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THE CRITICAL ROLE OF EARLY DIAGNOSIS IN EHLERS-DANLOS SYNDROME: A COMPREHENSIVE REVIEW

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ABSTRACT

Introduction and purpose: Ehlers- Danlos syndrome (EDS) is a group of genetic connective tissue disorders with 13 distinguished subtypes. Approximately, 1 in 5000 people receive a diagnosis; however, this number is likely underestimated due to frequent misdiagnosis and delayed identification. The aim of this literature review is to provide a comprehensive overview of EDS, with focus on diagnostic process, common comorbidities and consequences of delayed diagnosis.
State of knowledge: Among the 13 recognized EDS subtypes hypermobile EDS (hEDS), classical EDS (cEDS), and vascular EDS (vEDS) are the most prevalent. Most subtypes can be confirmed through genetic testing, however hEDS lacks a known genetic marker and is diagnosed solely on clinical criteria. This prolongs the diagnostic process-frequently exceeding a decade- leading to psychological distress and increased risk of complications in surgery or pregnancy. Comorbidities such as POTS, MCAS, and gastrointestinal dysmotility are prevalent and further complicate clinical management.
Conclusion: Early detection and accurate diagnosis are crucial for improving patient outcomes and quality of life. It reduces the risk of complications, enables tailored treatment plans and helps with psychological distress of medical uncertainty. Healthcare professionals must have higher awareness about EDS in order to provide integrated, comprehensive care.

KEYWORDS

Ehlers-Danlos Syndrome, Diagnosis, Comorbidities, Connective Tissue Disorder, Hypermobile EDS, Vascular EDS

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Introduction.

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of genetic connective tissue disorders characterized by joint hypermobility, skin fragility, pathological wound healing and increased susceptibility to injury. It is caused by inherited mutations in genes involved in structure and biosynthesis of collagen and extracellular matrix proteins. Individuals present faulty pathways of collagen formation since birth, but the symptoms often become apparent during adolescence. To date, 20 genes associated with different EDS types were identified (Colman et al., 2022). The estimated prevalence of EDS is approximately one in 5000 people worldwide. Although historically considered a rare disease, awareness of EDS has been steadily increasing. Despite more individuals receiving a diagnosis, the availability of adequate medical care often remains insufficient. According to data, approximately 25% of patients wait over 28 years to obtain a confirmed diagnosis, which suggests that true prevalence of EDS may be underestimated (Knight et al., 2022). Clinical manifestation is predominantly musculoskeletal, however gastrointestinal, respiratory, neurological gastrointestinal, respiratory, neurological features may be present (Reina-Gutiérrez et al., 2023). The diagnostic delay is correlated with psychological distress, reduced quality of life and increased risk of serious medical complications. A great portion of EDS patients experience chronic debilitating pain, and even with promising effects concluded from clinical studies, the findings are still limited by the sample size and they are rarely specific to individual EDS subtype (Basem et al., 2022).

The aim of this article is to raise awareness of the symptoms of EDS, provide an overview of its multisystemic nature and associated comorbidities, and highlight the consequences of delayed diagnosis.

Material and Methods

A systematic review of PubMed literature (2020–2025) was conducted using the terms "ehlers-danlos syndrome", "diagnosis", "comorbidity", "vascular ehlers-danlos syndrome", “classical ehlers-danlos syndrome” or “hypermobile ehlers-danlos syndrome” with studies manually screened for relevance and credibility.

State of Knowledge

Subtypes

The most recent, 2017 EDS International classification distinguished 13 main clinical subtypes: arthrochalasia EDS (aEDS), brittle cornea syndrome (BCS), cardiac valvular EDS (cvEDS), classical EDS (cEDS), classical-like EDS (clEDS), dermatosparaxis (dEDS), hypermobile EDS (hEDS), kyphoscoliotic EDS (kEDS), musculocontractural EDS (mcEDS), myopathic EDS (mEDS), periodontal EDS (pEDS), spondylodysplastic EDS (spEDS), vascular EDS (vEDS) (Malfait et al., 2020). Among these, hEDS, cEDS and vEDS are most prevalent and clinically significant (Haem et al., 2024).

Hypermobile EDS is the most common subtype; however, pathogenic gene alterations responsible for its phenotype remain unknown, making it entirely clinical diagnosis (Miklovic & Sieg, 2023). Symptoms involve multiple systems with numerous comorbidities such as widespread chronic pain, autonomic nervous system dysfunction or gastrointestinal issues- all of which significantly reduce quality of life (Gensemer et al., 2020).

