**Hypermobile Ehlers-Danlos Syndrome**

**Synonyms:** Benign Joint Hypermobility Syndrome, EDS Hypermobility Type, EDS Type III, Ehlers-Danlos Syndrome Hypermobility Type, EDS, Joint Hypermobility Syndrome

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**Summary**

**Clinical characteristics**

Hypermobile Ehlers-Danlos syndrome (hEDS) is generally considered the least severe type of EDS, although significant complications, primarily musculoskeletal, can and do occur. The skin is often soft and may be mildly hyperextensible. Subluxations and dislocations are common; they may occur spontaneously or with minimal trauma and can be acutely painful. Degenerative joint disease is common. Chronic pain, distinct from that associated with acute dislocations, is a serious complication of the condition and can be both physically and psychologically disabling. Easy bruising, functional bowel disorders, and cardiovascular autonomic dysfunction are common. Aortic root dilation, when present, is typically of a mild degree with no increased risk of dissection in the absence of significant dilation. Psychological dysfunction, psychosocial impairment, and emotional problems are common.

**Diagnosis/testing**

The diagnosis of hEDS is based entirely on clinical evaluation and family history. The gene(s) in which mutation causes hEDS are unknown and unmapped.

**Management**

*Treatment of manifestations:* Physical therapy tailored to the individual; assistive devices (braces to improve joint stability; wheelchair or scooter to offload stress on lower-extremity joints; suitable mattress to improve sleep quality); pain medication tailored to symptoms; appropriate therapy for gastritis/reflux/delayed gastric emptying/irritable bowel syndrome; psychological and/or pain-oriented counseling.

*Prevention of primary manifestations:* Low-resistance exercise to increase both core and extremity muscle tone for improved joint stability; appropriate writing utensils to reduce finger and hand strain.

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**Prevention of secondary complications:** Calcium, vitamin D, low-impact weight-bearing exercise to maximize bone density.

**Surveillance:** DEXA every other year if bone loss is confirmed.

**Pregnancy management:** Labor and delivery may progress very rapidly, even in primigravid women. There is no clear advantage to vaginal vs cesarean delivery. Pregnant women with known aortic root dilation should have an echocardiogram in each trimester.

**Agents/circumstances to avoid:** High-impact activity increases the risk of acute subluxation/dislocation, chronic pain, and osteoarthritis.

**Genetic counseling**

Hypermobile EDS is inherited in an autosomal dominant manner. Most individuals diagnosed with the syndrome have an affected parent. The proportion of cases caused by a de novo pathogenic variant is unknown. Each child of an individual with hEDS has a 50% chance of inheriting the disorder. Because the gene(s) and pathogenic variant(s) responsible for hEDS have not been identified, prenatal testing is not possible.

**Diagnosis**

**Suggestive findings**

Hypermobile EDS should be suspected in individuals with joint laxity, soft skin, and easy bruising. Other organ systems (especially gastrointestinal and cardiovascular) are frequently involved. None of these features is specific to EDS, and these features alone are insufficient to establish a diagnosis of any type of EDS [Malfait et al 2017].

**Establishing the Diagnosis**

The diagnostic criteria for hEDS (and all other types of EDS) were revised by the International EDS Consortium in 2017 [Malfait et al 2017]. No underlying genetic etiology has yet been identified in hEDS, and thus the diagnosis is based entirely on clinical evaluation and family history.

Joint hypermobility is a feature of many heritable and acquired disorders (see Differential Diagnosis), and may also occur as an asymptomatic and/or nonsyndromic finding. In order to reduce heterogeneity and enhance efforts to identify the genetic etiology, a formal diagnosis of hEDS should be made only when all of the diagnostic criteria are met. Individuals with signs and symptoms suggestive of a hereditary connective tissue disorder who fail to meet diagnostic criteria for hEDS or any other described condition should be considered to have hypermobility spectrum disorder (HSD) [Castori et al 2017].

The clinical diagnosis of hEDS requires the simultaneous presence of three criteria:

- Generalized joint hypermobility (Criterion 1)
- Evidence of syndromic features, musculoskeletal complications, and/or family history (Criterion 2)
- Exclusion of alternative diagnoses (Criterion 3)

Multiple other clinical features including (but not limited to) sleep disturbance, fatigue, postural orthostatic tachycardia, functional gastrointestinal disorders, dysautonomia, anxiety, and depression are associated with hEDS. Some of these features were formerly included as minor diagnostic criteria for hEDS [Beighton et al 1998]. They were excluded from the 2017 hEDS diagnostic criteria because they lack specificity for hEDS [Malfait et al 2017].
**Criterion 1**

**Generalized joint hypermobility.** The Beighton score [Beighton et al 1973] remains the best-validated tool for assessing joint hypermobility [Juul-Kristensen et al 2017]. In order to reduce false-positive Beighton scores, the 2017 hEDS diagnostic criteria recommend standardized performance of the Beighton test [Malfait et al 2017]. One point is scored for each of the following:

- Passive dorsiflexion of each fifth finger greater than 90°. 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°. 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°.
- 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°. This should be measured with a goniometer, with the hand supinated, elbow fully extended, and shoulder abducted to 90°.
- Hyperextension of each knee greater than 10°. This should be measured with a goniometer, with the patient 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 for false positive scoring of this point.

The original Beighton publication defines a score of ≥5 as indicative of generalized joint hypermobility [Beighton et al 1973]. However, joint range of motion typically decreases with age, leading to overdiagnosis of children and underdiagnosis of older adults with joint hypermobility. For the purposes of diagnosing hEDS, generalized joint hypermobility is confirmed by a score of [Malfait et al 2017]:

- ≥6 for prepubertal children
- ≥5 for pubertal children and adults up to age 50
- ≥4 for those age >50 years

Multiple other variables including (but not limited to) ethnicity, sex, trauma, surgery, arthritic change, conditioning, and stretching also affect the Beighton score. There is no validated method to account for this variation in assessing generalized joint hypermobility, but the 2017 hEDS diagnostic criteria include an allowance for individuals with acquired limitation of joint mobility [Malfait et al 2017]. 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]. Individuals with prior 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 not be considered to have generalized joint hypermobility and should instead be evaluated for HSD [Castori et al 2017].

The 5PQ:

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"?
Criterion 2

At least two of the following features (A, B, and/or C) must be present.

Feature A. Five or more of the following systemic manifestations of a more generalized connective tissue disorder (A Systemic Score calculator and a complete description of each component evaluation can be found at the National Marfan Foundation website):

- 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 at the back, groins, 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)
- 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, curural, 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 lacerations or single surgery that are unusually shallow and/or wider than the original wound. Atrophic scars as the result of multiple incisions, 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 condition
- 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 ≥1.05
- Mitral valve prolapse, based on strict echocardiographic criteria
- Aortic root dilatation with a Z score >+2

Feature B. Positive family history, with one or more first-degree relatives independently meeting the current diagnostic criteria for hEDS. Of note, a first-degree relative meeting prior diagnostic criteria for EDS, hypermobility type or type III EDS does not count toward this feature; the relative must meet current criteria for hEDS.

