and require more extensive criteria to fully encompass this complicated disease. Establishing additional detailed diagnostic guidelines will allow physicians to provide improved care crucial to their patients' health.

5. Differential diagnosis

EDS shares many characteristics with other similar disorders, and although distinguishability between these seemingly identical conditions is difficult, it is essential in ensuring proper patient care. The specific conditions being reviewed in this article are hypermobility spectrum disorders, Marfan syndrome, Loey-Dietz syndrome, Cutis laxa syndromes, autosomal dominant polycystic kidney disease, osteogenesis Imperfecta Type 1, fibromyalgia, depression, and chronic fatigue syndrome (Table 7).

Of the hypermobility spectrum disorders, joint hypermobility syndrome is one of the most common hypermobility diseases, affecting 10–20% of the general population. Researchers and clinicians alike often have a difficult time differentiating joint hypermobility syndrome from hypermobile EDS due to their nearly identical clinical presentation [32]. For example, joint hypermobility, chronic joint pain, and fatigue are present in both hypermobility spectrum disorders and various EDS subtypes. In addition, both conditions are most prevalent in adolescents, joint hypermobility lessening with age. Yet, unlike particular forms of EDS, patients with a hypermobility spectrum disorder typically show no atrophic scarring and no skin hyperextensibility. In order to truly identify the correct diagnosis, unique and thorough diagnostic criteria must be followed based on the Beighton score. Unlike EDS, no associated abnormalities in specific genes have been found in hypermobility spectrum disorders [33].

Table 7
Differential diagnosis of EDS.

Diagnostic	Similarities with EDS	Differences with EDS
Hypermobility Spectrum Disorders (e.g. Joint Hypermobility Syndrome)	•Joint hypermobility •Joint pain	•No atrophic scarring •No skin hyperextensibility
Marfan Syndrome	•Lense dislocation •Joint laxity •Aortic dilatation with increased risk of rupture •Mitral valves prolapse	•Abnormally long extremities •Pectus deformities •Involves FBN1 gene
Loey-Dietz Syndrome	•Aortic aneurysms with risk of dissection •Easy bruising •Velvety skin •Wide atrophic scars •Rupture of uterus	•Hypertelorism •Cleft palate •Bifid uvula •Club feet •Patent ductus arteriosus •Early death (average age of 26) •Involve TGFBR1 and TGFBR2 genes
Cutis Laxa Syndrome	•Hyperextensibility of skin	•No skin fragility •Normal wound healing •Involve ELN, FBLN4, FBLN5, ATP6V0A2, PYCR1 genes
Autosomal Dominant Polycystic Kidney Disease	•Intercranial aneurysms •Prolapse of the mitral valve •Dilations/dissections of the aortic root	•Enlarged, cystic kidneys •Cysts of the liver, pancreas, arachnoid membranes, and seminal vesicles •Involves PKD1 and PKD2 genes
Osteogenesis Imperfecta Type 1	•Joint hypermobility •Blue sclerae, sensorineural deafness, wormian bones, dental manifestations	•Involves COLIA1 and COLIA2 genes
Fibromyalgia, Depression, and Chronic Fatigue Syndrome	•Chronic pain •Psychosocial impact	•No physical features of EDS
Other diseases: •Menkes Syndrome •Familial Aortic Aneurysms •Pseudoxanthoma Elasticum	•Aortic aneurysm and dissection	•Involvement of other genes

Marfan syndrome, an autosomal dominant connective tissue disorder caused by a variant in the FBN1 gene, shares several common features with EDS subtypes, however, can be distinguished through its unique diagnostic criteria [4,11]. Genetic testing can be used to diagnose Marfan syndrome by identifying a variant in the FBN1 gene [34]. Although this disease has many commonalities with multiple EDS subtypes, it is most similar to hypermobile EDS. Patients with Marfan syndrome may experience arachnodactyly (abnormally long digits), lumber vertebrae scalloping, spondylosis, spondylolisthesis, a high arched pallet, crowding of the teeth, myopia, an increased axial globe length, ectopia lentis, corneal flatness, pneumothorax, aortic dilation and dissection, aortic valve regurgitation, and mitral valve prolapse and regurgitation [1,13]. Like EDS, this disease often shows wide CSF spaces when examined on MRI [31].

