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Hypermobile Ehlers-Danlos Syndrome

Synonyms: Ehlers-Danlos Syndrome Hypermobility Type, Ehlers-Danlos Syndrome Type III, hEDS

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Summary

Clinical characteristics

Hypermobile Ehlers-Danlos syndrome (hEDS) is characterized by generalized joint hypermobility, joint instability, pain, soft and hyperextensible skin with atrophic scars and easy bruising, dental crowding, abdominal hernias, pelvic organ prolapse, marfanoid body habitus, mitral valve prolapse, and aortic root dilatation. Subluxations, dislocations, and soft tissue injury are common; they may occur spontaneously or with minimal trauma and can be acutely painful. Degenerative joint and chronic soft tissue disorders may arise due to repeated injury. Chronic pain, distinct from that associated with acute injury, is common and often neuropathic in nature. Chronic fatigue, functional bowel disorders, cardiovascular autonomic dysfunction, swallow and phonation disorders, sleep disorders including apnea, migraine, entrapment and peripheral neuropathies, inflammation from mast cell activation disorders, anxiety disorders, and urogynecologic disorders are common. Mitral valve prolapse and aortic root dilatation, when present, are typically of a mild degree with no increased risk of cardiac complications.

Diagnosis/testing

The diagnosis of hEDS is established in an adult proband based on 2017 international clinical diagnostic criteria. Currently, no underlying genetic, epigenetic, or metabolomic etiology has been identified for hEDS.

Management

Treatment of manifestations: Tailored treatment with exercise to increase core and extremity muscle strength and tone, proprioception, and joint stability; braces and splints to improve alignment and control; occupational therapy for assistive devices (e.g., wide-grip writing utensils, home and work ergonomics); physical therapy for assistive devices (e.g., wheelchair or scooter, suitable mattress, soft neck collar); pain management tailored to cause and symptoms; platelet disorders may respond to tranexamic or mefenamic acid; nutrition advice for micronutrient deficiencies; gastritis, gastroparesis, and gastroesophageal reflux disease may require intensive pharmacotherapy; therapies for other gastrointestinal, cardiovascular, ocular, neurologic, and urogynecologic

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manifestations; orthodontic, maxillofacial, and ENT management for narrow palate, crowded teeth, temporomandibular joint laxity and dysfunction, and disorders of swallow and phonation; standard treatment of periodontal disease; avoidance of triggers for mast cell activation disorder and pharmacotherapy or monoclonal biologic therapy as needed; counseling and pharmacotherapy for neurobehavioral and psychiatric manifestations.

Surveillance: Assess for joint manifestations, pain, disability, bleeding issues, functional bowel disorders, autonomic dysfunction, oral health needs, phonation and respiratory issues, sleep issues, vision issues, headaches and other neurologic manifestations, inflammatory disease, neurobehavioral and psychiatric manifestations, and urogynecologic manifestations annually or at each visit. Dual-energy x-ray absorptiometry in those with height loss greater than one inch, atypical/low trauma fractures, or radiographs suggestive of osteopenia. Follow-up echocardiography in those with aortic root dilatation.

Agents/circumstances to avoid: High-impact activity may increase the risk of acute subluxation/dislocation and acute and chronic pain. Chiropractic adjustment and yoga are not contraindicated but like all other physical treatments must be performed in ways that avoid iatrogenic subluxations or dislocations. Autonomic concerns, gastrointestinal disorders, and intolerances may preclude use of medications or their excipients (e.g., common analgesics in someone with slow gastrointestinal transit, vasodilator in a person with orthostatic intolerance).

Pregnancy management: Preconceptual (e.g., musculoskeletal health and medication use), antenatal (e.g., joint instability, pelvic strength, hernias, and pain management), intrapartum (e.g., birth choices, mobility in labor, anesthesia), and postpartum (e.g., wound healing, pelvic health, newborn/infant care) issues should all be addressed.

Genetic counseling

Hypermobile EDS is inherited in an autosomal dominant manner with variable expression of signs and variable severity of symptoms among affected family members. Most individuals diagnosed with hEDS have an affected parent, although a detailed history and examination of the parents is often necessary to recognize that a parent has a current or prior history of joint laxity, easy bruising, and skin manifestations despite the absence of serious complications. Each child of an individual with hEDS has a 50% chance of inheriting hEDS. Because the gene(s) and pathogenic variant(s) responsible for hEDS have not been identified, prenatal and preimplantation genetic testing are not possible.

Diagnosis

The diagnostic criteria for hypermobile Ehlers-Danlos syndrome (hEDS) were revised by the International Consortium on Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders in 2017 [Malfait et al 2017].

Suggestive Findings

Hypermobile EDS should be suspected in adult probands (individuals who have reached biologic maturity) with the following clinical features [Malfait et al 2017]:

- Joint instability including subluxations and dislocations
- Musculoskeletal pain
- Soft, hyperextensible skin, with atypical stretchmarks and/or scarring
- Dental crowding and a high or narrow-arched palate
- Abdominal hernias
- Pelvic organ prolapse
- A marfanoid body habitus
- Mitral valve prolapse and/or aortic root dilatation

- Family history consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

In addition, hEDS is associated with clinical manifestations that are not included in the published diagnostic criteria including [Hakim et al 2021]:

- Chronic fatigue
- Easy bruising
- Functional bowel disorders (gastroesophageal reflux, gastritis, early satiety, delayed gastric emptying, irritable bowel syndrome, constipation)
- Additional cardiovascular manifestations (autonomic dysfunction, Raynaud phenomenon, acrocyanosis)
- Reduced efficacy of local anesthetics
- Laryngeal and breathing disorders including apnea
- Neurologic complications (migraine, Chiari I malformation, cerebrospinal fluid leaks, craniocervical instability and associated cord and nerve root pathology, tethered cord, entrapment and peripheral neuropathy, small fiber neuropathy)
- Mast cell activation disorders and immune deficiency including primary immune deficiency
- Anxiety disorders
- Autism and attention-deficit/hyperactivity disorder
- Urogynecologic manifestations (dysmenorrhea, menorrhagia, interstitial cystitis, urinary incontinence, pelvic organ prolapse)

Establishing the Diagnosis

The diagnosis of hEDS can be established in an adult proband based on clinical diagnostic criteria [Malfait et al 2017]. The 2017 clinical diagnostic criteria were developed for the diagnosis of adults; many of the clinical features arise over time and may not be present in childhood and adolescence. A clinical diagnostic classification for symptomatic joint hypermobility in younger individuals was developed by Tofts et al [2023]. Using this system, affected children are classified as having pediatric generalized hypermobility or pediatric hypermobility spectrum disorder with combinations of comorbid concerns and/or mild skin concerns (see Differential Diagnosis), with the recommendation that younger individuals should be monitored for evolving clinical manifestations and reevaluation for hEDS should be done when the individual reaches biologic maturity.

No underlying genetic etiology has been identified for hEDS, and thus molecular genetic testing cannot be used to establish the diagnosis.

The clinical diagnosis of hEDS can be established in an adult proband (an individual who has reached biologic maturity) with all three of the following criteria:

1. Generalized joint hypermobility with a Beighton score of:
   a. ≥5 for adolescents who have reached biologic majority and adults age ≤50 years
   b. ≥4 for those age >50 years
2. Evidence of two of the following: systemic manifestations of a more generalized connective tissue disorder, family history, and musculoskeletal complications
3. Exclusion of alternative diagnoses

Criterion 1

Generalized joint hypermobility. The following standardized performance of the Beighton test is recommended [Beighton et al 1973]. One point is scored for each of the following:

- **Passive dorsiflexion of each fifth finger greater than 90 degrees.** This should be assessed with the palm and forearm resting on a flat surface and is considered positive only if the fifth metacarpal-phalangeal

joint (MCP) can be extended more than 90 degrees. Ability to extend the tip of the fifth finger to a position proximal to the MCP is insufficient to be called positive if the MCP does not extend more than 90 degrees.

- **Passive apposition of each thumb to the flexor surface of the forearm.** This should be assessed with the elbow extended and hand pronated.
- **Hyperextension of each elbow greater than 10 degrees.** This should be measured with a goniometer, with the hand supinated, elbow fully extended, and shoulder abducted to 90 degrees.
- **Hyperextension of each knee greater than 10 degrees.** This should be measured with a goniometer, with the individual standing and knees fully extended.
- **Ability to place the palms flat on the floor with the knees fully extended.** This should be assessed with the knees locked in extension and the feet together and is considered positive only if the total palm of both hands lies flat on the floor just in front of the feet. Slight flexion of the knees, spreading of the feet, failure to get the heels of the palms to the floor, and positioning the hands more than a few inches in front of the feet are common causes of false positive scoring of this point.

In individuals with acquired limitation of joint mobility, generalized joint hypermobility may be confirmed in an individual whose Beighton score is one point below the age-specific cutoff if there are two or more positive answers to the five-point questionnaire (5PQ) [Hakim & Grahame 2003]:

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself "double-jointed"?

Note: In clinical practice, individuals with a history of joint hypermobility – suggested by a positive 5PQ (≥2 positive answers) – but scoring two or more points below the age-specific Beighton cutoff should be assessed further outside of the Beighton score (e.g., shoulders, hips, ankles, toes) for evidence of generalized joint hypermobility. In some individuals, joint hypermobility may be local or regional, and these individuals should be evaluated for hypermobility spectrum disorder [Castori et al 2017] (see Differential Diagnosis).

Criterion 2

At least two of Features A, B, and C must be present.