Feature C. At least one of the following musculoskeletal complications (but see Criterion 3, Note):

- 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 of the following prerequisites must be met:

- Absence of unusual skin fragility, which should prompt consideration of other types of EDS
- Exclusion of other heritable and acquired connective tissue disorders including autoimmune rheumatologic conditions (See Note.)
- Exclusion (based on history, physical exam, and/or molecular genetic testing) of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity such as neuromuscular disorders, other heritable connective tissue disorders and skeletal dysplasias (See Differential Diagnosis.)

Note: In individuals with an acquired connective tissue disorder (e.g., lupus, rheumatoid arthritis), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hEDS in this situation.

Testing

The etiology of hEDS is unknown. Genetic heterogeneity is likely. There are currently no biochemical or genetic tests clinically available to confirm or rule out a diagnosis of hEDS.

If an individual’s personal or family history is suggestive of one of the other types of EDS or another hereditary disorder of connective tissue or arterial fragility syndrome (see Differential Diagnosis), analysis of an associated gene or multigene connective tissue disease panel may be appropriate. Failure to identify a pathogenic variant with such multiple gene testing reduces the likelihood of an arterial fragility syndrome, but does not completely rule it out, especially in the setting of a positive personal or family history of arterial fragility. Negative testing for an arterial fragility syndrome also does not confirm a diagnosis of hEDS. Therefore, such testing is not recommended in the absence of specific suggestive signs, symptoms, or family history.

Clinical Characteristics

Clinical Description

Note: Clinical distinction between the hypermobile and classic types of EDS is sometimes very difficult. With the exception of skin and soft tissue complications, much of the information in this section is derived from publications that collectively analyzed individuals with hypermobile and classic EDS, without specifying whether there was any difference in manifestations between the two types.

Hypermoblie Ehlers-Danlos syndrome (hEDS) is generally considered the least severe type of EDS, although significant complications, primarily musculoskeletal, do occur. Clinical variability is substantial. Most individuals who seek medical care are female. Pain and major joint complications are much less common among affected males. This bias may result from differences between men and women with respect to pain perception and inherent joint stability, as well as the effects of sex hormones [Castori et al 2010b].

Skin

The skin is often soft and may be mildly hyperextensible.

Piezogenic papules (small herniations of subcutaneous fat through the underlying dermis of the heel occurring only with weight bearing) are common but rarely painful.

Keratosis pilaris may be more common than in the general population [Castori et al 2010a].

Subcutaneous spheroids and molluscoid pseudotumors are not features of this EDS type.
Clinically significant skin morbidity does not occur; its presence should prompt consideration of alternative diagnoses.

**Musculoskeletal**

**Joint instability.** Joint laxity and instability and excessive joint motion are frequently evident on routine activity, even in the absence of overt subluxation or dislocation.

- Subluxations and dislocations are common. They may occur spontaneously or with minimal trauma and can be acutely painful. Reduction often occurs spontaneously or can be accomplished by the affected individual or a bystander. For most affected individuals, medical intervention for an acute dislocation is not usually necessary, but pain can last for hours or days after an event.
- All sites can be involved, including the extremities, vertebral column, costo-vertebral and costo-sternal joints, clavicular articulations, and temporomandibular joints.
- Sprains or twisting of the ankles and buckling or "giving out" of the knees are common.
- Iliotibial band syndrome or "snapping hip" is a common symptom, often perceived by the affected individual as hip joint instability [Branson et al 2011].
- Temporomandibular dysfunction ("TMJ syndrome") is relatively common [Hagberg et al 2004, De Coster et al 2005], and can be thought of as a specific example of joint degeneration and osteoarthritis.
- Females tend to have more substantial laxity than males.
- Younger individuals tend to have more substantial laxity than older individuals [Castori et al 2010a].
- Tendinitis and bursitis may occur [Rombaut et al 2010b, Rombaut et al 2011a, Rombaut et al 2011b], especially greater trochanteric bursitis in those with iliotibial band syndrome. EDS does not directly cause inflammation, and these problems are likely secondary to joint instability.

**Osteoarthritis.** Degenerative joint disease occurs at a younger age than in the general population, possibly because of chronic joint instability resulting in increased mechanical stress.

**Bone density.** There is very limited and contradictory evidence regarding bone mineral density in hEDS. Dolan et al [1998] found bone density to be reduced by up to 0.9 SD in individuals with EDS compared to healthy controls, but that study did not look specifically at individuals with hEDS. Compared to age- and sex-matched controls, Gulbahar et al [2006] reported bone density reduction of up to 0.5 SD among premenopausal women with joint hypermobility syndrome (now considered identical to hEDS). However, Carbone et al [2000] found no difference in bone density between women with hEDS and normal controls after adjusting for height, weight, and physical activity.

**Pain**

Chronic pain, distinct from that associated with acute dislocations, is a serious complication of the condition and can be both physically and psychosocially disabling [Sacheti et al 1997, Hagberg et al 2004, Rombaut et al 2010a, Voermans et al 2010a, Rombaut et al 2011a, Rombaut et al 2011b].

It is variable in age of onset (as early as adolescence or as late as the 5th-6th decade), number of sites, duration, quality, severity, and response to therapy.

Severity is typically greater than expected based on physical and radiologic examinations.

Severity sometimes correlates with degree of joint instability and with sleep impairment [Voermans et al 2010a].

Fatigue and sleep disturbance are frequently associated [Rombaut et al 2010b, Voermans et al 2010a, Voermans et al 2010b, Rombaut et al 2011a, Rombaut et al 2011b, Rombaut et al 2012b]. Affected individuals are often diagnosed with chronic fatigue syndrome, fibromyalgia, depression, hypochondriasis, and/or malingering prior to recognition of joint laxity and establishment of the correct underlying diagnosis.
Headaches, especially migraine, are common [Rombaut et al 2010b, Rombaut et al 2011a, Rombaut et al 2011b]. Cervical muscle tension, temporomandibular dysfunction, and stress are some of the likely contributing factors.

Several recognizable pain syndromes are likely:

- **Muscular or myofascial pain**, localized around or between joints, often described as aching, throbbing, or stiff in quality, may be attributable to myofascial spasm, and palpable spasm with tender points (consistent with fibromyalgia) is often demonstrable, especially in the paravertebral musculature [Castori et al 2010a, Rombaut et al 2010b, Rombaut et al 2011a, Rombaut et al 2011b]. 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, numb, 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 [Camerota et al 2011]. Nerve conduction studies are usually not diagnostic. Skin biopsy may reveal reduction or absence of small nerve fibers, but may be normal. One hypothesis is that neuropathic pain may result from direct nerve impingement (e.g., by subluxed vertebrae, herniated discs, vertebral osteoarthritis, or peripheral joint subluxations). In addition, there may be mild-to-moderate nerve compression within areas of myofascial spasm. Neither of these possibilities has been evaluated clinically.

- **Osteoarthritic pain** occurs later in life (but earlier than in the general population) and typically presents as aching pain in the joints, frequently associated with stiffness. It is often exacerbated by stasis and by resistance and/or highly repetitive activity.

**Hematologic**

Easy bruising is quite common, frequently without obvious trauma or injury [Anstey et al 1991, De Paepe & Malfait 2004]. Mildly prolonged bleeding, epistaxis, bleeding from the gums (especially after dental extraction), and menometrorrhagia may also occur.