Similar to EDS, Loey-Dietz syndrome presents features of aortic aneurysms with risk of dissection, easy bruising, velvety skin, wide atrophic scars, and rupture of the uterus. This disease often leads to craniofacial manifestations and physical characteristics of Marfan syndrome, aortic aneurysms, bifid uvula, cleft palate, and hypertelorism; vascular aneurysms are also seen on CT scans [31,34]. These vascular aneurysms are

more widespread in the arterial system rather than clustered close to the aortic root, which is more typical of many EDS subtypes Craniosynostosis, clubfoot, instability of the cervical spine, and joint contractures differentiate this from Marfan's syndrome [20]. Loey-Dietz syndrome has an autosomal dominant inheritance pattern and is passed on by a variant in the TGFBR1 and TGFBR2 genes.

Another family of diseases, Cutis laxa syndromes share several characteristics with EDS such as heart valve abnormalities, vascular involvement, hernia, and hyperextensive skin, often making the diagnosis complicated and difficult. However, unlike that in EDS subtypes, Cutis laxa patients' skin typically takes longer to return to its normal state when extended or examined [11]. In addition, Cutis laxa syndromes do not present with skin fragility and have normal wound healing. This disease is caused by variants in the ELN, FBLN4, FBLN5, ATP6V0A2, and PYCR1 genes [1,35,36].

Autosomal dominant polycystic kidney disease is most notably known to cause enlarged cystic kidneys as well as cysts in the liver, pancreas, arachnoid membranes, and seminal vesicles. Like vascular EDS, autosomal dominant polycystic kidney disease can cause intercranial aneurysms, prolapse of the mitral valve, and dilatations or dissections of the aortic root. This disorder is carried by variants in the PKD1 and PKD2 genes.

Osteogenesis Imperfecta Type 1 is another condition that is often misdiagnosed for EDS subtypes due to the common feature of joint hypermobility. Characteristics of this disease include blue sclerae, wormian bones, deafness (sensorineural), and dental malformations. Genetic testing can ensure a correct diagnosis by identifying variants in the COLIA1 and COLIA2 genes [11,34].

Unfortunately, EDS is sometimes misdiagnosed as fibromyalgia, depression, and chronic fatigue syndrome as these conditions can coexist in some cases [2]. These diseases can be associated with chronic pain and take a toll on the psychosocial aspect of patients. Therefore, through the use of proper diagnostic measures and evaluation, it is important to rule out EDS to ensure that suspected patients are given appropriate care accordingly [11,37,38].

Other conditions including Menkes syndrome, familial aortic aneurysms, and pseudoxanthoma elasticum can also be confused with EDS and must be differentiated.

6. Etiology

EDS is caused by various genetic abnormalities and each subtype is associated with specific gene variants. Classical EDS is inherited through an autosomal dominant pattern and is caused by variants of the COL5A1 and COL5A2 genes, and in rare cases, the COL1A1 gene [1,11]. The COL1A1 gene encodes for Type I collagen. The COL5A1 and COL5A2 genes control Type V collagen's alpha1 and alpha2 chains, respectively, their variants resulting in a malfunctioning COL5A1 allele and haploinsufficiency of Type V collagen. These variants also minimize the amount of Type V collagen present in connective tissues, compromising the fibrillogenesis of collagen. Individuals diagnosed with classic EDS have a 50% chance of passing the variant on to each offspring. However, in 50% of patients with this EDS subtype, the condition results from a de novo pathogenic variant [1].