Vascular EDS is among the most severe form of EDS associated with reduced life expectancy (estimated to be approximately 51 years.) The rupture of an aneurysm or a pseudoaneurysm is considered the leading cause of death, usually occuring in the third or fourth decade of life. It has been observed that even minor trauma can precipitate aneurysm development in vEDS population. Sudden sigmoid colon perforation and uterine perforation (during pregnancy) also remain considerable death causes (Benrashid & Ohman, 2020).

Classical EDS is caused by heterozygous mutation in the COL5A1 or COL5A2 genes encoding collagen type V. The symptoms are mainly cutaneus and articular with abnormal, atrophic scarring being the most characteristic sign. Scars are especially prominent in areas prone to injury and over the pressure points (knees, elbows). Joint instability is often present. Minor muscle hypotonia with delayed motor development and skeletal malformations (e.g. scoliosis, flat feet) are frequently reported (De Paepe et al., 2018; Ritelli et al., 2020).

Table 1. Ehlers-Danlos Syndrome subtypes, with corresponding gene mutation and typical symptoms

SUBTYPE	GENE MUTATION	CLINICAL PRESENTATION
Hypermobile EDS	Unknown	Generalized joint hypermobility, hyperextensible skin, chronic pain
Vascular EDS	COL3A1 COL1A1	arterial aneurysm and ruptures, gastrointestinal tract perforation, uterus rupture
Classical EDS	COL5A1 COL5A2	Generalized joint hypermobility, hyperextensible skin, atrophic scarring
Classical-like EDS	TNXB	shoulder and ankle hypermobility, skin fragility, foot deformities, polyneuropathy,
Cardiac-valvular EDS	COL1A2	Joint hypermobility, skin hyperextensibility, Severe defects of cardiac valves, pectus deformities
Arthrochalasia EDS	COL1A1 COL1A2	Severe joint hypermobility at birth, congenital dislocation of bilateral hips, atrophic scarring
Dermatosparaxis EDS	ADAMTS2	Extreme skin fragility, short posture and fingers, delayed closure of fontanels, facial dysmporhism
Kyphoscoliotic EDS	PLOD1 FKBP14	Kyphoscoliosis, joint hypermobility, muscle hypotonia, vascular and ocular fragility
Brittle cornea Syndrome	ZNF469 PRDM5	Extreme cornea fragility, blue sclerae, severe myopia, retinal detachment, early keratoconus and keratoglobus, hearing loss
Spondylodysplastic EDS	B4GALT7 B3GALT6 SLC39A13	Muscle hypotonia, delayed cognitive and motor development, short stature, bowed limbs
Musculocontractural EDS	CHST14 DSE	Kidney stones, craniofacial dysmporhies, multiple contractures, club foot
Myopathic EDS	COL12A1	Muscle weakness and atrophy, joint hypermobility, delayed motor development, proximal joints contractures
Periodontal EDS	C1R C1S	Early, severe periodontitis, gingival detachment, pretibial plaques, increased risk of infection

Diagnosis

The diagnosis of Ehlers Danlos syndrome relies on a combination of family history, clinical evaluation and (in most subtypes) on genetic testing. It is important to note that general diagnosis of EDS is insufficient - each subtype has a different molecular background and phenotype. In order for patients to receive an adequate management of symptoms a specific subtype should be identified (van Dijk et al., 2023). Each subtype has its own diagnostic criteria and every diagnosis (if possible) should be confirmed by targeted genetic testing. In this paper, the criteria for hEDS, vEDS and cEDS will be highlighted as they account for approximately 90% of all EDS cases (Ritelli et al., 2020).

Hypermobile EDS

Diagnosis of hEDS remains the most challenging of all subtypes as no genetic cause has been identified to date. Final classification is made based upon three- criteria model proposed in 2017 by the international EDS Consortium. Criterion 1 examines the degree of joint hypermobility using the Beighton score. Beighton scale includes five joint assessments: extension of knees greater than 190°, extension of elbows greater than 190°, passive apposition of the thumbs to the 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. The maximum score is 9 with a score of 5 or more out of 9 can be indicative of joint hypermobility (Islam et al., 2021). However, it should be noted that joint hypermobility is often physiological in children. Therefore, distinction between developmental features and signs of EDS is even more difficult in pediatric population. A cut-off score of 6 or more out of 9 was established as an indicator of children joint hypermobility; nonetheless, a more extensive clinical examination is recommended in this age group (Tofts et al., 2023). However, since joint flexibility decreases with age, often leading to underdiagnosis in adults, a Beighton score of 4 out of 9 is considered sufficient in patients over the age of 50 (Islam et al., 2021).