The underlying cause of the hematologic manifestations is unknown.

- Bleeding time may or may not be prolonged, but no consistent abnormalities of coagulation factors, von Willebrand factor or platelet number, release or aggregation have been reported [Anstey et al 1991, Mast et al 2009].
- Capillary fragility and/or impaired soft tissue integrity may play a role [De Paepe & Malfait 2004].

**Gastrointestinal**

Functional bowel disorders are common and underrecognized, affecting 33%-67% of individuals with hEDS [Levy et al 1999, Castori et al 2010a].

Gastroesophageal reflux and gastritis may be symptomatic despite maximal doses of proton pump inhibitors with additional H2-blockers and acid-neutralizing medications.

Early satiety and delayed gastric emptying may occur and may be exacerbated by opioid (and other) medications.

Irritable bowel syndrome may manifest with diarrhea and/or constipation, associated with abdominal cramping and rectal mucus.

**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 [Rowe et al 1999, Gazit et al 2003, Mathias et al...
Holter monitoring usually shows normal sinus rhythm, but sometimes reveals premature atrial complexes or paroxysmal supraventricular tachycardia. Tilt table testing may reveal neurally mediated hypotension (NMH) and/or postural orthostatic tachycardia syndrome (POTS).

Raynaud syndrome and acrocyanosis occur at an increased frequency, which may be another manifestation of autonomic dysfunction [Castori et al 2010a].

Aortic root dilation, usually of a mild degree, occurs in 11%-33% of individuals with hEDS [Wenstrup et al 2002, McDonnell et al 2006, Atzinger et al 2011]. The severity appears to be much less than occurs in Marfan syndrome, and there is no increased risk of aortic dissection in the absence of significant dilation. Dilation onset is in childhood and is usually stable over time. It is unlikely to progress or to develop later in life [Atzinger et al 2011].

Mitral valve prolapse (MVP) was previously considered a common feature of EDS. Rigorous evaluations using modern diagnostic criteria have been inconsistent, with some studies showing no increase in the frequency of clinically significant MVP [Dolan et al 1997, McDonnell et al 2006, Atzinger et al 2011] and others showing an MVP frequency of 28%-67% [Camerota et al 2014, Kozanoglu et al 2016]. It is possible that mild MVP not meeting diagnostic criteria (and therefore not requiring special monitoring or treatment) may also explain some of the atypical chest pain and palpitations.

Oral/Dental

High, narrow palate and dental crowding are nonspecific features of most heritable disorders of connective tissue. Bifid uvula, submucous cleft palate, and overt cleft palate are not manifestations of hEDS, and should prompt consideration of alternative diagnoses (see Differential Diagnosis).

The frequency of periodontal manifestations such as friability, gingivitis, and gum recession is probably increased but has not been adequately studied specifically in the hypermobile type [Hagberg et al 2004, De Coster et al 2005, Castori et al 2010a]. De Felice et al [2004] reported an abnormally complex oral microvascular network in 12 individuals with classic or hypermobile EDS; potential correlation of this with periodontal disease has not been reported.

Obstetric/Gynecologic

Pregnancy may be complicated by rapid labor and delivery (<4 hours), with small studies suggesting a frequency of 28%-36% [Castori et al 2010a, Castori et al 2012].

Joint laxity and pain typically increase throughout gestation, especially in the third trimester, as normally occurs during pregnancy in unaffected women [Volkov et al 2007, Castori et al 2012].

There is no clear advantage to vaginal vs cesarean delivery. Cesarean delivery may reduce the risk of hip dislocation [Volkov et al 2007, Dutta et al 2011], but carries the same risk for surgical complications as in the general population.

There is no increase in risk for cervical incompetence, and no evidence to support use of prophylactic cerclage [Volkov et al 2007].

No other pregnancy complications are associated with hEDS.

Pelvic prolapse, dysmenorrhea, and dyspareunia occur at increased frequency in hypermobile EDS [McIntosh et al 1995, Castori et al 2010a, Castori et al 2012].
Psychiatric

Psychological dysfunction, psychosocial impairment, and emotional problems are common [Hagberg et al 2004, Rombaut et al 2011a].

Specific manifestations may include depression, anxiety, affective disorder, low self-confidence, negative thinking, hopelessness, and desperation [Hagberg et al 2004, Castori et al 2010a, Baeza-Velasco et al 2011, Branson et al 2011, Rombaut et al 2011a].

Fatigue [Voermans et al 2010b] and pain [Rombaut et al 2011a] exacerbate the psychological dysfunction.

Psychological distress exacerbates pain [Baeza-Velasco et al 2011, Branson et al 2011].

Fear of pain and/or joint instability may lead to avoidance behavior (kinesiophobia) and exacerbate dysfunction and disability [Baeza-Velasco et al 2011, Branson et al 2011].

Affected individuals may feel misunderstood, disbelieved, marginalized, and alone [Baeza-Velasco et al 2011].

Resentment, distrust, and hostility may develop between the affected individual/family and the health care team (in both directions), adversely affecting the therapeutic relationship [Branson et al 2011].

Ocular

Detailed and systematic evaluation of ocular findings in 44 eyes of 22 individuals with hEDS was compared to age- and sex-matched controls [Gharbiya et al 2012]. Findings included the following:

- Subjective and objective measures of xerophthalmia were rare, but more common in hEDS than controls. It is unknown whether this represents an intrinsic feature of EDS or possibly an indirect association (e.g., a side effect of medication).
- Clinically insignificant minor lens opacities were found in 13% of EDS eyes, compared to none among controls.
- High myopia (more than -6.0 diopters) and vitreous degeneration were found in 16% of EDS eyes and none of the controls. There was no difference in frequency of mild or moderate myopia between EDS and control eyes.
- There was no significant difference in axial length of the globe between EDS and control eyes.
- EDS eyes averaged slightly increased corneal curvature compared to controls, but there was no overt keratoconus.

Neurologic & Neuromuscular

Delayed onset and/or resistance to local anesthesia is a frequent complaint [Hakim et al 2005, Castori et al 2010a].

Dysautonomia may manifest as functional bowel disorders, cardiovascular autonomic dysfunction, and/or Raynaud syndrome/acrocyanosis.

Poor balance is common, with increased incidence of falls and occasionally fear of falling [Rombaut et al 2011c].

Diminished joint position sense has been reported at the knees, but not the shoulders. Vibration sensation is normal [Rombaut et al 2010a].

It is unclear whether weakness is an associated feature. Some studies suggest normal muscle strength [Castori et al 2010a, Rombaut et al 2010b], while others have demonstrated decreased ankle power [Galli et al 2011], reduced passive muscle tension, and increased Achilles tendon compliance [Rombaut et al 2012a, Rombaut et al 2012b]. One study reported lower-extremity weakness, but the findings could also be explained by reduced motor effort secondary to pain and/or fatigue [Rombaut et al 2012b].
Individuals with hEDS tend to have a slower-than-normal gait with shorter gait length [Cimolin et al 2011, Galli et al 2011, Rombaut et al 2011c].