Feature A. Five or more of the following systemic manifestations of a more generalized connective tissue disorder:

- **Unusually soft or velvety skin.** This is an inherently subjective feature. It should be assessed in the absence of recent application of moisturizer, and a high threshold is recommended.
- **Mild skin hyperextensibility,** assessed at a site lacking excess or loose skin and without evidence of prior trauma by gently pulling until resistance is met. An ideal location is the volar surface of the nondominant forearm, where the upper limit of normal extensibility is 1.5 cm. Extensor surfaces of joints have excess skin and should not be used. More significant extensibility (e.g., >2.0 cm) should prompt consideration of other EDS types.
- **Unexplained* striae on the back, groin, thighs, breast, and/or abdomen** in adolescents, men, or prepubertal females (* i.e., without a history of significant gain or loss of body fat or weight, or other medical conditions such as Cushing syndrome)
- **Bilateral piezogenic papules of the heel** (i.e., herniations of subcutaneous heel fat visible upon standing); must be present bilaterally to be considered positive.
- **Recurrent or multiple abdominal hernias,** such as umbilical, inguinal, or femoral. Hiatal hernia does not count toward this feature.

- **Atrophic scarring** involving at least two sites and without the formation of papyraceous and/or hemosideric scars as seen in classic EDS. Atrophic scarring is defined as scars from linear traumatic laceration(s) and/or surgical incision(s) that are unusually shallow and/or wider than the original wound. Atrophic scars as the result of wound infections or inflammatory conditions do not count toward this feature, and elliptical incisions (e.g., for removal of nevi) may be difficult to assess without knowing the size of the original wound.
- **Pelvic floor, rectal, and/or uterine prolapse** in children, men, or nulliparous women without a known predisposing medical cause for the prolapse
- **Dental crowding** (including a history of crowding corrected by orthodontia) and **high or narrow palate**. Both conditions must be positive to count toward this feature.
- **Arachnodactyly,** defined as either bilateral positive wrist sign or bilateral positive thumb sign
- **Arm span-to-height ratio ≥1.05**
- **Mitral valve prolapse,** based on echocardiographic criteria
- **Aortic root dilatation** with a z score >2 standard deviations above the mean

Feature B. Positive family history, with at least one first-degree relative independently meeting the current diagnostic criteria for hEDS.

Feature C. At least one of the following musculoskeletal complications that is most likely accounted for by the presence of joint hypermobility rather than primarily caused by another rheumatologic disorder (see Criterion 3; hEDS and other rheumatologic disorders can co-occur):

- Musculoskeletal pain in two or more limbs, recurring daily for at least three months
- Chronic widespread pain for at least three months
- Recurrent joint dislocations or frank joint instability, in the absence of trauma:
    - Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times

      OR
    - Medical confirmation of joint instability at two or more sites not related to trauma

Criterion 3

All the following must be met:

- Absence of unusual skin, ocular, periodontal, vascular, or visceral organ tissue fragility or skeletal dysplasia, which should prompt consideration of other types of EDS (See Differential Diagnosis.)
- Exclusion (based on history, physical exam, and/or molecular genetic testing) of alternative diagnoses associated with joint hypermobility due to hypotonia and/or connective tissue laxity such as neuromuscular disorders, other heritable connective tissue disorders, and skeletal dysplasias (See Differential Diagnosis.)
- Other rheumatologic disorders may be the cause of musculoskeletal pain and inflammation (e.g., osteoarthritis, systemic lupus erythematosus, and rheumatoid arthritis); these disorders may coexist with hEDS. In individuals with a rheumatologic disorder, the diagnosis of hEDS requires that sufficient features in Criterion 2, Feature C are due to hEDS and not the co-occurring rheumatologic disorder.

Molecular Genetic Testing

The etiology of hEDS is unknown; genetic heterogeneity is likely. There are currently no molecular genetic tests available to establish the diagnosis of hEDS.

Clinical Characteristics

Clinical Description

Hypermobile Ehlers-Danlos syndrome (hEDS) is characterized by generalized joint hypermobility, joint instability, pain, soft and hyperextensible skin with atrophic scars and easy bruising, dental crowding, abdominal hernias, pelvic organ prolapse, marfanoid body habitus, mitral valve prolapse, and aortic root dilatation. Subluxations, dislocations, and soft tissue injury are common; they may occur spontaneously or with minimal trauma and can be acutely painful. Degenerative joint and chronic soft tissue disorders may arise due to repeated injury. Chronic pain, distinct from that associated with acute injury, is common and often neuropathic in nature. Chronic fatigue, swallow and phonation disorders, functional bowel disorders, cardiovascular autonomic dysfunction, migraine, entrapment and peripheral neuropathies and dystonia, urogynecologic disorders, anxiety disorders, and inflammation from mast cell activation disorders are common. Mitral valve prolapse and aortic root dilatation, when present, are typically of a mild degree with no increased risk of cardiac complications.

Joint hypermobility and joint instability. Excessive joint range of motion with or without instability in the form of subluxations and/or dislocations is evident in the history and on examination. Younger individuals tend to have more joint laxity than older individuals, and females tend to have more joint laxity than males. Joint laxity with instability, with or without reduced proprioception, increases the risk of the following complications:

- **Acute joint / soft tissue injury** that can last for hours or days after an event. All sites can be involved, including the extremities, vertebral column, costovertebral and costosternal joints, clavicular articulations, and temporomandibular joints. A person may also develop abnormal movement patterns and experience reduced physical function when compensating for joint instability and injury, including fear of movement (kinesiophobia) [Pacey et al 2013, Engelbert et al 2017, Simmonds 2021].
- **Chronic joint / soft tissue injury.** Osteoarthritis and chronic tendinopathies and bursitis may occur at a younger age than in the general population, possibly because of chronic joint instability resulting in increased mechanical stress. Temporomandibular joint (TMJ) dysfunction is relatively common and is an example of joint degeneration and osteoarthritis [Willich et al 2023]. Hip degenerative disease can lead to conditions such as femoroacetabular impingement [Clapp et al 2021]. Recurring displacement of the patella may contribute to chondromalacia [al-Rawi & Nessan 1997].

Pain. Pain is variable in age of onset (childhood to late adulthood), location, duration, quality, severity, and response to therapy. Chronic pain, distinct from that associated with acute injury, can be physically and psychosocially disabling [Chopra et al 2017]. Fatigue and sleep disturbance are frequently associated with pain. Headaches, especially migraines, are common. Cervical muscle tension, temporomandibular dysfunction, and stress may be contributing factors. Several recognizable pain syndromes are reported:

- **Muscular or myofascial pain,** localized around or between joints, often described as aching, throbbing, or stiff in quality, may be attributable to myofascial spasm. Palpable spasm with tender points (consistent with fibromyalgia) is often demonstrable, especially in the paravertebral musculature [Fairweather et al 2023]. Myofascial spasm possibly occurs in response to chronic joint instability, but this has not been systematically studied. Myofascial release often provides temporary relief.
- **Neuropathic pain,** variably described as electric, burning, shooting, tingling, or hot or cold discomfort, may occur in a radicular or peripheral nerve distribution or may appear to localize to an area surrounding one or more joints [Chopra et al 2017]. Nerve conduction studies are usually not diagnostic. Skin biopsy may reveal reduction or absence of small nerve fibers [Fernandez et al 2022]. Neuropathic pain may result from direct nerve impingement due to subluxated vertebrae, herniated discs, vertebral osteoarthritis, or joint subluxations and dislocations. In addition, there may be mild-to-moderate nerve compression within

areas of myofascial spasm or compression, for example, as seen in thoracic outlet syndrome [Levine & Rigby 2018].
- **Pain may arise from tissue damage,** including tendon injury and cartilage tears.
- **Visceral pain arising from the gastrointestinal tract and urogynecologic tissues** are common presenting concerns.
- **Osteoarthritic pain** typically presents as aching pain in the joints, frequently associated with stiffness. It is often exacerbated by activity.

Skin. The skin is often soft and mildly hyperextensible. Piezogenic papules (small herniations of subcutaneous fat through the underlying dermis of the heel occurring only when weight-bearing) are common but rarely painful. Atypical stretchmarks (e.g., across the back, chest, axilla), atrophic scars, and easy bruising are common findings [Doolan et al 2023]. Spontaneous bruising without obvious trauma or injury is common and can be mistaken for nonaccidental trauma [Castori 2015].

Hematologic. Mildly prolonged bleeding, epistaxis, bleeding from the gums, and menorrhagia may also occur. The bleeding time may or may not be prolonged, and abnormalities of von Willebrand factor and platelet function have been reported. Capillary fragility and/or impaired soft tissue integrity may also play a role [Jesudas et al 2019].

Gastrointestinal (GI). Functional GI disorders, now termed disorders of gut-brain interaction, are common and underrecognized in individuals with hEDS [Thwaites et al 2022]. Gastroesophageal reflux and gastritis may persist despite polytherapy with maximal doses of proton pump inhibitors, H2 blockers, and acid-neutralizing medications. Early satiety and delayed gastric emptying may occur and may be exacerbated by opioids and other medications. Irritable bowel syndrome may manifest with diarrhea and/or constipation, bloating, abdominal cramping, and rectal mucus. Anorectal manifestations include rectocele, rectal prolapse, and hemorrhoids. GI manifestations are associated with cardiovascular autonomic manifestations, mast cell activation disorders, and nutritional deficiencies [Lam et al 2022]. Abdominal wall herniation may be present. In individuals with unexplained GI and pelvic pain, the symptoms may be arising from nerve entrapment in the abdominal wall or from vascular compression syndromes [Sandmann et al 2021].