Table 2. The Beighton scale for joint hypermobility assessment.

	Left limb	Right limb	Both limbs	Spine
Extension of knees greater than 190°	**1**	**1**	**2**	**-**
Extension of elbows greater than 190°	**1**	**1**	**2**	**-**
Passive apposition of the thumbs to the forearm	**1**	**1**	**2**	**-**
Extension of fifth fingers greater than 90°	**1**	**1**	**2**	**-**
Forward flexion of the trunk with palms flat on the ground while knees are fully extended	**-**	**-**	**-**	**1**

The Beighton scale is followed by a five-point questionnarie:

1. Can you now (or could you ever) place your palms flat against the ground while keeping your knees fully extended?
2. Can you now (or could you ever) flex your thumb to touch the forearm?
3. As a child, were you capable of performing certain acrobatic figures such as the splits?
4. During adolescence, did you have recurrent dislocations of the shoulders or knees?
5. Are you “double-jointed”?

If a patient agrees with more than two of these statements, joint hypermobility can be diagnosed with a Beighton score that is one point below the specific diagnostic threshold.

Criterion 2 consists of three domains: family history, skin involvement and systemic manifestations. It is considered met if at least two of these features are present.

Feature A examines the presence of soft or hyperextensible skin, unexplained stretch marks, recurrent abdominal hernias, hand nodules, atrophic scars, a dilated aortic root, prolapsed mitral valve, organ descent, dental crowding, arachnodactyly, arm span greater than height. Feature A is satisfied if at least five of these features can be confirmed.

Feature B is met if an individual has a positive family history defined as a first-degree relative with a diagnosis of hEDS according to current criteria.

Feature C evaluates musculoskeletal symptoms: chronic widespread pain lasting for three or more months, recurrent joint dislocations without trauma involved, musculoskeletal pain involving at least two extremities every day for three or more months. Reporting any of these symptoms supports feature C.

Criterion 3 incorporates the exclusion of other connective tissue diseases.

Classical EDS

At present, the clinical diagnosis of cEDS is established based on the presence of either skin hyperextensibility and atrophic scars or generalized joint hypermobility (assessed using the Beighton scale) accompanied by at least three of the minor criteria.

Minor criteria include:

– Increased suscepectibility to bruising (especially in unusual sites)
– Soft and doughy skin
– Fragile skin
– Molluscoid pseudotumors (abnormal growth associated with scars over pressure points such as knees, elbows)
– Subcutaneous spheroids (firm, palpable spheroid masses, usually appearing on the shins and forearms; they can be calcified)
– Hernias
– Epicanthal folds
– Sprains, joint pain, subluxations, and other complications resulting from joint hypermobility
– First degree family member with a diagnosis of cEDS according to current criteria.

When the clinical presentation fulfills these criteria, the patient should be referred for molecular testing to confirm this specific EDS subtype (Caliogna et al., 2021). However, the negative molecular testing does not rule out the cEDS diagnosis, especially if the phenotype strongly aligns with clinical criteria (Ritelli et al., 2020).

Vascular EDS

Major diagnostic criteria for vEDS consist of:

– Family member with diagnosed vEDS confirmed by COL3A1 mutation
– A history of arterial rupture at a young age
– Sudden perforation of sigmoid colon without any known bowel pathology
– Uterine rupture in the third trimester of the pregnancy without history of c-section or significant perineal trauma
– Formation of carotid-cavernous sinus fistula in the absence of an earlier trauma

Minor criteria:

– Bruises in atypical areas and not correlated with identified injury
– Thin and transparent skin with visible subcutaneous veins
– Sudden onset pneumothorax
– Acrogeria (premature aging of the hands and the feet)
– Congenital talipes equinovarus (“clubfoot”)
– Developmental dysplasia of the hip
– Small joints hypermobility
– Tendon and muscle injuries
– Keratoconus
– Characteristic facial features (sunken eyes, narrow nose, absent earlobes)
– Recedeing gums
– Varicose veins before age 30

If a patient presents with at least one of the major criteria or any combination of minor criteria, the genetic testing should be performed (Demirdas et al., 2024).