Kinematic studies are normal at the hips and knees [Galli et al 2011], but the ankles demonstrate excess plantar flexion at ground contact and decreased dorsiflexion during motion [Cimolin et al 2011, Galli et al 2011, Rigoldi et al 2012].

In a series of 2,813 individuals with Chiari malformation type 1, 12.7% were felt to also have a hereditary disorder of connective tissue, including many with hEDS [Milhorat et al 2007]. Among those with independently confirmed EDS, Chiari malformation was found in only one (4.7%) of 21 individuals with hypermobile EDS [Castori et al 2010a] and one (5.5%) of 18 individuals with headache and unspecified types of EDS [Jacome 1999]. The incidence of Chiari malformation among individuals with EDS has not been systematically studied, and the clinical relevance of this potential association is uncertain.

**Disability**

Functional and psychosocial impairment are common, manifesting with decreased sport-related physical activity, diminished health-related quality of life, and significant impact on daily function [Rombaut et al 2010b, Voermans et al 2010a, Rombaut et al 2011a, Rombaut et al 2011b].

Pain, fatigue, and sleep disturbance all may contribute to disability and functional impairment [Rombaut et al 2010b, Voermans et al 2010a, Rombaut et al 2011a, Voermans & Knoop 2011].

**Other**

**Fragility of soft tissues** with spontaneous ruptures or tears of internal organs is, by definition, not a feature of hEDS. Such manifestations should prompt consideration of other hereditary connective tissue disorders (see Differential Diagnosis).

**Penetrance**

Penetrance is believed to be 100%, although expressivity is extremely variable, and careful examination may be required to demonstrate typical features, especially in adult men who have never experienced a major joint complication or significant pain.

**Anticipation**

Anticipation is not believed to occur.

**Nomenclature**

The 1997 Villefranche conference [Beighton et al 1998] simplified the classification and nomenclature of the Ehlers Danlos syndromes. The former EDS type III was renamed the hypermobility type. In 2017, the International Ehlers Danlos Syndrome Consortium published revised diagnostic criteria, and the name was modified slightly to hypermobile EDS (hEDS) [Malfait et al 2017].

It is now generally accepted that "benign familial articular hypermobility syndrome" and "joint hypermobility syndrome" are identical to hEDS and no longer thought to represent unique conditions [Grahame 1999, Tinkle et al 2009].
Prevalence

The prevalence of hEDS is unknown, with estimates ranging between 1:5,000 and 1:20,000. Given the clinical variability and low probability of affected males being ascertained, the prevalence is likely much higher than estimated. hEDS may be the most common heritable disorder of connective tissue.

Differential Diagnosis

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]:

- **Classic EDS (cEDS)** includes skin and soft tissue fragility. Mild presentations of the classic type may be mistaken for the hypermobile type, including similar degrees of joint laxity, pain, pelvic prolapse, dyspareunia, and manifestations in the hematologic, gastrointestinal, cardiovascular, and dental systems. The diagnosis is sometimes revised from hypermobile to classic when the individual or a family member later develops more significant skin and soft tissue manifestations. Among individuals with all of the skin features of cEDS, including dystrophic scarring, more than 90% have an identifiable pathogenic variant in COL5A1 or COL5A2, the two genes encoding type V collagen [Symoens et al 2012]. In individuals with milder skin manifestations (but still more than typically seen in the hypermobile type), no consistent pathogenic variants in any genes have been found. The diagnosis of cEDS is based on clinical findings and confirmed by molecular genetic testing. cEDS is inherited in an autosomal dominant manner. See Classic Ehlers-Danlos Syndrome.

- **In vascular EDS (vEDS)**, the joint laxity is predominantly in small joints, as opposed to the generalized laxity typically observed in hypermobile EDS. Vascular EDS also usually manifests thin, translucent skin, fragility of skin and soft tissue, and atrophic scarring. Predisposition to spontaneous rupture of hollow organs (primarily arteries, intestines, and uterus) is a hallmark of the vascular type, but not all individuals with vEDS develop such complications. A family history of unexplained sudden death is potentially consistent with catastrophic internal organ rupture and could be sufficient to prompt diagnostic testing for the vascular type, especially if the event(s) occurred in a first-degree relative, multiple second-degree relatives, and/or at a young age (e.g., <50 years). Nonspecific venous and hematologic abnormalities including varicose veins, hemorrhoids, easy bruising, and bleeding diathesis are not suggestive of vEDS, and should not prompt additional evaluation for this type. Dysfunction and/or deficiency of type III collagen, caused by pathogenic variants in COL3A1, is responsible for all cases of vEDS. The diagnosis of vEDS is based on clinical findings and confirmed by molecular genetic testing. Vascular EDS is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported. See Vascular Ehlers-Danlos Syndrome.

- **PLOD1-related kyphoscoliotic EDS (kEDS-PLOD1) and dermatosparaxis (dermatosparaxis EDS, dEDS)** (OMIM 225410) are autosomal recessive, rare, and distinguished by more severe skin manifestations and other features. kEDS-PLOD1 is caused by deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1: lysyl hydroxylase 1); the diagnosis can be established by demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine measured by HPLC, assay of lysyl hydroxylase enzyme activity in skin fibroblasts, or molecular genetic testing of PLOD1. Dermatosparaxis EDS is caused by deficient activity of the enzyme procollagen I N-proteinase (ADAMTS2) and is diagnosed by molecular genetic testing of ADAMTS2 or biochemical analysis of type I procollagen extracted from dermis or in fibroblast cultures.

- **Arthrochalasia EDS (aEDS)** (OMIM 130060) is autosomal dominant, rare, and distinguished by congenital hip dislocation and more severe skin manifestations. Pathogenic variants occur in exon 6 of
COL1A1 and COL1A2, causing impaired cleavage of the amino terminal propeptide of the corresponding type 1 procollagen molecules.

- **Classic-like EDS (cLEDs)** (OMIM 606408) is caused by deficiency of tenascin-X, resulting from compound heterozygous or homozygous TNXB mutation/deletion. Classic-like EDS is autosomal recessive and manifests joint laxity, hyperextensible skin, and easy bruising with normal wound healing and absence of atrophic scarring. Some, but not all, also have congenital adrenal hyperplasia as a result of contiguous gene deletion involving CYP21A2 [Bristow et al 2005]. Heterozygous mutation of TNXB has been reported in a small subset of individuals with joint laxity and soft skin typical of hEDS, but skin hyperextensibility, easy bruising, and other hematologic manifestations are not part of this phenotype [Zweers et al 2003, Zweers et al 2005].

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

Most of the following disorders 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.

- **Marfan syndrome** results in additional skeletal, ocular, cardiovascular, pulmonary, and skin/integument manifestations beyond those seen in EDS. Specific clinical criteria are available to establish a diagnosis of Marfan syndrome, and it can be confirmed by demonstration of a pathogenic variant in FBN1. Joint hypermobility is common in the MASS phenotype (myopia, mitral valve prolapse, mild aortic root dilatation, striae, and minor skeletal manifestations of Marfan syndrome; OMIM 604308), also caused by pathogenic variants in FBN1. Sometimes individuals with hypermobile EDS can have a Marfanoid build and as such resemble individuals with Marfan syndrome or a Marfan-related disorder. However, application of the clinical diagnostic criteria for Marfan syndrome and FBN1 molecular analysis allow differentiation of these conditions. Marfan syndrome is inherited in an autosomal dominant manner. See Marfan Syndrome.