Cardiovascular

- **Autonomic dysfunction.** Many affected individuals report atypical chest pain, palpitations at rest or on exertion, and/or orthostatic intolerance with syncope or near syncope [Hakim et al 2017, Roma et al 2018]. Clinic room testing may demonstrate postural hypotension and/or postural tachycardia. Ambulatory 24-hour monitoring of heart rate, blood pressure, and symptoms is also an effective method of identifying autonomic dysfunction. Tilt table testing with ancillary supplementary testing such as catecholamine levels can delineate the nature and relationships of hypotension, tachycardia, and syncope, revealing, for example, neurally mediated hypotension [Cheshire & Goldstein 2019].
- **Mitral valve prolapse (MVP).** The incidence of MVP was 7% in one study of 258 individuals with either hEDS or hypermobility spectrum disorder [Rashed et al 2022]. A similar incidence of MVP was reported in a study of 209 individuals with hEDS or classic EDS (cEDS) [Asher et al 2018]. Studies suggest that MVP is mild, nonprogressive, and does not require routine monitoring.
- **Aortic root dilatation.** The incidence of aortic root dilatation was 15% in one study of 258 individuals with either hEDS or hypermobility spectrum disorder [Rashed et al 2022]. A study of 95 children diagnosed with hEDS or cEDS showed approximately 2% had aortic root dilatation [Paige et al 2020]. The same 2% incidence of aortic root dilatation was found in a study of 62 adults with hEDS [Pietri-Toro et al in 2023].
- **Abdominal vascular compression syndromes** such as median arcuate ligament syndrome and superior mesenteric artery syndrome have been identified as a cause of pain, disordered eating, and GI dysfunction in individuals with hEDS. In those with GI manifestations that cannot be readily attributed to structural

malfunction, autonomic dysfunction, or inflammation of the GI tract, abdominal compression syndromes should be considered; symptoms can improve significantly following decompressive surgery [Sandmann et al 2021].

Oral/dental. High, narrow palate and dental crowding are common in individuals with hEDS. Gastroesophageal reflux may cause dental erosion. Many individuals with hEDS report poor efficacy of local anesthetic, often first realized during dental treatment and requiring additional dosage or alternative methods of analgesia [Schubart et al 2019]. In addition, many have TMJ dysfunction, which can impede oral assessment [Willich et al 2023], and oral and TMJ concerns may impede use of positive pressure therapies for apnea [Gaisl et al 2017, Sedky et al 2019]. Severe periodontal disease and early-onset dental decay not accounted for by lifestyle is not common in individuals with hEDS and should prompt assessment for periodontal EDS (see Differential Diagnosis) [Lepperdinger et al 2021].

ENT. Hypermobile EDS is associated with variable laryngeal and upper airway inflammation, dysphagia, and dysphonia. Individuals with hEDS are also more likely to report severe airway disease [Williams et al 2023]. Gastroesophageal reflux and mast cell activation disorders both contribute to pharyngeal and throat inflammation.

Sleep disturbance. Sleep can be disrupted in individuals with hEDS due to pain and cardiovascular autonomic disturbance. Sleep disorders also appear to be common in hEDS, including obstructive sleep apnea, insomnia, hypersomnia, and periodic limb movement disorder [Gaisl et al 2017, Domany et al 2018, Sedky et al 2019]. Sleep apnea may be underrecognized in women with hEDS, as it is in the general population [Shepertycky et al 2005].

Ocular. Detailed and systematic evaluation of ocular findings in several small cohorts and case control studies have demonstrated that xerophthalmia (dry eye), high myopia (more than −6 diopters), increased lens curvature (but not keratoconus), eyelid laxity, minor lens opacities, and convergency insufficiency are more common in individuals with hEDS. Minor increases in corneal curvature and lens opacities are incidental findings in those with hEDS and do not cause problems with vision [Asanad et al 2022].

Neurologic/neuromuscular. Neurologic and neuromuscular diseases reported to be more common in those with hEDS include headaches (primarily migraines, TMJ dysfunction-induced headaches, and relating to neck pathology), intracranial hypertension, intracranial hypotension (e.g., due to cerebrospinal fluid leak), Chiari I malformation, craniocervical instability leading to cervicomedullary syndrome, dystonia, tethered cord, Tarlov cysts, nerve entrapment and deformation neuropathies, reduced proprioception, small fiber neuropathy, and autonomic dysfunction [Hamonet et al 2016, Henderson et al 2017, Malhotra et al 2020, Fernandez et al 2022, Zingman et al 2022].

Mast cell activation disorders (MCAD) and immune deficiencies. MCAD reported in individuals with hEDS include single-organ disease such as asthma, urticaria, and gastroenteritis, as well as multiorgan systemic involvement such as mast cell activation syndrome and anaphylaxis. MCAD may contribute to several of the clinical manifestations of hEDS, including headache, upper and lower airway inflammation, gastrointestinal and urologic manifestations, autonomic dysfunction, and joint inflammation [Afrin 2021, Brock et al 2021, Monaco et al 2022]. Primary immune deficiencies such as complement and immunoglobulin deficiencies are also reported in individuals with hEDS.

Neurobehavioral/psychiatric manifestations (neurodivergence). Autism and attention-deficit/hyperactivity disorder are reported to occur more frequently in those with hEDS and impact psychological, social, and emotional processes [Baeza-Velasco 2021, Csecs et al 2022].

Psychiatric manifestations in individuals with hEDS include depression, anxiety disorders, affective disorder, low self-confidence, negative thinking, hopelessness, and desperation. Fatigue and pain exacerbate the psychological

dysfunction, and psychological distress exacerbates pain [Bulbena et al 2017, Bulbena-Cabré et al 2021, Eccles et al 2022]. In addition to anxiety disorders, many with hEDS experience a reactive state of anxiety and low mood due to the symptoms and challenges of managing multiple morbidities and the impact these have on daily activities and quality of life. Affected individuals often feel misunderstood, disbelieved, and marginalized. Many with hEDS report difficult encounters with health care professionals and experience clinician-associated traumatization. Resentment and distrust may develop between the affected individual/family and the health care team, adversely affecting the therapeutic relationship [Halverson et al 2023].

Gynecologic/obstetric. Pelvic floor manifestations reported in individuals with hEDS include urinary incontinence, fecal incontinence, pelvic organ prolapse, rectal prolapse, pelvic pain, and sexual dysfunction with dyspareunia, with 20%-75% of individuals reporting at least one of these [Glayzer et al 2021, Patel & Khullar 2021, Kciuk et al 2023, Nazemi et al 2023]. Dysmenorrhea and menorrhagia are also more common in individuals with hEDS [Hugon-Rodin et al 2016].

Several studies have reviewed the evidence for medical issues reported in childbearing women with hEDS, including those related to preconception (e.g., musculoskeletal health and medication use), antenatal (e.g., joint instability, pelvic strength, hernias, and pain management), intrapartum (e.g., birth choices, mobility in labor, anesthesia), and postpartum (e.g., wound healing, pelvic health, newborn/infant care adjustments) health [Pezaro et al 2021, Nazemi et al 2023]. In a large (n=947, with 1,338 pregnancies) international survey of pregnancy complications in individuals with hEDS, a higher incidence was reported for preeclampsia, eclampsia, preterm rupture of membranes, preterm birth, antepartum hemorrhage, postpartum hemorrhage, hyperemesis gravidarum, shoulder dystocia, caesarean wound infection, postpartum psychosis, post-traumatic stress disorder, precipitous labor, and delivery prior to arrival at planned place of birth [Pearce et al 2023].

Nomenclature

The 1997 Villefranche criteria [Beighton et al 1998] broadened the classification and nomenclature of the Ehlers-Danlos syndromes based on phenotypic and genetic characteristics. The former EDS type III was renamed the hypermobile type. In 2017, the International Consortium on the Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders published revised diagnostic criteria, and the name was modified slightly to hypermobile EDS (hEDS) [Malfait et al 2017].

The terms "benign familial articular hypermobility syndrome" and "joint hypermobility syndrome" are no longer used [Grahame et al 2000]. Individuals with hypermobility-related musculoskeletal concerns who do not fulfill the hEDS criteria and are not syndromic in any other way (which would suggest another underlying disorder) are diagnosed with hypermobility spectrum disorders (HSD) [Castori et al 2017, Castori & Hakim 2017].

The 2017 criteria were constructed with adults in mind. Many of these features arise over time and may not be present in childhood and adolescence. In addition, many of the clinical manifestations are common in younger individuals. A framework for the diagnosis in younger people was developed by Tofts et al [2023]. In this framework most individuals with symptomatic joint hypermobility are classified as having HSD, with the guidance that younger individuals should be monitored and that their diagnosis can change as concerns arise or resolve.

Prevalence

A study of health care records in the Welsh population found an hEDS prevalence of approximately 1:3,100 [Demmler et al 2019]. A similar prevalence was found in a study of US hospital admissions [Brooks et al 2021]. The reported prevalence of hEDS is likely underestimated due to missed diagnosis.

Differential Diagnosis

Pediatric generalized joint hypermobility (pGJH) and pediatric generalized hypermobility spectrum disorder (pgHSD). A clinical diagnostic classification system to assess joint hypermobility in individuals age five through 18 years (or biologic maturity) has been published [Tofts et al 2023]. The classification system defines eight subtypes based on the presence or absence of skin and tissue involvement, musculoskeletal complications, and other comorbidities. Using this classification system, affected children are classified as having one of eight subtypes of pediatric generalized hypermobility or pediatric hypermobility spectrum disorder (HSD), with the recommendation that younger individuals be monitored for evolving clinical manifestations. Individuals diagnosed with pediatric generalized hypermobility or pediatric hypermobility spectrum disorder should be reevaluated once they reach biologic maturity (or age 18 years) using the 2017 clinical diagnostic criteria for hypermobile Ehlers-Danlos syndrome (see Establishing the Diagnosis). A description of the clinical assessment and the diagnostic framework in children and adolescents can be found at the Ehlers-Danlos Society website (see 2023 Diagnostic Framework for Pediatric Joint Hypermobility and Diagnostic Checklist [pdf]).