Vascular EDS is typically passed autosomal dominantly, however, few instances in which affected individuals inherited the disease through a biallelic inheritance pattern have occurred [9,31]. This EDS subtype often occurs in the presence of variants of the COL3A1 gene, located on chromosome 2 at position 31. COL3A1 regulates the pro-alpha1 chain of Type III collagen [8,39]. These gene variants may slow the synthesis or release of collagen and disrupt the structural integrity of Type III collagen, ultimately rendering it nonfunctional [40,41]. Variants in the COL1A1 gene, which controls Type I collagen, have also been identified in some cases of Vascular EDS [11]. Missense variants account for two thirds of vascular EDS cases, while null variants and partial gene deletions can also occur. Studies have indicated that the most severe cases of vascular EDS may be associated with missense variants at the C-terminal end of the molecule. Conversely, milder forms of this EDS subtype may be associated with null variants of the COL3A1 gene [42]. Approximately 50% of patients with vascular EDS inherit a variant in the COL3A1 gene from their affected parent, while the remaining 50% acquire the disease due to the presence of a de novo pathogenic variant. There is a 50% chance in which the child of an individual diagnosed with vascular EDS will inherit the gene variant and develop the condition.

Kyphoscoliotic EDS results from the deficiency of the procollagen-lysine, 2-oxoglutarate 5-dioxygenase enzyme, FKBP14. Kyphoscoliotic EDS has an autosomal recessive inheritance pattern and involves a variant that most often causes the FKBP14 gene at chromosome locus 7p14.3 to become nonfunctional. In rare cases, however, the gene variant results in a missense variant or an in-frame deletion [43,44]. This gene encodes for peptidyl-prolyl cistrans isomerase FKBP14 protein and affects Type III, VI, X collagen. Each child of an affected patient has an approximately 25% chance of developing the condition, a 25% chance of neither developing the disorder nor being a carrier for it, and a 50% chance of being a carrier for this EDS subtype. Carriers, or heterozygotes, of this disease present no symptoms or phenotypic features of FKBP14 kyphoscoliotic EDS [22].

Unfortunately, there is still limited knowledge on the etiology of the remaining EDS subtypes. For example, according to most recent data (2017 EDS Classification System), the causative gene of hypermobile EDS remains unidentified [11]. In a minority of cases, however, variants in the TNXB and COL3A1 genes have been reported [1,45] and the condition is passed through via an autosomal dominant pattern. Similarly, classical-like EDS involves a variant in the tenascin XB coding gene, TNXB, and has an autosomal recessive inheritance pattern [11]. Cardiac valvular EDS form is associated with variants in NMD and/or COL1A2 genes, affecting Type I collagen. This EDS subtype has an autosomal recessive inheritance pattern [11]. Arthrochalasia EDS, which is autosomal dominant, is caused by variants in the Type I collagen alpha1 chain encoding gene, COL1A1, and the Type 1 collagen alpha2 encoding gene, COL1A2 [1]. Dermatosparaxis EDS, on the other hand, is an autosomal recessive disorder and arises from a functional abnormality of the amino (N)-terminal propeptide controlling enzyme, procollagen-N-proteinase, affecting procollagen Types I,II, and III [46,47]. The ADAMTS2 gene is also associated with this EDS subtype [21]. Brittle cornea syndrome is an autosomal recessive disorder and is caused by variants of the ZNF469 and PRDM5 genes. Spondylodysplastic EDS has an autosomal dominant inheritance pattern and is caused by variants of the B4GALT7 and B3GALT6 genes, affecting galactosyltransferase Type I and II respectively [20]. Variants of the SLC39A13 gene have also been associated with spondylodysplastic EDS. Musculocontractural EDS is passed through an autosomal recessive pattern and involves variants of the CHST14 and DSE genes [20]. Myopathic EDS's causative gene is COL12A1 which controls the alpha chain of collagen Type 12. The inheritance of this EDS subtype can be autosomal dominant or autosomal recessive [20]. Periodontal EDS, an autosomal dominant disorder, is caused by variants of the C1R and C1S genes, affecting C1r and C1s [19]. Further studies are needed to better understand the genetic profiles of EDS patients, which could potentially give rise to yet unknown treatment modalities in the future.

7. An immunologic link to the etiology of EDS

Although connective tissue diseases are often treated by rheumatologists and there has been an immunological component to the pathogenesis of diseases involving joints and bone, there has yet to be a clearly defined role of the immune system in any of the subtypes of EDS. Case reports have suggested that there may be an association between hEDS [48], allergies and immunodeficiency; however, these associations may in fact be no more than a coincidence. Further research is needed to define the extent of involvement of the immune system in the pathogenesis of EDS.