- **Loeys-Dietz syndrome (LDS)** is characterized by vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections) and skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus). Approximately 75% of affected individuals have LDS type I with craniofacial manifestations (widely spaced eyes, bifid uvula/cleft palate, craniosynostosis); approximately 25% have LDS type II with systemic manifestations of LDSI but minimal or absent craniofacial features. LDSI and LDSII form a clinical continuum. The presentation often mimics Marfan syndrome or vEDS, but prior to detection of the arterial abnormalities, individuals may be misdiagnosed with classic or hypermobile EDS. The diagnosis is established by detection of a pathogenic variant in TGFBR1, TGFBR2, SMAD3, or TGFB2. LDS is inherited in an autosomal dominant manner. See Loeys-Dietz Syndrome.

- **Arterial tortuosity syndrome (ATS)**, in addition to aneurysm, dissection, tortuosity, and stenosis of larger and medium-sized arteries, manifests craniofacial and skeletal features similar to Loeys-Dietz syndrome. In contrast to dominantly inherited connective tissue disorders predisposing to arterial fragility (vascular EDS, Marfan syndrome, and LDS), ATS is inherited in an autosomal recessive manner. A diagnosis of ATS is confirmed by identifying biallelic (homozygous or compound heterozygous) pathogenic variants in SLC2A10 in an individual with generalized arterial tortuosity and other typical features. See Arterial Tortuosity Syndrome.

- **Shprintzen-Goldberg syndrome (SGS)** is distinguished by cardinal features of craniosynostosis and mild-to-moderate intellectual disability. Cerebral abnormalities may include hydrocephalus, dilatation of the
lateral ventricles, and Chiari 1 malformation. Aortic root dilation may occur, but less commonly than in Marfan syndrome or LDS. Some additional characteristic findings include C1/C2 spine malformation, reduced subcutaneous fat, abdominal wall defects, and cryptorchidism in males. SGS is confirmed in individuals with typical findings by identifying a pathogenic variant in SKI. SKI-related SGS is inherited in an autosomal dominant manner. See Shprintzen-Goldberg Syndrome.

- **Stickler syndrome.** Distinguishing features include sensorineural hearing loss, vitreoretinal abnormalities, and cleft palate. Six genes have been associated with Stickler syndrome. However, a few families with features of Stickler syndrome are not linked to any of these loci; thus, pathogenic variants in other genes may also cause the disorder. Stickler syndrome is diagnosed based on clinical features. In many affected individuals and families the diagnosis can be confirmed by molecular genetic testing, although a negative test does not rule out the diagnosis. Stickler syndrome caused by mutation of COL2A1, COL11A1, or COL11A2 is inherited in an autosomal dominant manner; Stickler syndrome caused by mutation of COL9A1, COL9A2, or COL9A3 is inherited in an autosomal recessive manner. See Stickler Syndrome.

- **Williams syndrome (WS)** is a contiguous gene deletion syndrome characterized by cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvar aortic stenosis, hypertension), distinctive facies, connective tissue abnormalities, intellectual disability (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty). The mainstay for diagnosis is detection of the contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses the elastin gene (ELN). More than 99% of individuals with the clinical diagnosis of WS have this contiguous gene deletion, which can be detected using fluorescent in situ hybridization (FISH) or deletion/duplication analysis. Supravalvar aortic stenosis (SVAS) is caused by mutation (rather than deletion) of ELN. Individuals with either deletion or mutation of ELN have joint laxity, but the classic elastin arteriopathy is not seen in any type of EDS. WS is transmitted in an autosomal dominant manner. See Williams Syndrome.

- **Aarskog-Scott syndrome (faciogenital dysplasia)** (OMIM 305400) is an X-linked condition resulting from mutation of FGD1. The most significant distinguishing feature is shawl scrotum, which may become less obvious in adulthood. Widow’s peak, short upturned nose, other dysmorphic features, and the inheritance pattern can be additional diagnostic clues. Intellectual disability, which is not associated with any of the types of EDS, is sometimes present.

- **Fragile X syndrome** is not typically confused with hEDS. When a full pathogenic variant of FMR1 is present, fragile X syndrome is characterized by moderate intellectual disability in affected males and mild intellectual disability in affected females. Males may have a characteristic appearance (large head, long face, prominent forehead and chin, protruding ears), joint laxity, and large testes (post-puberty). However, premutation carriers may have joint laxity and EDS-like skin findings without other major manifestations. Family history of intellectual disability, premature ovarian failure, and/or fragile X tremor/ataxia syndrome is helpful when present. The frequency of FMR1 premutation among individuals diagnosed clinically with hEDS has not been studied, but fragile X syndrome has not been reported among offspring of women with hEDS. Fragile X syndrome is inherited in an X-linked manner. See FMR1 Disorders.

- **Achondroplasia** and **hypochondroplasia** are distinguished by short stature with characteristic skeletal features (marked in achondroplasia, milder in hypochondroplasia). Achondroplasia can be diagnosed by characteristic clinical and radiographic findings in most affected individuals. Molecular genetic testing reveals a pathogenic variant in FGFR3 in 99% of individuals with achondroplasia and about 70% of individuals with hypochondroplasia. However, it is clear that locus heterogeneity exists for hypochondroplasia because pathogenic variants in other as-yet unidentified genes can result in similar, if not identical, phenotypes. Achondroplasia and hypochondroplasia are inherited in an autosomal dominant manner. See Achondroplasia, Hypochondroplasia.

- **Osteogenesis imperfecta (OI)** is distinguished by the presence of fractures and, in some cases, dentinogenesis imperfecta (grey or brown teeth). Biochemical testing (i.e., analysis of the structure and
quantity of type I collagen synthesized in vitro by cultured dermal fibroblasts) detects abnormalities in 98% of individuals with OI type II, about 90% with OI type I, about 84% with OI type III, and about 84% with OI type IV. About 90% of individuals with OI types I, II, III, and IV (but none with OI types V, VI, and VII) have an identifiable pathogenic variant in either COL1A1 or COL1A2. COL1A1/COL1A2-related OI is inherited in an autosomal dominant manner. See COL1A1/2 Osteogenesis Imperfecta.

- **Mitochondrial myopathies** may cause joint hypermobility as a result of hypotonia, rather than the ligamentous laxity assumed to be the underlying mechanism in hereditary disorders of connective tissue. It can be difficult to distinguish between ligamentous laxity and hypotonia on physical exam, especially in adolescents and adults. Other features of mitochondrial disease 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 intellectual 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 those symptoms is very long. Some conditions that may overlap with or complicate hEDS:

- A subset of individuals with fibromyalgia and/or chronic fatigue syndrome may have EDS as the underlying etiology, but not all individuals with chronic pain and/or fatigue have EDS.

- **Celiac disease** may coexist with EDS or be misdiagnosed as EDS. Common features may include pain, fatigue, functional gastrointestinal disorders, and cardiovascular autonomic dysfunction. See Celiac Disease.