All types of Ehlers-Danlos syndrome (EDS) share some degree of joint laxity and skin / soft tissue manifestations. The other forms of EDS are distinguished by additional connective tissue manifestations [Malfait et al 2017] (see Table 1).

Table 1. EDS Types in the Differential Diagnosis of Hypermobile Ehlers-Danlos Syndrome

Gene(s)	Disorder [1]	MOI	Selected Features / Comments
COL5A1 *COL5A2* (*COL1A1*) [2]	Classic EDS (cEDS)	AD	• Classic EDS is assoc w/skin & soft tissue fragility. • Mild cEDS presentations – i.e., similar degrees of joint laxity, pain, pelvic prolapse, dyspareunia, & manifestations in the hematologic, gastrointestinal, cardiovascular, & ocular systems – may be mistaken for hEDS. The diagnosis may be revised from hEDS to cEDS if there is later development of more significant skin & soft tissue manifestations in the individual or a family member. • Among persons w/all of the skin features of cEDS, incl dystrophic scarring, ~90% have an identifiable pathogenic variant in *COL5A1* or *COL5A2*. [3] In those w/milder skin manifestations (but still more than typically seen in hEDS), no consistent pathogenic variants in any genes have been found.
COL3A1 (*COL1A1*) [4]	Vascular EDS (vEDS)	AD[3]	• Joint laxity is predominantly in small joints in vEDS; generalized laxity is common in hEDS. • Vascular EDS usually manifests as thin, translucent skin, fragility of skin & soft tissue, & atrophic scarring. • Predisposition to spontaneous rupture of arteries &/or hollow organs or family history of unexplained sudden death is a hallmark of vEDS. • Nonspecific venous & hematologic abnormalities incl varicose veins, hemorrhoids, easy bruising, & bleeding diathesis are not suggestive of vEDS.
ADAMTS2	Dermatosparaxis EDS (dEDS) (OMIM 225410)	AR	Dermatosparaxis EDS is distinguished by more severe skin manifestations & other features.
COL1A1 *COL1A2*	Arthrochalasia EDS (aEDS) (OMIM 130060 & 617821)	AD	Arthrochalasia EDS is distinguished by congenital hip dislocation & more severe skin manifestations.

Table 1. continued from previous page.

Gene(s)	Disorder [1]	MOI	Selected Features / Comments
PLOD1 *FKBP14*	Kyphoscoliotic EDS (kEDS) (See *PLOD1*-related kEDS & *FKBP14*-related kEDS.)	AR	• Kyphoscoliotic EDS is distinguished by more severe skin manifestations & other features (e.g., hypotonia, early-onset kyphoscoliosis, & ocular abnormality). • Scoliosis in kEDS is usually more severe & of earlier onset than in other EDS types.
TNXB	*TNXB*-related classic-like EDS (clEDS)	AR	• *TNXB*-related clEDS manifests as joint laxity, hyperextensible skin, & easy bruising w/normal wound healing & absence of atrophic scarring. Some, but not all, persons also have congenital adrenal hyperplasia as a result of contiguous gene deletion involving *CYP21A2*. • Heterozygous *TNXB* pathogenic variants have been reported in a small subset of persons w/joint laxity & soft skin typical of hEDS, but skin hyperextensibility, easy bruising, & other hematologic manifestations are not assoc w/*TNXB*-related clEDS.
COL1A2	Cardiac-valvular EDS (cvEDS) (OMIM 225320)	AR	Cardiac-valvular EDS is assoc w/severe, progressive heart valve disease in addition to similar findings to cEDS & clEDS.
ZNF469 *PRDM5*	Brittle cornea syndrome (BCS) (OMIM 229200 & 614170)	AR	BCS manifests as progressive keratoconus & keratoglobus, thin cornea w/risk of rupture, myopia, retinal detachment, deafness, hip dysplasia, scoliosis, hypermobile distal joints, & soft & translucent skin.
B4GALT7 *B3GALT6* *SLC39A13*	Spondylodysplastic EDS (spEDS) (OMIM 130070, 615349, & 612350)	AR	Spondylodysplastic EDS is assoc w/short stature & bowed limbs, muscle hypotonia, soft, doughy, & translucent skin, delayed motor & cognitive development, craniofacial abnormalities, kyphoscoliosis, contractures, aortic aneurysm, & dental dysplasia.
CHST14 *DSE*	Musculocontractual EDS (mcEDS) (OMIM 601776 & 615539)	AR	The cardinal feature of mcEDS is multiple contractures. Other findings incl craniofacial abnormalities, hyperextensible skin w/ atrophic scars, bruising, & hematomas, kyphoscoliosis, hand & foot deformities, pneumothorax, & myopia.
COL12A1	Myopathic EDS [5]	AD AR	Myopathic EDS typically presents w/muscle hypotonia &/or atrophy & myopathy, joint contractures, hypermobile distal joints, soft, doughy skin & atrophic scars, & motor developmental delay.
C1R *C1S*	Periodontal EDS (pEDS)	AD	The cardinal feature of pEDS is severe, early-onset periodontitis in a person who otherwise might typically appear to have cEDS or hEDS.
AEBP1	Classic-like EDS type 2 [6]	AR	Classic-like EDS type 2 is assoc w/thin & hyperextensible skin, poor wound healing w/prominent atrophic scarring, joint hypermobility, osteoporosis, pectus deformity, premature aged appearance, & sparse & frizzled hair.

Table 1. continued from previous page.

Gene(s)	Disorder [1]	MOI	Selected Features / Comments
COL1A1 *COL1A2*	*COL1*-related overlap disorder [7]	AR	The condition manifests in a similar way to hEDS but is dominated by reduced bone mass, fractures, & short stature.

AD = autosomal dominant; AR = autosomal recessive; EDS = Ehlers-Danlos syndrome; hEDS = hypermobile Ehlers-Danlos syndrome; MOI = mode of inheritance

1. Ordered based on prevalence

2. The proportion of cEDS attributed to pathogenic variants in *COL5A1* is 75%-78%; in *COL5A2*, 14%; and in *COL1A1*, <1%. The associated gene is unknown in <10% of individuals with cEDS.

3. Symoens et al [2012]

4. Pathogenic variants in *COL1A1* are listed as a rare cause of vEDS in the 2017 International Classification of the Ehlers-Danlos Syndromes [Malfait et al 2017]. Vascular EDS is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported.

5. Malfait et al [2017]

6. Described after the publication of the 2017 International Classification of EDS [Blackburn et al 2018, Syx et al 2019]

7. Described after the publication of the 2017 International Classification of EDS [Morlino et al 2020]

Joint laxity is a nonspecific manifestation of dozens of other disorders and syndromes. Functionally, joint hypermobility may be the result of ligamentous laxity and joint deformity (as in the heritable disorders of connective tissue and skeletal dysplasias) or hypotonia (as in mitochondrial disorders and other neuromuscular conditions). It can be difficult to distinguish between these mechanisms of pathology. When there is symptomatic joint hypermobility and no other specific diagnosis can be established, it is reasonable to diagnose hypermobility spectrum disorder (HSD) [Castori et al 2017].

Most of the disorders in Table 2 are easily distinguished from EDS by characteristic features and/or involvement of systems other than the joints and skin, but mild presentations can sometimes be misdiagnosed as hEDS.

Table 2. Disorders with Joint Laxity in the Differential Diagnosis of Hypermobile Ehlers-Danlos Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Selected Features / Comment
1.5- to 1.8-Mb deletion at 7q11.23	Williams syndrome	AD	Assoc w/cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvar aortic stenosis, hypertension), distinctive facies, connective tissue abnormalities, ID (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, & endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, & early puberty)
COL1A1 *COL1A2*	*COL1A1/2* osteogenesis imperfecta	AD	Distinguished by the presence of fractures &, in some persons, dentinogenesis imperfecta (grey or brown teeth)
COL2A1 *COL11A1* *COL11A2* *COL9A1* *COL9A2* *COL9A3*	Stickler syndrome	AD AR [1]	Distinguishing features incl sensorineural hearing loss, vitreoretinal abnormalities, & cleft palate.
FBN1	*FBN1*-related Marfan syndrome	AD	• Skeletal, ocular, cardiovascular, pulmonary, & skin/integument manifestations beyond those seen in hEDS. Joint hypermobility is common in the MASS phenotype (myopia, mitral valve prolapse, mild aortic root dilatation, striae, & minor skeletal manifestations of Marfan syndrome). • Persons w/hEDS can have a marfanoid body habitus & resemble persons w/Marfan syndrome or a Marfan-related disorder. [2]

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Selected Features / Comment
FGD1	Aarskog-Scott syndrome (faciogenital dysplasia) (OMIM 305400)	XL	• The most significant distinguishing feature is shawl scrotum, which may become less obvious in adulthood. Widow's peak, short upturned nose, & other dysmorphic features can be additional diagnostic clues. • ID, which is not assoc w/any of the types of EDS, is sometimes present.
FMR1	Fragile X syndrome (See *FMR1* Disorders.)	XL	Fragile X syndrome is not typically confused w/hEDS; however, females heterozygous for a premutation-sized CGG repeat may have joint laxity & EDS-like skin findings w/o other major manifestations. [3] The frequency of *FMR1* premutations among persons diagnosed clinically w/hEDS has not been studied, but fragile X syndrome has not been reported among offspring of females diagnosed w/hEDS.
SLC2A10	Arterial tortuosity syndrome (ATS)	AR	In addition to aneurysm, dissection, tortuosity, & stenosis of large- & medium-sized arteries, ATS manifests as craniofacial & skeletal features similar to Loeys-Dietz syndrome.
SMAD2 *SMAD3* *TGFB2* *TGFB3* *TGFBR1* *TGFBR2*	Loeys-Dietz syndrome (LDS)	AD	• Features incl vascular findings (cerebral, thoracic, & abdominal arterial aneurysms &/or dissections) & skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus). • The LDS presentation often mimics Marfan syndrome or vEDS, but prior to detection of the arterial abnormalities, persons may be misdiagnosed w/cEDS or hEDS. [2]

AD = autosomal dominant; AR = autosomal recessive; cEDS = classic Ehlers-Danlos syndrome; EDS = Ehlers-Danlos syndrome; hEDS = hypermobile Ehlers-Danlos syndrome; ID = intellectual disability; MOI = mode of inheritance; vEDS = vascular Ehlers-Danlos syndrome

1. Stickler syndrome caused by pathogenic variants in *COL2A1*, *COL11A1*, or *COL11A2* is inherited in an autosomal dominant manner; Stickler syndrome caused by pathogenic variants in *COL9A1*, *COL9A2*, or *COL9A3* is inherited in an autosomal recessive manner.

