

# **EHLERS-DANLOS SYNDROME, HYPERMOBILITY TYPE**

(Adapted from EDS Hypermobility Type, EDS Type III, Ehlers-Danlos Syndrome Type III, By Howard P. Levy, MD, PhD, Department of Medicine, Division of General Internal Medicine McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine)

**Disease characteristics.** Ehlers-Danlos syndrome (EDS), hypermobility type is generally considered the least severe type of EDS, although significant complications, primarily musculoskeletal, can and do occur. The skin is often soft or velvety 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 is common. Functional bowel disorders are likely underrecognized. Autonomic dysfunction, such as orthostatic intolerance, may also be seen. Aortic root dilation 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.

## **CLINICAL MANIFESTATIONS:**

### **Musculoskeletal:**

#### Joint instability:

Joint laxity, instability and excessive joint motion is 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 friend/family member. 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.

Osteoporosis. Bone mineral density in EDS, hypermobility and classic types may be reduced by up to 0.9 SD compared to healthy controls, even in young adulthood [Dolan et al 1998].

## **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 fifth or sixth 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 2012a]. 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 2010]. Nerve conduction studies are usually non-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 in all types of EDS, 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.

Bleeding time may or may not be prolonged, but no consistent coagulation factor abnormalities have been reported [Anstey et al 1991, Mast et al 2009].

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. It is, however, possible for von Willebrand disease, idiopathic thrombocytopenia purpura, or other hemorrhagic conditions to be present independent of EDS.

The underlying cause of the hematologic manifestations is unknown.

- Capillary fragility and/or impaired soft tissue integrity may play a role [De Paepe & Malfait 2004].
- Defects in platelet release or aggregation have been found in some individuals with various types of EDS [Anstey et al 1991, Yenicesu et al 2000].

## **Gastrointestinal**

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

- Gastroesophageal reflux and gastritis may be symptomatic despite maximal doses of proton pump inhibitors with additional H<sub>2</sub>-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 individuals with EDS, hypermobility (and classic) type 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 2012].

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 EDS, classic and

hypermobility types [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 manifestation of all types of EDS, but clinically significant MVP has not been confirmed in rigorous evaluations using modern diagnostic criteria [Dolan et al 1997, McDonnell et al 2006, Atzinger et al 2011]. 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 EDS, hypermobility type, and should prompt consideration of alternative diagnoses (see Differential Diagnosis).

Periodontal disease (friability, gingivitis, gum recession) occurs in some individuals with EDS [Letourneau et al 2001, Hagberg et al 2004, De Coster et al 2005, Castori et al 2010a] and is no longer considered a unique subtype of EDS [Beighton et al 1998]. The frequency of periodontal manifestations in the hypermobility type is undetermined. De Felice et al [2004] reported an abnormally complex oral microvascular network in 12 individuals with classic or hypermobility type EDS; potential correlation of this with periodontal disease has not been reported.

### **Obstetric/Gynecologic**

Pregnancy may be complicated by premature rupture of membranes or rapid labor and delivery (<4 hours), but this is less likely than in the classic type [Volkov et al 2007, Castori et al 2010a].

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].

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 EDS, hypermobility type.

Pelvic prolapse and dyspareunia occur at increased frequency in at least the classic and hypermobility types of EDS [McIntosh et al 1995, Carley & Schaffer 2000].

## **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 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 healthcare 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 EDS, hypermobility type was compared to age- and gender matched controls [Gharbiya et al 2012]. Findings included the following:

- Subjective and objective measures of xerophthalmia were rare, but more common in EDS, hypermobility type 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 or not 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 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 2012a].

Individuals with EDS, hypermobility type 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 2813 individuals with Chiari malformation type 1, 12.7% were felt to also have a hereditary disorder of connective tissue, including many with EDS, hypermobility type [Milhorat et al 2007]. The incidence of Chiari malformation among individuals with EDS has not been systematically studied, and the clinical relevance of this association is uncertain.

## **Skin**

The skin is often soft or velvety 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 type.

Clinically significant skin morbidity does not occur, and should prompt consideration of alternative diagnoses.

## **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 EDS, hypermobility type. Such manifestations should prompt consideration of other hereditary connective tissue disorders (see Differential Diagnosis).

## **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.

#### **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.

Crutches, canes, and walkers should be used cautiously as they may put increased stress on the upper extremities.

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, 4000 mg 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, costochondritis, 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.
- Tramadol can be added to acetaminophen plus an NSAID or Cox-2 inhibitor before resorting to opioids. Nausea is the most common side effect.
- 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.
- 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 three times daily 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.
- 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.

- Supplemental magnesium and/or potassium anecdotally may provide some muscle relaxation and pain relief. Diarrhea, nausea, and sedation are the most common side effects. Specific validated dose recommendations do not exist.
- 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.

### Medication precautions

- It is critically important to evaluate all potential sources of acetaminophen and assure that total daily use does not exceed 4000 mg.
- Abrupt cessation of anti-seizure medications can precipitate a seizure. When discontinuing, they should be tapered gradually.
- Chronic opioid use can result in 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**

### Surgery

Many individuals will have undergone several orthopedic procedures prior to diagnosis. These often include joint debridement, tendon relocations, capsulorrhaphy, 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 EDS, hypermobility type [Chaudhury et al 2012]. It is not yet known if this approach will be successful in other affected individuals. Unlike the classic and vascular types of EDS, the hypermobility type is not associated with increased risk for perioperative skin and soft tissue complications.

Both Chiari malformation (CM) and tethered cord are frequently seen in EDS patients. It is not clear at this point what the nature of this association is.