8. Laboratory and imaging studies

Laboratory and imaging studies are crucial in identifying gene variants and abnormalities as well as severe clinical features. Laboratory testing techniques including ultrastructural studies, biochemical testing, and molecular testing can be used to identify gene variants or any other genetic abnormalities, playing a crucial role in the evaluation of EDS. For example, ultrastructural studies such as electron microscopy of a skin biopsy is used to determine collagen deformities [1,49]. Pathologists must ensure that the skin biopsy is of full thickness as the ultrastructural alterations are most prominent in the central reticular dermis. Gel electrophoresis helps identify the collagen protein that may be altered in various forms of EDS [1,50]. This form of collagen protein analysis does not act as a diagnostic evaluation; however, it can help differentiate certain EDS subtypes.

Another technique used in laboratory testing is molecular investigation, encompassing single-gene testing (concurrent or serial), multigene panel, and comprehensive gene testing. This involves extracting genomic DNA and messenger RNA from cultured cutaneous fibroblasts. For example, in an individual with Classical EDS, molecular testing is used to determine if they are heterozygous for one of the COL5A1 polymorphic exonic markers and if both alleles are expressed. Single-gene testing begins with the sequence analysis of various collagen types. If this process does not reveal pathogenic abnormalities, further testing is carried out by gene-targeted deletion and duplication analysis. Multigene panel testing examines several genes simultaneously and is most efficient if clinicians are able to narrow down the panel to the genes they suspect. In phenotypically indistinguishable diseases, comprehensive gene testing, including exome and genome sequencing, can be performed in hopes of determining the responsible gene.

Imaging studies such as arterial angiograms, CT scans, and MRIs can be particularly helpful in the evaluation of EDS patients, especially in vascular EDS. For patients diagnosed with this disorder, these tests can exhibit cardinal features including arterial dilatations, aneurysms, dissections, hernia, and organ ruptures [10,31].

9. Management strategies

Management, consisting of treatment, surveillance, and prevention of complications, requires a multidisciplinary approach, involving multiple subspecialities in order to ensure optimum care. Although no cure for EDS has been found, continuous monitoring and reevaluation is important in managing this chronic disease. Treatment involves management of skin wounds, physical and occupational therapy, pharmacotherapy, surgical procedures, psychiatric treatments, and genetic counseling.

Cutaneous wounds, a common feature of EDS, should be closed with the application of deep stiches. Due to the increased risk of wound dehiscence, it is recommended that sutures be kept in place for double the usual time [1,11]. Adhesive tape and glues may also be used to prevent the scar from opening or stretching further [51].

Physical and occupational therapy play a key role in treating not only hypermobile EDS, but other EDS subtypes as well. These strategies may only provide temporary relief (hours or days). Exercise, generalized or targeted, that does not involve extensive weight-bearing is also important in rebuilding muscle strength and coordination, and managing joint pain [1,16,24]. Additionally, physiotherapeutic programs have been proven to be very helpful in treating musculoskeletal manifestations in children with inadequate motor development and hypotonia. Other techniques used to relieve joint pain include application of heat or cold, acupuncture, massage, biofeedback, electrical stimulation, and the use of assistive devices. For example, braces are used to help support and stabilize weak joints, specifically the wrists, hands, knees, and ankles. For individuals suffering from severe pain in the lower extremities, wheelchairs and scooters are advised.

Pharmacotherapy may help with pain management. It is important that anti-inflammatory and other medications are neither over nor under prescribed. A wide spectrum of pain medications is available, but should be individualized for specific patients' needs. These include acetaminophen, nonsteroidal Anti-Inflammatory Drugs, cox-2 inhibitors, topical anesthetics, muscle relaxants, magnesium, tricyclic antidepressants, serotonin/norepinephrine receptor inhibitors, anti-seizure medications, short courses of steroids, glucosamine, chondroitin, tramadol, benzodiazepines, and opioids. Because many of these medications pose potential risks for side effects and drug abuse, close monitoring is imperative [2].