2. Grahame & Hakim [2013]

3. Tassanakijpanich et al [2022]

Other disorders with joint laxity include the following:

- M**itochondrial myopathies** may cause joint hypermobility because of hypotonia, rather than the ligament and tendon laxity in hereditary disorders of connective tissue. Other features of mitochondrial disorders that overlap with those seen in hEDS include headache, neuropathy, myopathy, and autonomic dysfunction. Gastrointestinal dysmotility may also occur in mitochondrial disorders, especially mitochondrial neurogastrointestinal encephalopathy disease. See also Primary Mitochondrial Disorders Overview.
- Many other **neuromuscular disorders** can also cause hypotonia, neuropathy, autonomic dysfunction, functional gastrointestinal abnormalities, and other features overlapping with hEDS. Since there are currently no laboratory tests available to definitively confirm or rule out hEDS, it is important to thoroughly consider the possibility of a mitochondrial or other neuromuscular disorder in the differential diagnosis.
- **Aneuploidies,** including Down, Turner, and Klinefelter syndromes, are usually easily recognized based on dysmorphic features and/or learning disability. Small duplications or deletions may be less clinically obvious but could be suggested by reduced fertility or recurrent pregnancy loss.

Chronic pain and **fatigue** are common in the general population, and the differential diagnosis of these symptoms is large. Some conditions that may overlap with or complicate hEDS include fibromyalgia, myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS), micronutrient deficiencies, sleep disorders, and adrenal insufficiency.

Management

Treatment recommendations for hypermobile Ehlers-Danlos syndrome (hEDS) have been published [Malfait et al 2017, Hakim et al 2021].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hEDS, the evaluations summarized in Table 3 are recommended.

Table 3. Hypermobile Ehlers-Danlos Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Musculoskeletal	• Assess for joint manifestations, pain, & disability. • Assess prior mechanical, pharmacologic, &/or surgical treatment of joint instability & pain.	• Imaging as needed for joint & tissue damage; may incl radiographs, CT, &/or MRI • Flexion/extension/rotation studies to assess for craniocervical instability as needed
Pain/ Fatigue	• Assess nature of pain & possible causes of pain & fatigue incl musculoskeletal, neuropathic, visceral, & mast cell activation disorder. • Consider laboratory assessment for causes of fatigue: clotting disorders, assessment for autoimmune disorders (e.g., rheumatologic, endocrine, & gastrointestinal), micronutrient deficiencies, & mast cell activation disorders.	There are many causes of fatigue in hEDS (e.g., physical fatigue from additional effort required to maintain joint stability, autonomic dysfunction).
Hematologic	Assess for bleeding issues.	In those w/severe or prolonged bleeding, consider eval for von Willebrand disease, thrombocytopenia, platelet aggregation disorders, or other bleeding diathesis.
Gastrointestinal	Assess for clinical manifestations of swallowing concerns, gut-brain disorders, slow gut transit, vascular-compression syndromes, & anorectal concerns.	• Transit studies for those with slow gut transit (e.g., radiopaque marker method for upper & lower tract) • Doppler ultrasound for vascular compression syndromes
Cardiovascular	Assess for clinical manifestations of autonomic dysfunction, incl tachycardia, hypotension, & syncope.	There is no data to advise on age of initial echocardiogram.
Oral/ Dental	Assess for orthodontia needs & periodontal disease.	
ENT/ Pulmonary	• Assess for phonation & breathing difficulties, incl asthma-like symptoms & apnea. Thoracic cage, musculoskeletal, & diaphragmatic concerns may also be a cause of shortness of breath. • Assess for sleep issues.	
Ocular	Assess for xerophthalmia, refractive errors, & diplopia.	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Assess for causes of headache (incl craniocervical instability), cord & nerve root pathology, dystonia, & peripheral neuropathy.	
Inflammation	Assess for soft tissue inflammation, co-occurring rheumatologic disorders, & mast cell activation disorders.	
Psychological/ Neurobehavioral	Psychosocial assessment for depression, anxiety, affective disorder, autism, & ADHD	
Urogynecologic	Assess for interstitial cystitis, urinary incontinence, pelvic organ prolapse, dysmenorrhea, menorrhagia & dyspareunia.	
Genetic counseling	By genetics professionals [1]	Inform affected persons & their families re nature, MOI, & implications of hEDS to facilitate medical & personal decision making.

ADHD = attention-deficit/hyperactivity disorder; hEDS = hypermobile Ehlers-Danlos syndrome; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Musculoskeletal. Improvement in musculoskeletal function includes tailored treatment with exercise to increase core and extremity muscle strength and tone, proprioception, and joint stability. Improved joint stability may be achieved with exercises to increase muscle strength and reduce muscle tension. Emphasis is often placed on improving movement patterns and on physical function. Braces and splints are useful to improve alignment and control. They may allow an injured joint to rest and support joints during normal activities and exercising to allow greater duration, frequency, and level of activities. Occupational and physical therapy can assist in recommending wide-grip writing utensils to reduce finger and hand strain and evaluate home and work ergonomics as well as assistive devices (e.g., wheelchair or scooter, suitable mattress, soft neck collar). Orthopedists, rheumatologists, and podiatrist can assist in additional recommendations for problematic joints such as the fingers, hands, wrists, shoulders, knees, ankles, and feet.

Some individuals will have undergone orthopedic and orthognathic procedures prior to diagnosis. Anecdotally, a lack of awareness of the joint hypermobility and tissue fragility may lead to poorer surgical outcomes, but datasets of outcomes are lacking. Some will require surgical procedures if conservative therapies for hEDS fail or there are significant pathologies present (e.g., impingement disorders, dysplasias, and cord/nerve entrapment with neurologic deficit) [Ericson & Wolman 2017, Henderson et al 2017, Homere et al 2020, Santore et al 2020, Clapp et al 2021, DeLeonibus et al 2023].

Prolotherapy, in which saline and/or other irritants are injected in tendons or around joints to induce scar formation and increase stability, has been objectively shown to be safe and effective in one study [Burling 2019].

Pain. Physical and occupational therapies, dry needling, behavioral therapies, and complimentary therapies are among the treatments reported as most helpful for pain management. Among the pharmacologic options, nonsteroidal anti-inflammatory drugs, acetaminophen, and opioids are reported as the most beneficial [Chopra et al 2017, Demes et al 2020]. To date, there is little or mixed outcome data on efficacy of magnesium, muscle relaxants, and neuropathic analgesia such as duloxetine, gabapentin, and tricyclics for pain treatment in individuals with hEDS, and insufficient published evidence on the efficacy of medical marijuana for hEDS. All of these treatments have been used in clinical practice in the management of pain in individuals with hEDS and must be tailored to the individual needs and adjusted or avoided as required in those with comorbidities.

Hematologic. Platelet disorders may respond to tranexamic or mefenamic acid. For severe bleeding or operative prophylaxis, desmopressin acetate (DDAVP®) may be beneficial. Micronutrient deficiencies may also be responsible for bleeding (e.g., low vitamin C) and anemia (e.g., folate and vitamin B_{12}).

Gastrointestinal (GI). Gastritis and gastroesophageal reflux disease may require intensive therapy, including proton pump inhibitor twice daily before meals, high-dose H2 blocker at bedtime (e.g., famotidine, 20-40 mg), sucralfate (one gram four times daily), and over-the-counter acid-neutralizing agents. Other treatable causes such as *H pylori* infection and small intestinal bacterial overgrowth (SIBO) should be investigated and treated. Upper endoscopy is indicated for resistant symptoms, but frequently is normal. Delayed gastric and colonic emptying should be identified and treated, as should causes of anorectal pain and prolapse. Assistance from a gastroenterologist experienced in managing GI dysmotility and pelvic floor pathology is required. Visceral mobilization therapies may also help. Irritable bowel syndrome is treated as usual with dietary modification, fiber, antispasmodics, antidiarrheals, and laxatives as needed. Motility enhancers may be helpful for those with constipation only. Tricyclic antidepressants may be helpful for persons with neuropathic pain. If no cause for abdominal pain is identified following GI evaluation, doppler ultrasound should be considered to evaluate for vascular compression syndromes that may require surgical correction.

Cardiovascular. Standard treatments for neurally mediated hypotension and postural orthostatic tachycardia are advised, including avoidance of sudden postural change, consideration of lower extremity and/or abdominal compression garments, exercise to increase muscle strength and improve tone, supplementation of sodium and water to expand the blood volume, and sometimes pharmacologic treatment with beta-blockers, midodrine, fludrocortisone, ivabradine, and/or other medications initiated by a clinician experienced in autonomic medicine. Commercially available electrolyte tablets can facilitate oral expansion of blood volume.

Other vascular concerns, including significant aortic root dilatation and abdominal and pelvic vascular compression syndromes, require referral to a cardiovascular specialist. Rapid aortic root growth, an indication for intervention, is defined as ≥0.5 cm in one year.