Differential Diagnosis

Additionally, many EDS subtypes share overlapping clinical characteristics with other connective tissue disorders, making differential diagnosis a crucial aspect of clinical examination.

Marfan syndrome and Loyes-Dietz syndrome are particularly important to consider as they both present with vascular involvement that closely resembles manifestations observed in vascular EDS. For example, arterial dissections and aortic aneurysms can occur in all three conditions; however, the underlying genetic causes differ- mutations in the FBN1 gene are responsible for Marfan syndrome, whereas mutations in TGFBR1 or TGFBR2 are characteristic of Loeys-Dietz syndrome (Johansen et al., 2021; Udugampolage et al., 2025).

Osteogenesis imperfecta and Stickler syndrome may also display significant joint hypermobility, a hallmark of several EDS subtypes, although they differ in skeletal fragility and ocular manifestations (Neto et al., 2024). Abnormal skin findings seen in EDS may be similar to those found in various neuromuscular conditions, while hypotonia combined with generalized joint hypermobility may also be seen in rare genetic syndromes (van Dijk et al., 2023).

Table 3. Comparison of key clinical features of Ehlers-Danlos syndrome, Marfan syndrome, and Loeys-Dietz syndrome

	Ehlers-Danlos Syndrome (EDS)	**Marfan Syndrome**	**Loeys-Dietz Syndrome**
Inheritance Pattern	AD or AR (depending on subtype)	AD	AD
Main Genes Involved	COL5A1, COL3A1, others	FBN1	TGFBR1, TGFBR2, SMAD3, TGFB2
Vascular Involvement	Fragile vessels, aneurysms (esp. vEDS)	Aortic root dilation, dissection	Widespread aneurysms, dissections
Joint Manifestations	Marked hypermobility	Sometimes mild hypermobility	Mild joint laxity
Skin Findings	Thin, stretchy, hyperextensible	Thin skin, not significantly elastic	Translucent skin, easy bruising
Skeletal Features	Scoliosis, joint dislocations	Tall stature, arachnodactyly	Chest wall deformities, arachnodactyly
Facial Features	Varies by subtype	Long face, deep-set eyes	Hypertelorism, retrognathia
Prevalence	~1:5,000 (varies by subtype)	~1:5,000	Rare, <1:100,000

Benefits of an Early Diagnosis

One of the greatest challenges in the treatment of Ehlers-Danlos syndrome is the delay in receiving an accurate diagnosis. Some studies suggest that, on average, patients with hEDS spend 10.39 years and consult approximately 15.6 specialists before being correctly diagnosed. At the beginning of this diagnostic journey, many patients already experiencing symptoms from multiple systems, with pain and chronic fatigue prompting the need for diagnosis (Halverson et al., 2023).

Prolonged path to diagnosis of EDS has been linked with psychological distress and increased risk of suicidal ideation or attempts. Patients report often feeling ignored by healthcare professionals, as their symptoms are frequently dismissed as having purely psychological or psychiatric basis. Some studies have found that individuals suspected of having EDS, but without confirmed diagnosis, experience the highest levels

of emotional distress. It has been suggested that medical uncertainty may further worsen the mental health (Rocchetti et al., 2021).

Confirmation of specific EDS subtype diagnosis is essential for establishing an effective, individualized treatment plan. Patients should be warned against hyperextension or overstretching and informed about appropriate preventive measures to reduce the risk of subluxations, joint dislocations, overuse-related pain. It is recommended that physical therapy focuses on improving joint stability and preventing painful muscle spasms. Exercises must remain low resistance to minimize the risk of injury (Song et al., 2020). Avoiding injury is particularly important for individuals with EDS, as orthopedic surgeries are one of the most prevalent surgeries in this group (Gagnon et al., 2023). However, every surgical intervention in patients with EDS should be closely evaluated, because of significantly higher percentage of postoperative complications such as impaired wound healing. One study investigating the outcomes of total knee arthroplasty in EDS patients emphasized the need for attentive pre- and postoperative monitoring to reduce the likelihood of any wound complications (Fuqua et al., 2024).