- **Vitamin D deficiency** may also cause or exacerbate pain and fatigue.

- **Familial Mediterranean fever (FMF)** most classically presents with episodic abdominal pain associated with fever, but low-grade fever may not be detected and the manifestations could be confused with irritable bowel syndrome. Joint pain may also occur in FMF. See Familial Mediterranean Fever.

Clinically, the **hematologic manifestations** of EDS mimic von Willebrand disease and respond to similar treatments, but von Willebrand factor and platelet number are almost always normal. Easy bruising and prolonged bleeding alone are insufficient to establish a diagnosis of EDS, and the diagnostic evaluation of such problems should also consider von Willebrand disease, idiopathic thrombocytopenia purpura, and other hemorrhagic conditions. See von Willebrand Disease.

**Management**

**Evaluations Following Initial Diagnosis**

To establish the extent of disease and needs in an individual diagnosed with hEDS, the following evaluations are recommended:

- Thorough history and physical examination, especially for musculoskeletal, skin, cardiovascular, gastrointestinal, and oral/dental manifestations

- Assessment of prior experience with mechanical, pharmacologic, and/or surgical treatment of pain and joint instability, as well as current degree of pain and disability
Baseline echocardiogram to evaluate aortic root diameter, as adjusted for age and body surface area [Campens et al 2014]. Significant aortic enlargement and/or other cardiac abnormalities should prompt consideration of alternative diagnoses.

The following evaluations should not be routine, but may be appropriate in some situations:

- For individuals with significant orthostatic intolerance and/or tachycardia, consider tilt-table testing to help confirm postural orthostatic tachycardia and/or neurally mediated hypotension. However, treatment of the symptoms may not differ based on the outcome, so tilt-table testing is optional. It is also sometimes appropriate to rule out adrenocortical insufficiency.
- If irritable bowel syndrome is suspected, consider formal gastroenterology consultation and possible endoscopy to rule out other treatable diagnoses. Celiac disease, inflammatory bowel disease, and other causes of malabsorption or bowel dysfunction are not associated with EDS, but may be coexisting diagnoses.
- Dual-energy x-ray absorptiometry (DEXA) is appropriate at any age if height loss greater than one inch is documented or x-rays are suggestive of osteopenia. Screening DEXA in those without suggestive signs or symptoms is not currently recommended.
- If a history of severe or prolonged bleeding is present, consider hematologic evaluation for von Willebrand disease, thrombocytopenia, or other bleeding diathesis. Although pathophysiologically unrelated, these conditions may coexist with hEDS and exacerbate the hematologic manifestations.
- When needed, the pain management recommendations in Treatment of Manifestations can be implemented by any member of the care team who feels confident enough to do so, or evaluation by a pain management specialist could be considered.
- If there is suspicion of Chiari malformation, consider cerebral MRI, possibly with CSF flow studies.
- Clinical genetics consultation is appropriate if there is uncertainty about the diagnosis or for assistance in evaluation and management.

**Treatment of Manifestations**

**Physical Therapy**

Myofascial release (any physical therapy modality that reduces spasm) provides short-term relief of pain, lasting hours to days. While the duration of benefit is short and it must be repeated frequently, this pain relief may be critical to facilitate participation in toning exercise for stabilization of the joints. Modalities must be tailored to the individual; a partial list includes heat, cold, massage, ultrasound, electrical stimulation, acupuncture, acupressure, biofeedback, and conscious relaxation.

Low-resistance muscle toning exercise can improve joint stability and reduce future subluxations, dislocations, and pain. See Prevention of Primary Manifestations.

Transvaginal pelvic physical therapy and myofascial release (in which massage or ultrasound is applied to the pelvic musculature via a transvaginal approach) may improve dyspareunia, abdominal pain, back pain, and sometimes radicular lower-extremity pain. This should only be performed by a physical therapist with training and expertise in pelvic floor physical therapy and with patient consent.

**Assistive Devices**

Braces are useful to improve joint stability. Orthopedists, rheumatologists, and physical therapists can assist in recommending appropriate devices for commonly problematic joints such as knees and ankles. Shoulders and
hips present more of a challenge for external bracing. Occupational therapists may be consulted for ring splints (to stabilize interphalangeal joints) and wrist or wrist/thumb braces in affected individuals with small joint instability. A soft neck collar, if tolerated, may help with neck pain and headaches.

A wheelchair or scooter may be necessary to offload stress on lower-extremity joints. Special wheelchair customizations such as lightweight and/or motorized chairs, seat pads, and specialized wheels and wheel grasps may be necessary to accommodate pelvic and upper-extremity issues.

A waterbed, adjustable air mattress, or viscoelastic foam mattress (and/or pillow) may provide increased support with improved sleep quality and less pain.

**Pain Medication**

Pain medication is frequently underprescribed, and should be tailored to the individual’s subjective symptoms and objective measures of pain, not to physical examination or radiologic findings. Individuals with mild to moderate pain may get sufficient relief from as-needed use. Those with more significant pain typically require higher doses and combinations of multiple medications. Prevention or control of pain with regularly scheduled dosing is often more successful than acute treatment with as-needed dosing. Many clinicians recruit a pain management specialist, but pain can be managed by the primary physician if desired.

Note: All of the following dose recommendations are for adults without hepatic or renal disease; adjustments may be necessary for other populations.

- Acetaminophen, 4,000 mg daily in three or four divided doses, will not completely alleviate pain but is a useful and well-tolerated adjunct in combination with other agents. Acetaminophen is often present in combination with other analgesic medications and cold/flu preparations, and careful attention should be paid to the total daily dose to avoid exceeding 4000 mg/day.
- NSAIDs (nonsteroidal anti-inflammatory drugs) (e.g., ibuprofen, naproxen, meloxicam, nabumetone) should be titrated to the maximum dose or as tolerated by upper gastrointestinal symptoms. NSAIDs are particularly useful for arthralgia, myalgia, and secondary inflammatory conditions (e.g. bursitis, tendinitis, costochodritis, or post-dislocation pain). Bruising is not a contraindication to NSAID therapy, but occasionally requires dose reduction or change to a Cox-2 inhibitor.
- Cox-2 inhibitors (e.g., celecoxib) in maximal doses are no stronger than dose-equivalent NSAIDS, but may be better tolerated and thus more effective.
- Topical lidocaine as a cream or patch is sometimes useful for localized areas of pain. Topical capsaicin is of questionable utility, but is safe.
- Skeletal muscle relaxants are useful in combination with all of the above to treat myofascial spasm. They are also sometimes helpful in treating neuropathic pain. Metaxalone may be the least sedating, but all are potentially limited by sedation. There is theoretic risk that skeletal muscle relaxants can increase joint instability by reducing muscle tone. This is not a contraindication to their use, but does justify monitoring for potential complications.
- Magnesium, either topically as Epsom salt baths or orally in any form, may also reduce muscle spasm and pain. No specific formulation or dosage has been established as superior to any other. The most common adverse effects – sedation, nausea, abdominal pain, and diarrhea – are more likely to occur with oral rather than topical supplementation.
- Tricyclic antidepressants are often effective for neuropathic pain, with additional benefits of mild sedation (for those with sleep disturbance) and a little mood elevation. Constipation, a common side effect, can be managed with fluids, fiber, stool softeners, and laxatives. For those with diarrhea-predominant irritable bowel syndrome, the constipating effect may be therapeutic. Typical doses are nortriptyline (25-150 mg) or trazadone (50-300 mg) every evening.
Serotonin/norepinephrine receptor inhibitors (SNRIs), such as venlafaxine, desvenlafaxine, duloxetine, and milnacipran also offer combined benefit for depression and neuropathic pain. Venlafaxine may raise the blood pressure a few points, which potentially could be helpful for individuals with neurally mediated hypotension.