Medications such as proton pump inhibitors and H2-blockers may also be needed for the management of gastritis and acid reflex. In EDS patients with aortic dilatations and aneurysms, beta-blockers may be beneficial [22]. Ascorbic acid has shown to help with wound healing, chronic bruising, and hematoma formation in individuals as it is a collagen fibril cross-linking cofactor. Other medications that treat bleeding complications in EDS patients include desmopressin acetate, 1-desamino-8-*d*-arginine vasopressin, and recombinant factor VIIa [8,52,53].

In the presence of EDS complications, surgical procedures may be required, but generally are only recommended when other treatment strategies are ineffective or in emergency situations. Orthopedic procedures that may be needed include tendon repair and joint replacement. Individuals with vascular EDS experiencing arterial complications or risk of organ rupture may require surgical treatment options. Surgery is often discouraged by clinicians due to the increased risk of poor wound healing [31]. In addition, surgical procedures are not proven to provide sufficient benefit for patients with hypermobile EDS. Other procedures including prolotherapy, steroid injections, and anesthetic nerve block may also be considered.

Pregnant patients are advised to have vaginal delivery if there are no contraindications. However, if caesarean section is required, prophylactic oxytocin may be used to combat the increased risks of postpartum hemorrhage due to surgery.

Psychiatric therapy can help aid EDS patients who suffer from anxiety, depression, addiction, chronic pain, and negative emotion by educating them about their chronic disease, helping to develop coping mechanisms, and treating cognitive and neurodevelopmental disorders [18]. In addition, patients may benefit from genetic counseling by understanding the risk of disease in family members [9]. Nutritional changes may also be of benefit in hypermobile EDS [16].

Surveillance plays an important role in the management of EDS and can be carried out by consistent testing and regular checkups. Patients who show signs of aortic dilatation or mitral valve prolapse should be followed up with an echocardiogram annually to monitor their condition. In patients not presenting with cardiac abnormalities, an echocardiogram every 3 years is advised [8,30]. EDS patients face particular challenges during pregnancy which can be addressed by continuous prenatal care overseen by a high risk obstetrician or perinatologist [12]. This close monitoring is especially critical for patients in their third trimester of pregnancy as uterine rupture is a common complication of EDS. Regular blood pressure monitoring, ultrasounds, MRAs, angiographies, and other arterial screenings are recommended for individuals diagnosed with vascular EDS [9]. In addition, hypermobile EDS patients with noted bone loss should receive DEXA (Dual energy X-ray absorptiometry) about every other year [2].

Prevention of potential complications in EDS is of utmost importance as it may delay or control significant problems experienced later in life. Patients at risk for complications of EDS should refrain from activities that may cause trauma to the skin or organ systems. To prevent cutaneous manifestations, pads or bandages can be worn and contact sports or heavy lifting should be avoided to protect skin from bruising. Because EDS often results in musculoskeletal manifestations as well, excessive stretching of the joints should be limited. Aggressive management of hypertension is crucial in preventing vascular complications of EDS [11]. It is also recommended that antiplatelet and anticoagulant medications be avoided due to the increased risk of bleeding from potential injuries [8].

10. Associations

In the past few years, an association between mast cell activation syndrome (MCAS), hypermobile EDS and postural orthostatic tachycardia syndrome (POTS) has been reported in several reviews. It should be noted that the evidence for the existence of this association is scant and unsubstantiated. There is virtually no original research on such association. Moreover, mast cell activation syndrome itself is a poorly defined entity with vague and confusing criteria, and POTS has no plausible pathogenic mechanism that has been clearly defined. A review of the literature regarding this association was recently published by one of the authors of this paper [54].

11. Conclusion

Because EDS affects numerous body systems and presents with many diverse clinical features, it requires detailed clinical evaluation, genetic testing, and laboratory studies to truly understand its nature. Despite the already extensive research and evaluation of these varied subtypes, much is still unknown. Randomized clinical trials (RTC) are needed to assess the effectiveness of various management strategies such as physical therapy and pharmacotherapy on EDS patients. Additional studies must be carried out to fully grasp the significance of this disorder, and to break monumental boundaries of the medical world in this genomic era. Recognizing and discovering new aspects of genetic etiology, varied clinical presentations, and pathophysiology of EDS subtypes will allow for the expansion of a new understanding of this complex family of heritable disorders.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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