Oral/dental/ENT. Standard treatment of periodontal disease is advised, noting that many individuals may have more fragile periodontal tissues and often have a poor response to local anesthetic that requires additional doses throughout dental procedures or other analgesia. Treatment may also be hampered in those with temporomandibular joint (TMJ) laxity and dysfunction, craniocervical instability, and intolerance of specific or prolonged head and neck positions.

For TMJ dysfunction, intraoral devices/retainers may be helpful. Oral rest, local myofascial release, and muscle relaxant medications may be beneficial for acute flares. Surgical intervention may be required.

Issues with swallow and phonation should be assessed by an otolaryngologist.

A pulmonology, otolaryngology, or sleep specialist assessment is recommended for apnea.

Ocular. Standard treatment of ocular concerns is advised.

Neurologic/neuromuscular. No specific pharmacologic treatments have been reported for neurologic and neuromuscular diseases in those with hEDS. Standard pharmacologic treatment for neuropathies is advised. Physical therapies are adjusted to account for joint instability, low muscle tone, and fatigue. Surgical stabilization of the craniocervical junction and spinal surgeries require subspecialty expert neurosurgical or orthopedic management.

Mast cell activation disorder. Treatments include avoidance of triggers (though for many this is challenging, as they are common in most environments), use of H1 and H2 antihistamines, aspirin, ketotifen, and the mast cell stabilizers montelukast and sodium cromoglycate. In those with severe disease and/or those unresponsive to

these treatments, monoclonal biologic therapy may be appropriate; this treatment requires expert assessment and management.

Neurobehavioral/psychiatric manifestations (neurodivergence). Validation of symptoms can be immensely helpful, as many with hEDS have been accused by health care professionals of malingering or diagnosed with primary psychiatric disorders. Establishing trust, rapport, and a supportive relationship with the affected individual is important. Anxiety and depression are a common result of the many morbidities a person with hEDS may experience. Psychological and/or symptom-oriented counseling can improve adaptation to and acceptance of these issues and their impact on quality of life. Cognitive behavioral therapy can be beneficial but requires active participation. Antidepressants may also be of benefit. Standard behavioral and pharmacologic therapies should be offered for the management of autism and attention-deficit/hyperactivity disorder.

Urogynecologic. There are no specific guidelines for the management of urinary tract and gynecologic manifestations of hEDS. Within the limited peer-reviewed literature, adjustments to pelvic floor therapies may be warranted, and one study showed that connective tissue disorders including hEDS had the same pelvic surgery outcomes as controls [Nazemi et al 2023]. Other potentially more specific treatments include use of antifibrinolytics for pain and bleeding given their platelet effect, and reduced histamine intake, antihistamines, and mast cell stabilizers for mast cell-induced interstitial cystitis [Patel & Khullar 2021].

Surveillance

There are no specific surveillance guidelines for hEDS. Specific concerns should be followed up based on clinical need and standard protocols. See Table 4 for recommended evaluations.

Table 4. Hypermobile Ehlers-Danlos Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Musculoskeletal	Assess for joint manifestations & current degree of pain & disability.	Annually or at each visit
	DXA scan	In those w/height loss >1 inch, atypical/low trauma fractures, or radiographs suggestive of osteopenia
Hematologic	Assess for bleeding issues.	Annually or at each visit
Gastrointestinal	Assess for clinical manifestations of functional bowel disorders.	
Cardiac	Assess for clinical manifestations of autonomic dysfunction.	
	Echocardiography	In those w/aortic root dilatation on initial echocardiogram: [1] • Follow-up echocardiogram 1 yr after initial echocardiogram & if no change, follow-up echocardiogram in 5 yrs • In those w/progressive aortic dilatation: continue annual echocardiography; if progressive dilatation stops, then echocardiogram every 3 yrs

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Oral/ Dental	Assess for orthodontia needs & periodontal disease.	Annually or at each visit
ENT/ Pulmonary	• Assess for phonation & respiratory issues. • Assess for sleep issues.	
Ocular	Assess for xerophthalmia, refractive errors, & diplopia.	
Neurologic	Assess for headaches, cord & nerve root pathology, dystonia, & peripheral neuropathy.	
Inflammation	Assess for soft tissue inflammation, co-occurring rheumatologic disorders, & mast cell activation disorders.	
Neurobehavioral/ Psychiatric	Psychosocial assessment for depression, anxiety, affective disorder, autism, & ADHD	
Urogynecologic	Assess for interstitial cystitis, urinary incontinence, pelvic organ prolapse, dysmenorrhea, menorrhagia & dyspareunia.	

ADHD = attention-deficit/hyperactivity disorder; DXA = dual-energy x-ray absorptiometry
1. Since the risk of progression of aortic root dilatation has not yet been defined by longitudinal studies, surveillance should follow the American College of Cardiology / American Heart Association (ACC/AHA) guidelines for EDS [Isselbacher et al 2022].

Agents/Circumstances to Avoid

High-impact activity may increase the risk for acute subluxation/dislocation and acute and chronic pain. Some sports, such as tackle football, may not be suitable but should be discussed on an individual basis. Most sports and activities are acceptable with appropriate precautions.

Chiropractic adjustment and yoga are not contraindicated but must be performed in ways that avoid subluxations or dislocations.

Joint hyperextension may not need to be avoided. In a randomized controlled trial of physical therapy among 26 children and adolescents with joint hypermobility and knee pain, those allowed to exercise into hyperextension had similar improvement in pain score and better improvement in psychosocial score compared to those restricted to neutral joint position [Pacey et al 2013].

Autonomic concerns, gastrointestinal disorders, and intolerances, for example, may preclude use of medications or their excipients (e.g., common analgesics in someone with slow gastrointestinal transit, vasodilator in a person with orthostatic intolerance).

Topical agents and adhesives should be used cautiously in those with skin fragility and/or allergy.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Management of women with hEDS should include preconception assessment (e.g., musculoskeletal health and medication use), antenatal evaluation (e.g., joint instability, pelvic strength, hernias, and pain management), intrapartum planning (e.g., birth choices, mobility in labor, anesthesia), and postpartum care (e.g., wound healing, pelvic health, newborn/infant care).

Musculoskeletal complications of hEDS including pain and joint instability may arise for the first time or worsen during pregnancy. In women with hEDS there is a higher incidence of preeclampsia, eclampsia, preterm rupture of membranes, preterm birth, antepartum hemorrhage, postpartum hemorrhage, hyperemesis gravidarum, shoulder dystocia, caesarean wound infection, postpartum psychosis, post-traumatic stress disorder, precipitous labor, and delivery prior to arrival at planned place of birth [Alrifai et al 2023, Pearce et al 2023].

Pregnant women with known aortic root dilatation should have an echocardiogram in each trimester. Echocardiography is not needed if the aortic root is normal prior to pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hypermobile Ehlers-Danlos syndrome (hEDS) is inherited in an autosomal dominant manner with variable expression of signs and variable severity of symptoms among affected family members.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with hEDS are likely to have an affected parent, although a detailed history and examination of the parents is often necessary to recognize that a parent has a current or prior history of joint laxity, easy bruising, and skin concerns despite the absence of serious complications.
- A proband with hEDS may be the only family member known to be affected.

Sibs of a proband. The risk to sibs of the proband depends on the clinical status of the proband's parents.

- If a parent of the proband is affected, the risk to the sibs is 50%.
- If both parents are clinically unaffected, the risk to the sibs is likely to be low.

Offspring of a proband

- Each child of an individual with hEDS has a 50% chance of inheriting hEDS.
- Because of marked clinical variability, it is difficult to predict severity among affected offspring.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring) to young adults who are affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from a proband diagnosed with hEDS. For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Because the gene(s) and pathogenic variant(s) responsible for hEDS have not been identified, prenatal and preimplantation genetic testing are not possible at this time.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Ehlers-Danlos Society - Europe**
  United Kingdom
  Phone: +44 203 887 6132
- **MedlinePlus**
  Ehlers-Danlos Syndrome
- **The Ehlers-Danlos Society**
  Phone: 410-670-7577
  ehlers-danlos.com
- **Ehlers-Danlos Support UK**
  United Kingdom
  Phone: 0208 736 5604; 0800 9078518
  ehlers-danlos.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table B. OMIM Entries for Hypermobile Ehlers-Danlos Syndrome (View All in OMIM)

130020	EHLERS-DANLOS SYNDROME, HYPERMOBILITY TYPE; EDSHMB

Molecular Pathogenesis

No pathogenic variants in any genes have as yet been associated with hypermobile Ehlers-Danlos syndrome (hEDS).

Chapter Notes

Author Notes

Assoc Prof Dr Alan Hakim is an adult certified consultant in Medicine and Rheumatology based in the United Kingdom. Having practiced for more than 30 years in medicine, he has 28 years of experience in rheumatology and translational medicine and 23 years of experience in hypermobility-related disorders. In hospital and community clinical commissioning and administration, he has worked at divisional, director, executive, and board levels. He has project-managed multiple large-scale programs of work across the health sector in the UK.

Dr Hakim has published widely in clinical research and education, including more than 100 original scientific and review papers, six books, and multiple chapters and online pages and webinars. He has also held several roles as a Principal and Chief Investigator in pharmaceutical studies related to rheumatic disorders and been awarded numerous major grants in support of his research. He is a Fellow of The Royal College of Physicians, London, UK; an Adjunct Associate Professor in Medicine at The School of Medicine, Penn State, USA; Honorary Consultant at UCLH, London; Chief Medical Officer, Director of Education, Director of Research, and Lead for EDS ECHO at The Ehlers-Danlos Society; and a member of the Steering Committee and Chair of the hEDS/HSD Working Group of the International Consortium on the Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders.