Some anti-seizure medications are also effective for neuropathic pain and can be used in addition to tricyclic and/or SNRI antidepressants. All require gradual titration before reaching therapeutic levels. Gabapentin should be titrated as tolerated up to at least 1200 mg/3x/day before declaring failure, but is often limited by sedation and/or gastrointestinal side effects. Pregabalin can be dosed twice or three times daily up to a total daily dose of at least 300 mg, and tends to be better tolerated than gabapentin. Topiramate and lamotrigine have also been used successfully.

Short courses of steroids can be very effective for controlling acute flares of pain associated with secondary inflammation. EDS is not an intrinsically inflammatory condition, and there is no role for chronic steroid use.

Glucosamine and chondroitin may help to prevent or treat osteoarthritis in the general population. They have not been studied specifically in EDS, but are not contraindicated.

Cannabinoids such as dronabinol and (where legal) marijuana may be helpful for several different types of pain. Their benefits should be weighed against the potential for dependency and/or psychoactive effects.

Tramadol can be added to acetaminophen plus an NSAID or Cox-2 inhibitor before resorting to opioids. Nausea is the most common side effect.

Opioids are effective for both myofascial pain and neuropathic pain, but should be reserved for use after failing the above medications. They should be administered in conjunction with all of the above, except tramadol, in order to minimize total opioid requirements. Since they are typically used chronically (or at least several months), the primary formulation should be long acting (e.g., sustained-release oxycodone or morphine or topical fentanyl patch) with short-acting forms of the same drug used as needed for breakthrough pain. Routine use of two or more daily doses of a short-acting form should prompt an increase in the long-acting dose or another adjustment to the pain regimen.

Benzodiazepines may offer some short-term reduction in muscle spasm, but are poor choices for long-term muscle relaxation and carry high risk of tolerance, dependency, and addiction. Routine use of benzodiazepines is not recommended.

**Medication precautions**

- It is critically important to evaluate all potential sources of acetaminophen and assure that total daily use does not exceed 4,000 mg.
- Abrupt cessation of anti-seizure medications can precipitate a seizure. When discontinuing, they should be tapered gradually.
- Chronic opioid use can result in tolerance and dependency with escalating dose requirements and diminishing effect. Narcotic bowel syndrome can also develop, and may be confused with irritable bowel syndrome.
- Serotonin syndrome can occur when combining multiple serotonergic medications, such as tramadol, tricyclic antidepressants, SNRI antidepressants, anti-seizure medications, and opioids. Symptoms and signs may include agitation, restlessness, tremor, hyperreflexia, ataxia, confusion, irritability, nausea, diarrhea, hyperthermia, tachycardia, hyper/hypotension, and/or diaphoresis. Severity can range from mild to life threatening. Many of these manifestations overlap those associated with EDS, making diagnosis difficult. Some individuals find mild-to-moderate serotonergic symptoms acceptable in order to achieve adequate pain control.
Surgery and Other Procedures

Many individuals will have undergone several orthopedic procedures prior to diagnosis. These often include joint debridement, tendon relocations, capsulorraphy, and arthroplasty. The degree of stabilization and pain reduction, overall patient satisfaction, and duration of improvement are variable, but usually less than in individuals without EDS [Aldridge et al 2003, Rose et al 2004, Rombaut et al 2011b]. In general, orthopedic surgery should be delayed in favor of physical therapy and bracing. When surgery is performed, the affected individual and physician should cautiously anticipate some improvement but expect less than optimal results. There is one report of long-term improvement in shoulder stability with Achilles tendon allograft reconstruction of the joint capsule in an individual with hEDS [Chaudhury et al 2012]. It is not yet known if this approach will be successful in other affected individuals. Unlike classic and vascular EDS, hypermobile EDS is not associated with increased risk for perioperative skin and soft tissue complications.

Prolotherapy, in which saline and/or other irritants are injected in tendons or around joints to induce scar formation and increase stability, has not been objectively studied. It is probably safe and probably subject to the same limitations as orthopedic surgery.

Anesthetic/corticosteroid injections for localized areas of pain and acute inflammation are often helpful, but cannot be repeated indefinitely. "Dry needling" without injection of any material sometimes provides similar benefit.

Anesthetic nerve blocks can provide temporary relief of neuropathic pain. These are sometimes followed by surgical nerve root destruction and/or implantable stimulators (sensory or motor), with variable results.

Constant intrathecal delivery of anesthetic and/or opioid medication may reduce the need for oral/systemic medications, but should only be considered as a last resort.

Bone Density

Therapy is the same as for any other individual with low bone density, including supplementation of calcium and vitamin D. Simple weight-bearing exercise, such as walking or use of an elliptical trainer, should not be overlooked as a means to help maintain bone density as well as improve resting muscle tone.

Hematologic

Easy and spontaneous bruising does not require treatment, and does not require avoidance of NSAIDs.

For severe bleeding (e.g., epistaxis, menometrorrhagia) or operative prophylaxis, desmopressin acetate (ddAVP) is often beneficial [Stine & Becton 1997, Mast et al 2009].

Gastrointestinal

Gastritis and reflux symptoms may require intensive therapy, including proton pump inhibitor twice daily before meals, high-dose H2-blocker at bedtime (e.g., famotidine 20-40 mg or ranitidine 150-300 mg), sucralfate one gram four times daily, and over-the-counter acid-neutralizing agents. Other treatable causes, such as *H. pylori* infection, should be investigated. Upper endoscopy is indicated for resistant symptoms, but frequently is normal other than chronic gastritis.

Delayed gastric emptying should be identified if present and treated the same way as in individuals without EDS. Assistance from a gastroenterologist experienced in managing GI dysmotility can be helpful.

Irritable bowel syndrome is treated as usual with dietary modification, fiber, antispasmodics, antidiarrheals, and laxatives as needed. Lubiprostone is a motility enhancer that may be helpful for those with constipation only. Tricyclic antidepressants may be helpful for persons with both neuropathic pain and diarrhea.
Cardiovascular

Beta-blockade is rarely necessary, but should be considered for progressive aortic enlargement. Rarely, severe enlargement (>4.5-5.0 cm) requires surgical evaluation. When such severe enlargement is noted, other hereditary disorders of connective tissue should be considered (see Differential Diagnosis).

Neurally mediated hypotension and postural orthostatic tachycardia are treated as usual, with avoidance of sudden postural change, consideration of lower-extremity and/or abdominal compression garments, exercise to increase muscle tone, supplementation of sodium and water to expand the blood volume, and sometimes pharmacologic treatment with beta-blockers, midodrine, fludrocortisone, and/or other medications [Mathias et al 2011]. Commercially available electrolyte tablets can be added to water to facilitate oral expansion of blood volume.