In addition, due to high incidence of arterial aneurysms and ruptures in vascular EDS, aortic and peripheral arterial repairs, are performed at significantly higher rates compared to the general population. Not only are vascular surgeries are more frequent in this group-, but they are also more often followed by hemorrhagic complications (Jayarajan et al., 2020). Individuals with undiagnosed vEDS diagnosis are at increased risk of intraoperative mortality and require more emergency surgeries. These findings further highlight the importance of early detection and diagnosis of EDS (Benrashid & Ohman, 2020).

Comorbidities

Not only is Ehlers-Danlos syndrome itself a debilitating disease, but it is associated with various comorbidities, complicating both diagnosis and manegment. The most prevalent disorders include:

- Postural orthostatic tachycardia (POTS)
- Complex regional pain syndrome (CRPS)
- Temporomandibular disorders (TMD)
- Mast cell activation syndrome (MCAS)
- Gastrointestinal dysmotility (gastroesophageal reflux disease (GERD), chronic nasuea)
- Endometriosis
- Polycystic ovarian syndrome (PCOS)
- Neurological complications (craniocervical instability (CCI), migraines (Halverson et al., 2023))

A broad spectrum of gastrointestinal symptoms is commonly observed in EDS patients such as diarrhea, constipation, abdominal pain, bloating, dysphagia, rumination, dyspepsia, GERD, obstructive defecation, and early satiety. These symptoms not only occur more frequently in individuals with EDS, but also tend to be more severe and resistant to treatment. Furthermore, evidence suggests a potential association between EDS and autoimmune or inflammatory gastrointestinal diseases such as celiac disease, Crohn's disease, and ulcerative colitis (Thwaites et al., 2022).

TMD encompass a group of conditions affecting temporomandibular joint, masticatory muscles and surrounding structures. These disorders usually present with pain, restricted jaw movement and functional impairment, leading to difficulties with eating and speaking. Studies have shown that TMD may negatively impact oral health- related quality of life (Yekkalam et al., 2024).

An increasing number of patients present with a combination of POTS, MCAS and EDS diagnosis. Although a definitive pathophysiological link between these three conditions has not yet been established, POTS remains poorly understood, and diagnostic criteria for MCAS are still imprecise, which makes it a frequent diagnosis among patients with a broad spectrum of non-specific systemic symptoms (Kohn & Chang, 2019).

Even up to 31.6% of individuals with hEDS may experience (CCI) as a result of ligament laxity. Neurological and musculoskeletal symptoms are determined by the spinal level of instability, but some examples are headaches, vision changes, limb pain and weakness, dysphagia, and tinnitus. In some cases, CCI may coexist with tethered cord syndrome which can manifest as lower back pain, leg cramps, loss of sensation, bladder incontinence, and sexual dysfunction. The awareness of this potential overlap in hEDS patients is still limited resulting in underdiagnosis and reduced quality of life (Gensemer et al., 2024).

Pregnancy in women with EDS has been shown to carry remarkably higher risk of complications and maternal deaths, Obstetric complications are more common in this population compared to healthy pregnant women and the most common ones include placenta previa, prepartum haemorrhage, cervical insufficiency,

and pelvic floor pain. It has been hypothesized that this group of patients may benefit from early cesarean delivery potentially reducing the risk of painful and severe perineal tears. However, there is still limited research on that subject and more detailed observations should be carried out, with a focus on pregnancy risks specific to each EDS subtype (Kang et al., 2020).

Conclusions

Ehlers-Danlos syndrome (EDS) remains an underdiagnosed condition, likely due to the wide variety of symptoms, which are often multisystemic and non-specific. Most subtypes can be confirmed through molecular testing targeting specific mutations. However, the most prevalent form- hypermobile EDS, accounting for approximately 90% of all EDS cases- lacks a known genetic cause, and its diagnosis relies solely on clinical criteria. This prolongs the diagnostic process, which typically exceeds 10 years and involves consultations with multiple specialists. It contributes to psychological distress and increased risk of suicidal ideation.

Without confirmed diagnosis, personalized treatment plans cannot be effectively implemented, despite the fact that tailored medical care is crucial for EDS patients. Surgical procedures, as well as pregnancy, are both associated with a higher risk of complications, further emphasizing the importance of accurate and timely diagnosis. In addition, untreated EDS may result in serious consequences such as craniocervical instability or obstetric complications. Patients frequently present with a variety of comorbidities, suggesting the need for multidisciplinary specialist care.

Healthcare professionals should adopt a more comprehensive and integrative approach to EDS as there is no known etiological treatment. Further research is needed to develop therapeutic strategies specific to each EDS subtype.

Author's contribution

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