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References

Literature Cited

Afrin LB. Some cases of hypermobile Ehlers-Danlos syndrome may be rooted in mast cell activation syndrome. Am J Med Genet C Semin Med Genet. 2021;187:466-72. PubMed PMID: 34719842.

al-Rawi Z, Nessan AH. Joint hypermobility in patients with chondromalacia patellae. Br J Rheumatol. 1997;36:1324-7. PubMed PMID: 9448595.

Alrifai N, Alhuneafat L, Jabri A, Khalid MU, Tieliwaerdi X, Sukhon F, Hammad N, Al-Abdouh A, Mhanna M, Siraj A, Sharma T. Pregnancy and fetal outcomes in patients with Ehlers-Danlos syndrome: a nationally representative analysis. Curr Probl Cardiol. 2023;48:101634. PubMed PMID: 36806636.

Asanad S, Bayomi M, Brown D, Buzzard J, Lai E, Ling C, Miglani T, Mohammed T, Tsai J, Uddin O, Singman E. Ehlers-Danlos syndromes and their manifestations in the visual system. Front Med (Lausanne). 2022;9:996458. PubMed PMID: 36237549.

Asher SB, Chen R, Kallish S. Mitral valve prolapse and aortic root dilation in adults with hypermobile Ehlers-Danlos syndrome and related disorders. Am J Med Genet A. 2018;176:1838-44. PubMed PMID: 30063091.

Baeza-Velasco C. Neurodevelopmental atypisms in the context of joint hypermobility, hypermobility spectrum disorders, and Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2021;187:491-9. PubMed PMID: 34741402.

Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet. 1998; 77:31-7. PubMed PMID: 9557891.

Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. Ann Rheum Dis. 1973;32:413-8. PubMed PMID: 4751776.

Blackburn PR, Xu Z, Tumelty KE, Zhao RW, Monis WJ, Harris KG, Gass JM, Cousin MA, Boczek NJ, Mitkov MV, Cappel MA, Francomano CA, Parisi JE, Klee EW, Faqeih E, Alkuraya FS, Layne MD, McDonnell NB, Atwal PS. Bi-allelic alterations in AEBP1 lead to defective collagen assembly and connective tissue structure resulting in a variant of Ehlers-Danlos syndrome. Am J Hum Genet. 2018;102:696-705. PubMed PMID: 29606302.

Brock I, Prendergast W, Maitland A. Mast cell activation disease and immunoglobulin deficiency in patients with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorder. Am J Med Genet C Semin Med Genet. 2021;187:473-81. PubMed PMID: 34747107.

Brooks RS, Grady J, Lowder TW, Blitshteyn S. Prevalence of gastrointestinal, cardiovascular, autonomic and allergic manifestations in hospitalized patients with Ehlers-Danlos syndrome: a case-control study. Rheumatology (Oxford). 2021;60:4272-80. PubMed PMID: 33410480.

Bulbena A, Baeza-Velasco C, Bulbena-Cabré A, Pailhez G, Critchley H, Chopra P, Mallorquí-Bagué N, Frank C, Porges S. Psychiatric and psychological aspects in the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:237-45. PubMed PMID: 28186381.

Bulbena-Cabré A, Baeza-Velasco C, Rosado-Figuerola S, Bulbena A. Updates on the psychological and psychiatric aspects of the Ehlers-Danlos syndromes and hypermobility spectrum disorders. Am J Med Genet C Semin Med Genet. 2021;187:482-90. PubMed PMID: 34806831.

Burling F. Comparison of tetradecyl sulfate versus polidocanol injections for stabilisation of joints that regularly dislocate in an Ehlers-Danlos population. BMJ Open Sport Exerc Med. 2019;5:e000481. PubMed PMID: 30792884.

Castori M. Ehlers-Danlos syndrome(s) mimicking child abuse: Is there an impact on clinical practice? Am J Med Genet C Semin Med Genet. 2015;169:289-92. PubMed PMID: 26452443.

Castori M, Hakim A. Contemporary approach to joint hypermobility and related disorders. Curr Opin Pediatr. 2017;29:640-9. PubMed PMID: 28906340.

Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. Am J Med Genet C Semin Med Genet. 2017;175:148-57. PubMed PMID: 28145606.

Cheshire WP Jr, Goldstein DS. Autonomic uprising: the tilt table test in autonomic medicine. Clin Auton Res. 2019;29:215-30. PubMed PMID: 30838497.

Chopra P, Tinkle B, Hamonet C, Brock I, Gompel A, Bulbena A, Francomano C. Pain management in the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:212-9. PubMed PMID: 28186390.

Clapp IM, Paul KM, Beck EC, Nho SJ. Hypermobile disorders and their effects on the hip joint. Front Surg. 2021;8:596971. PubMed PMID: 33842528.

Csecs JLL, Iodice V, Rae CL, Brooke A, Simmons R, Quadt L, Savage GK, Dowell NG, Prowse F, Themelis K, Mathias CJ, Critchley HD, Eccles JA. Joint hypermobility links neurodivergence to dysautonomia and pain. Front Psychiatry. 2022;12:786916. PubMed PMID: 35185636.

DeLeonibus A, Bogart J, Gharb BB, Rampazzo A. Orthognathic surgery in Ehlers-Danlos syndrome: review of the literature and case report. Cleft Palate Craniofac J. 2023. Epub ahead of print. PubMed PMID: 36683425.

Demes JS, McNair B, Taylor MRG. Use of complementary therapies for chronic pain management in patients with reported Ehlers-Danlos syndrome or hypermobility spectrum disorders. Am J Med Genet A. 2020;182:2611-23. PubMed PMID: 32909698.

Demmler JC, Atkinson MD, Reinhold EJ, Choy E, Lyons RA, Brophy ST. Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case-control comparison. BMJ Open. 2019;9:e031365. PubMed PMID: 31685485.

Domany KA, Hantragool S, Smith DF, Xu Y, Hossain M, Simakajornboon N. Sleep disorders and their management in children with Ehlers-Danlos syndrome referred to sleep clinics. J Clin Sleep Med. 2018;14:623-9. PubMed PMID: 29609717.

Doolan BJ, Lavallee M, Hausser I, Pope FM, Seneviratne SL, Winship IM, Burrows NP. Dermatologic manifestations and diagnostic assessments of the Ehlers-Danlos syndromes: a clinical review. J Am Acad Dermatol. 2023;89:551-9. PubMed PMID: 36764582.

Eccles JA, Quadt L, McCarthy H, Davies KA, Bond R, David AS, Harrison NA, Critchley HD. Variant connective tissue (joint hypermobility) and its relevance to depression and anxiety in adolescents: a cohort-based case-control study. BMJ Open. 2022;12:e066130. PubMed PMID: 36450437.

Engelbert RH, Juul-Kristensen B, Pacey V, de Wandele I, Smeenk S, Woinarosky N, Sabo S, Scheper MC, Russek L, Simmonds JV. The evidence-based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome. Am J Med Genet C Semin Med Genet. 2017;175:158-67. PubMed PMID: 28306230.

Ericson WB Jr, Wolman R. Orthopaedic management of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:188-94. PubMed PMID: 28192621.

Fairweather D, Bruno KA, Darakjian AA, Bruce BK, Gehin JM, Kotha A, Jain A, Peng Z, Hodge DO, Rozen TD, Munipalli B, Rivera FA, Malavet PA, Knight DRT. High overlap in patients diagnosed with hypermobile Ehlers-Danlos syndrome or hypermobile spectrum disorders with fibromyalgia and 40 self-reported symptoms and comorbidities. Front Med (Lausanne). 2023;10:1096180. PubMed PMID: 37181352.

Fernandez A, Aubry-Rozier B, Vautey M, Berna C, Suter MR. Small fiber neuropathy in hypermobile Ehlers Danlos syndrome/hypermobility spectrum disorder. J Intern Med. 2022;292:957-60. PubMed PMID: 35781355.

Gaisl T, Giunta C, Bratton DJ, Sutherland K, Schlatzer C, Sievi N, Franzen D, Cistulli PA, Rohrbach M, Kohler M. Obstructive sleep apnoea and quality of life in Ehlers-Danlos syndrome: a parallel cohort study. Thorax. 2017;72:729-35. PubMed PMID: 28073822.

Glayzer JE, McFarlin BL, Castori M, Suarez ML, Meinel MC, Kobak WH, Steffen AD, Schlaeger JM. High rate of dyspareunia and probable vulvodynia in Ehlers-Danlos syndromes and hypermobility spectrum disorders: an online survey. Am J Med Genet C Semin Med Genet. 2021;187:599-608. PubMed PMID: 34747110.

Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol. 2000;27:1777-9. PubMed PMID: 10914867.

Grahame R, Hakim AJ. Arachnodactyly--a key to diagnosing heritable disorders of connective tissue. Nat Rev Rheumatol. 2013;9:358-64. PubMed PMID: 23478494.

Hakim AJ, Grahame R. A simple questionnaire to detect hypermobility: an adjunct to the assessment of patients with diffuse musculoskeletal pain. Int J Clin Pract 2003;57:163–6. PubMed PMID: 12723715.

Hakim A, O'Callaghan C, De Wandele I, Stiles L, Pocinki A, Rowe P. Cardiovascular autonomic dysfunction in Ehlers-Danlos syndrome-Hypermobile type. Am J Med Genet C Semin Med Genet. 2017;175:168-74. PubMed PMID: 28160388.

Hakim AJ, Tinkle BT, Francomano CA. Ehlers-Danlos syndromes, hypermobility spectrum disorders, and associated co-morbidities: Reports from EDS ECHO. Am J Med Genet C Semin Med Genet. 2021;187:413-5. PubMed PMID: 34793630.