Dental

Orthodontic and palatal corrections may tend to relapse, requiring prolonged use of a retainer.

Periodontal disease should be identified and treated.

Temporomandibular joint laxity and dysfunction are difficult to treat. There are no specific interventions of proven benefit. Intra-oral devices are sometimes helpful. Oral rest (minimization of chewing and talking), local myofascial release, and muscle relaxant medications may be beneficial for acute flares. Surgical intervention is often disappointing and should be considered only as a last resort.

Psychiatric

Validation of the affected individual's symptoms can be immensely helpful, as many with hEDS have been accused of malingering or diagnosed with primary psychiatric disorders by previous physicians.

Establishing trust, rapport, and a supportive relationship between patient and provider is important. Emphasis should be placed on chronic, rather than acute, pain management. Distraction and hypnosis are often helpful [Branson et al 2011].

Depression is a common result of the chronic pain, disability, and other complications. Psychological and/or pain-oriented counseling can improve adaptation to and acceptance of these issues and the necessary physical limitations. Cognitive behavioral therapy can be particularly beneficial, but requires active patient participation [Baeza-Velasco et al 2011]. Antidepressants are also of great benefit. Many individuals initially resist a diagnosis of or therapy for depression because of concern that their problems are being written off as purely psychiatric.

Consumer support groups are available and can be very beneficial.

Prevention of Primary Manifestations

Improved joint stability may be achieved by low-resistance exercise to increase muscle tone (subconscious resting muscle contraction), as opposed to muscle strength (voluntary force exerted at will). Emphasis should be placed on both core and extremity muscle tone. Examples include walking, bicycling, low-impact aerobics, swimming or water exercise, and simple range-of-motion exercise without added resistance. Core toning activities, such as balance exercises and repetitive motions focusing on the abdominal, lumbar, and interscapular muscles, are also important. Progress should be made by gradually increasing repetitions, frequency, or duration, not resistance. It often takes months or years for significant progress to be recognized.

Wide-grip writing utensils can reduce strain on finger and hand joints. An unconventional grasp of a writing utensil, gently resting the shaft in the web between the thumb and index finger and securing the tip between the distal interphalangeal joints or middle phalanges of the index and third fingers (rather than using the tips of the
fingers), results in substantially reduced axial stress to the interphalangeal, metacarpophalangeal, and carpometacarpal joints. These adjustments frequently result in marked reduction of pain in the index finger and at the base of the thumb.

**Prevention of Secondary Complications**

Calcium (500-600 mg/2x/day), vitamin D (400 or more units daily), and low-impact weight bearing exercise should be encouraged to maximize bone density.

**Surveillance**

DEXA should be repeated approximately every other year if bone loss is confirmed. Otherwise, routine population surveillance of bone density is all that is necessary.

Annual echocardiography is not necessary in those with a normal initial echocardiogram [Atzinger et al 2011]. In children and adolescents with a normal aortic root diameter, it is the author’s practice to repeat every two to three years until young adulthood (age ~25 years). If the aortic root diameter is increased or accelerating faster than body surface area, more frequent monitoring is appropriate. In adults with a normal aortic root diameter, no further monitoring is needed.

**Agents/Circumstances to Avoid**

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].

Resistance exercise can exacerbate joint instability and pain. In general, it is preferable to increase the number of repetitions of exercise rather than to increase the resistance.

High-impact activity increases the risk for acute subluxation/dislocation, chronic pain, and osteoarthritis. Some sports, such as tackle football, are therefore contraindicated. However, most sports and activities are acceptable with appropriate precautions.

Chiropractic adjustment is not strictly contraindicated, but must be performed cautiously to avoid iatrogenic subluxations or dislocations.

**Evaluation of Relatives at Risk**

All first-degree relatives are at a 50% risk of having hEDS, and may wish to undergo formal clinical assessment. Those without significant clinical manifestations may not benefit directly from knowing that they are affected, but may benefit from knowing that their children are at risk. Evaluation of children younger than age ten years (and especially age <5 years) is difficult because of the normal joint laxity in that age group.

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

**Pregnancy Management**

Labor and delivery may progress very rapidly. Even in primigravid women, any perception of labor should be taken seriously and she should promptly report to her intended place of delivery.

There is no clear advantage to vaginal vs cesarean delivery. Cesarean delivery may reduce the risk of hip dislocation [Volkov et al 2007, Dutta et al 2011], but carries the same risk for surgical complications as in the general population.
There is no increase in risk for cervical incompetence, and no evidence to support use of prophylactic cerclage [Volkov et al 2007].

Pregnant women with known aortic dilation 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](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://www.clinicaltrials.eu) 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.

**Other**

Vitamin C is a cofactor for cross-linking of collagen fibrils. Supplementation with up to 500 mg daily may improve some of the manifestations, but this has not been studied. Higher doses are likely excreted and probably offer no additional clinical benefit.

**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 EDS (hEDS) is inherited in an autosomal dominant manner.

**Risk to Family Members**

**Parents of a proband**

- Most individuals diagnosed with hEDS have an affected parent, although a careful history and examination of the parents is often necessary to recognize that, despite absence of serious complications, one and sometimes both parents have current or prior history of joint laxity, easy bruising, and soft skin.
- A proband with hEDS may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include a careful history and physical examination seeking current or prior history of joint laxity, easy bruising, and soft skin.
- Although most individuals diagnosed with hEDS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members.

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

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

**Offspring of a proband.** Each child of an individual with hEDS has a 50% chance of inheriting the same pathogenic variant (and thus the same type of EDS). However, 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 genetic status of the proband’s parents: if a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

It is worthwhile to emphasize to affected individuals and family members that hEDS does not evolve into any of the other types, either in the affected individual or in their offspring, and that the hypermobile type does not confer increased risk for early mortality.

Considerations in families with an apparent de novo pathogenic variant. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder, the pathogenic variant is likely de novo. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration could be given to banking DNA of affected individuals.

Prenatal Testing

Because the gene(s) and pathogenic variant(s) responsible for hEDS have not been identified, prenatal testing is 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**
  35-37 Ludgate Hill
  Office 7
  London EC4M 7JN
  United Kingdom
  Phone: +44 203 887 6132

- **Ehlers-Danlos Society Headquarters**
  P.O. Box 87463
  Montgomery Village MD 20886
  **Phone:** 410-670-7577
  **Email:** info@ehlers-danlos.com
  **www.ehlers-danlos.com**
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 hEDS.

References

Literature Cited


Chapter Notes

Revision History

- 21 June 2018 (ha) Revision: new diagnostic criteria [Malfait et al 2017]
- 31 March 2016 (ha) Comprehensive update posted live
- 13 September 2012 (me) Comprehensive update posted live
- 14 December 2010 (cdl) Revision: sequence analysis of the entire coding region available on a limited basis for TNXB mutations
- 27 April 2010 (me) Comprehensive update posted live
- 1 May 2007 (me) Comprehensive update posted live
- 22 October 2004 (me) Review posted live
- 1 June 2004 (hpl) Original submission

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