Halverson CME, Penwell HL, Francomano CA. Clinician-associated traumatization from difficult medical encounters: Results from a qualitative interview study on the Ehlers-Danlos syndromes. SSM Qual Res Health. 2023;3:100237. PubMed PMID: 37426705.

Hamonet C, Ducret L, Marie-Tanay C, Brock I. Dystonia in the joint hypermobility syndrome a.k.a. Ehlers-Danlos syndrome hypermobility type. SOJ Neurol. 2016;3:1-3.

Henderson FC Sr, Austin C, Benzel E, Bolognese P, Ellenbogen R, Francomano CA, Ireton C, Klinge P, Koby M, Long D, Patel S, Singman EL, Voermans NC. Neurological and spinal manifestations of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:195-211. PubMed PMID: 28220607.

Homere A, Bolia IK, Juhan T, Weber AE, Hatch GF. Surgical management of shoulder and knee instability in patients with Ehlers-Danlos syndrome: joint hypermobility syndrome. Clin Orthop Surg. 2020;12:279-85. PubMed PMID: 32904109.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Hugon-Rodin J, Lebègue G, Becourt S, Hamonet C, Gompel A. Gynecologic symptoms and the influence on reproductive life in 386 women with hypermobility type Ehlers-Danlos syndrome: a cohort study. Orphanet J Rare Dis. 2016;11:124. PubMed PMID: 27619482.

Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, Collins TJ, DeAnda A Jr, Fanola CL, Girardi LN, Hicks CW, Hui DS, Schuyler Jones W, Kalahasti V, Kim KM, Milewicz DM, Oderich GS, Ogbechie L, Promes SB, Gyang Ross E, Schermerhorn ML, Singleton Times S, Tseng EE, Wang GJ, Woo YJ. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2022;146:e334-e482. PubMed PMID: 36322642.

Jesudas R, Chaudhury A, Laukaitis CM. An update on the new classification of Ehlers-Danlos syndrome and review of the causes of bleeding in this population. Haemophilia. 2019;25:558-66. PubMed PMID: 31329366.

Kciuk O, Li Q, Huszti E, McDermott CD. Pelvic floor symptoms in cisgender women with Ehlers-Danlos syndrome: an international survey study. Int Urogynecol J. 2023;34:473-83. PubMed PMID: 35751670.

Lam C, Amarasinghe G, Zarate-Lopez N, Fikree A, Byrne P, Kiani-Alikhan S, Gabe S, Paine P. Gastrointestinal symptoms and nutritional issues in patients with hypermobility disorders: assessment, diagnosis and management. Frontline Gastroenterol. 2022;14:68-77. PubMed PMID: 36561778.

Lepperdinger U, Zschocke J, Kapferer-Seebacher I. Oral manifestations of Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2021;187:520-6. PubMed PMID: 34741498.

Levine NA, Rigby BR. Thoracic outlet syndrome: biomechanical and exercise considerations. Healthcare (Basel). 2018;6:68. PubMed PMID: 29921751.

Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I,

Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:8-26. PubMed PMID: 28306229.

Malhotra A, Pace A, Ruiz Maya T, Colman R, Gelb BD, Mehta L, Kontorovich AR. Headaches in hypermobility syndromes: a pain in the neck? Am J Med Genet A. 2020;182:2902-8. PubMed PMID: 32940405.

Monaco A, Choi D, Uzun S, Maitland A, Riley B. Association of mast-cell-related conditions with hypermobile syndromes: a review of the literature. Immunol Res. 2022;70:419-31. PubMed PMID: 35449490.

Morlino S, Micale L, Ritelli M, Rohrbach M, Zoppi N, Vandersteen A, Mackay S, Agolini E, Cocciadiferro D, Sasaki E, Madeo A, Ferraris A, Reardon W, Di Rocco M, Novelli A, Grammatico P, Malfait F, Mazza T, Hakim A, Giunta C, Colombi M, Castori M. COL1-related overlap disorder: a novel connective tissue disorder incorporating the osteogenesis imperfecta/Ehlers-Danlos syndrome overlap. Clin Genet. 2020;97:396-406. PubMed PMID: 31794058.

Nazemi A, Shapiro K, Nagpal S, Rosenblum N, Brucker BM. Pelvic organ prolapse in Ehlers-Danlos syndrome. Case Rep Urol. 2023;2023:6863711. PubMed PMID: 36875296.

Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. Exercise in children with joint hypermobility syndrome and knee pain: a randomised controlled trial comparing exercise into hypermobile versus neutral knee extension. Pediatr Rheumatol Online J. 2013;11:30-40. PubMed PMID: 23941143.

Paige SL, Lechich KM, Tierney ESS, Collins RT 2nd. Cardiac involvement in classical or hypermobile Ehlers-Danlos syndrome is uncommon. Genet Med. 2020;22:1583-8. PubMed PMID: 32518415.

Patel M, Khullar V. Urogynaecology and Ehlers-Danlos syndrome. Am J Med Genet C Semin Med Genet. 2021;187:579-85. PubMed PMID: 34799982.

Pearce G, Bell L, Pezaro S, Reinhold E. Childbearing with hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders: a large international survey of outcomes and complications. Int J Environ Res Public Health. 2023;20:6957. PubMed PMID: 37887695.

Pezaro S, Pearce G, Reinhold E. A clinical update on hypermobile Ehlers-Danlos syndrome during pregnancy, birth and beyond. Br J Midwifery. 2021;29:492-500.

Rashed ER, Ruiz Maya T, Black J, Fettig V, Kadian-Dodov D, Olin JW, Mehta L, Gelb BD, Kontorovich AR. Cardiovascular manifestations of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders. Vasc Med. 2022;27:283-9. PubMed PMID: 35000503.

Roma M, Marden CL, De Wandele I, Francomano CA, Rowe PC. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. Auton Neurosci. 2018;215:89-96. PubMed PMID: 29519641.

Sandmann W, Scholbach T, Verginis K. Surgical treatment of abdominal compression syndromes: the significance of hypermobility-related disorders. Am J Med Genet C Semin Med Genet. 2021;187:570-8. PubMed PMID: 34747562.

Santore RF, Gosey GM, Muldoon MP, Long AA, Healey RM. Hypermobility assessment in 1,004 adult patients presenting with hip pain: correlation with diagnoses and demographics. J Bone Joint Surg Am. 2020;102:27-33. PubMed PMID: 32890043.

Schubart JR, Schaefer E, Janicki P, Adhikary SD, Schilling A, Hakim AJ, Bascom R, Francomano CA, Raj SR. Resistance to local anesthesia in people with the Ehlers-Danlos Syndromes presenting for dental surgery. J Dent Anesth Pain Med. 2019;19:261-70. PubMed PMID: 31723666.

Sedky K, Gaisl T, Bennett DS. Prevalence of obstructive sleep apnea in joint hypermobility syndrome: a systematic review and meta-analysis. J Clin Sleep Med. 2019;15:293-9. PubMed PMID: 30736885.

Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep. 2005;28:309-14. PubMed PMID: 16173651.

Simmonds JV. Advances in assessment of hypermobility-related disorders. Am J Med Genet C Semin Med Genet. 2021;187:453-7. PubMed PMID: 34741798.

Symoens S, Syx D, Malfait F, Callewaert B, De Backer J, Vanakker O, Coucke P, De Paepe A. Comprehensive molecular analysis demonstrates type V collagen mutations in over 90% of patients with classic EDS and allows to refine diagnostic criteria. Hum Mutat. 2012;33:1485-93. PubMed PMID: 22696272.

Syx D, De Wandele I, Symoens S, De Rycke R, Hougrand O, Voermans N, De Paepe A, Malfait F. Bi-allelic AEBP1 mutations in two patients with Ehlers-Danlos syndrome. Hum Mol Genet. 2019;28:1853-64. PubMed PMID: 30668708.

Tassanakijpanich N, McKenzie FJ, McLennan YA, Makhoul E, Tassone F, Jasoliya MJ, Romney C, Petrasic IC, Napalinga K, Buchanan CB, Hagerman P, Hagerman R, Casanova EL. Hypermobile Ehlers-Danlos syndrome (hEDS) phenotype in fragile X premutation carriers: case series. J Med Genet. 2022;59:687-90. PubMed PMID: 34193467.

Thwaites PA, Gibson PR, Burgell RE. Hypermobile Ehlers-Danlos syndrome and disorders of the gastrointestinal tract: what the gastroenterologist needs to know. J Gastroenterol Hepatol. 2022;37:1693-709. PubMed PMID: 35750466.

Tofts LJ, Simmonds J, Schwartz SB, Richheimer RM, O'Connor C, Elias E, Engelbert R, Cleary K, Tinkle BT, Kline AD, Hakim AJ, van Rossum MAJ, Pacey V. Pediatric joint hypermobility: a diagnostic framework and narrative review. Orphanet J Rare Dis. 2023;18:104. PubMed PMID: 37143135.

Williams HR, Wood G, Hakim AJ, Birchall M, Hirani SP. Self-reported throat symptoms in Ehlers–Danlos syndromes and hypermobility spectrum disorders: a cross-sectional survey study. Laryngoscope Investig Otolaryngol. 2023;8:1259-64. PubMed PMID: 37899864.

Willich L, Bohner L, Köppe J, Jackowski J, Hanisch M, Oelerich O. Prevalence and quality of temporomandibular disorders, chronic pain and psychological distress in patients with classical and hypermobile Ehlers-Danlos syndrome: an exploratory study. Orphanet J Rare Dis. 2023;18:294. PubMed PMID: 37726791.

Zingman A, Tuchman K, Henderson F Sr, Francomano CA. Patient-reported outcomes following sectioning of the filum terminale for treatment of tethered cord syndrome associated with Ehlers-Danlos syndrome. Cureus. 2022;14:e24679. PubMed PMID: 35663696.

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