According to Hakim AJ (reference 26), there is some evidence suggesting that the cause of a CM in EDS may be different. There is one published large study that has looked at the association between type 1 CM and EDS (reference 37). The study included 2813 patients with a known diagnosis of type 1 CM and found that 357 (12-13%) had features of EDS.

In a separate study an association was found between tethering of the spinal cord and type 1 CM (reference 38). Tethering arose in 14% of 408 patients studied.

Although the association between EDS, spinal cord tethering and type 1 CM is not clear at this point, corrective surgery for both tethered cord and Chiari malformation is regarded as a reasonable course of action when these conditions are found in patients with EDS.

In a 2010 published article, Henderson FC and colleagues (reference 28), reported on a cohort of children with Chiari I malformation or basilar invagination, who underwent suboccipital decompression where indicated, open reduction of the abnormal clivo-axial angle or basilar invagination to correct ventral brainstem deformity, and stabilization/ fusion. The results were concurrent with others, that normalization of the clivo-axial angle and fusion-stabilization is associated with clinical improvement.

Fusion and stabilization to address spinal instability at different levels (cervical, thoracic or lumbar), Tarlov cyst surgery, shunt placement for pseudotumor cerebri and hydrocephalus are all commonly performed procedures to treat conditions often seen in EDS patients.

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. 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 H<sub>2</sub>-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 as usual with promotility agents (e.g., erythromycin, metoclopramide).

Irritable bowel syndrome is treated as usual with antispasmodics, antidiarrheals, and laxatives as needed. Lubiprostone is a motility enhancer that may be helpful for those with constipation only.

Tricyclic antidepressants may be especially 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.

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 2012].

## **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 EDS, hypermobility type 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 voluntarily recruited muscle strength). 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 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 twice daily), 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 every other year if bone loss is confirmed.

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 must be avoided. Individuals with EDS, hypermobility type usually need to be educated about the normal range of joint extension and cautioned not to exceed it.

Resistance exercise can exacerbate joint instability and pain. Elastic resistance bands should be used with caution, if at all. In general, it is preferable to increase the number of repetitions of exercise rather than to increase the resistance.

Isometric exercise are recommended, but caution should be exercised not to exceed the amount of force (resistance) applied.

High-impact activity increases the risk for acute subluxation/dislocation, chronic pain, and osteoarthritis. Some sports, such as 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.

Crutches, canes, and walkers should be used cautiously as they may put increased stress on the upper extremities.

### **Evaluation of Relatives at Risk**

All first-degree relatives are at a 50% risk of having EDS, hypermobility type, 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 under age ten years (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 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.

### **Registries**

Contact information for voluntary patient registries is provided by *GeneReviews* staff.

National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)

Phone: 800-334-8571 ext. 24640  
Email: [gentac-registry@rti.org](mailto:gentac-registry@rti.org)  
Web: [gentac.rti.org](http://gentac.rti.org)

## **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.

Losartan is under investigation for treatment and prophylaxis of aortic aneurysm in Marfan syndrome and Loeys-Dietz syndrome. If proven safe and effective, it may be reasonable to use it similarly for individuals with EDS, hypermobility type who have aortic enlargement.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the Gene Tests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

## **DIAGNOSIS**

The diagnosis of EDS, hypermobility type is based entirely on clinical evaluation and family history. In most individuals with EDS, hypermobility type, the gene in which mutation is causative is unknown and unmapped. Haploinsufficiency of tenascin-X (encoded by *TNXB*) has been associated with EDS, hypermobility type in a small subset of affected individuals. Testing for *TNXB* mutations is available on a limited clinical basis.

### **Clinical Diagnosis**

Clinical diagnostic criteria and a revised nomenclature for all forms of Ehlers-Danlos syndrome (EDS) were proposed by Beighton et al [1998]. EDS, hypermobility type is characterized chiefly by joint laxity with soft skin and easy bruising, but other organ systems (especially gastrointestinal and cardiovascular) are frequently involved. EDS, classic type has more significant skin and soft tissue manifestations, but in mild cases may be difficult to clearly distinguish from EDS, hypermobility type. The diagnosis of EDS, hypermobility type is based entirely on clinical evaluation and family history. The criteria listed below reflect those proposed by Beighton et al [1998] as modified by the author's experience.

**Major diagnostic criteria** should all be met to establish a diagnosis of EDS, hypermobility type:

- **Joint hypermobility**, which is often confirmed by a score of five or more on the nine-point Beighton scale [Beighton et al 1973], although some individuals with objective joint laxity score fewer than five points (see below for the sensitivity and specificity of examination for joint hypermobility). One point is scored for each of the following:
  - Passive dorsiflexion of each fifth finger greater than 90°
  - Passive apposition of each thumb to the flexor surface of the forearm

- Hyperextension of each elbow greater than  $10^{\circ}$
- Hyperextension of each knee greater than  $10^{\circ}$
- Ability to place the palms on the floor with the knees fully extended
- **Soft skin with normal or only slightly increased extensibility**
- Soft skin is subjectively assessed, preferably in an area in which moisturizer has not been applied.
- Skin hyperextensibility is 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 distal forearm or wrist, where the upper limit of normal extensibility is 1-1.5 cm. Extensor surfaces of joints have excess skin and should not be used.
- **Absence of fragility or other significant skin or soft tissue abnormalities**, which are suggestive of other types of EDS. Such findings could include:
  - Spontaneous or easily induced skin cuts or tears
  - Spontaneous or easily induced tears or ruptures of tendons, ligaments, arteries, or other internal organs
  - Surgical complications, such as arterial rupture or sutures tearing through tissues and failing to hold
  - Spontaneous wound dehiscence
  - Recurrent or incisional hernias
  - Significant skin hyperextensibility ( $>1.5$  cm on the volar wrist)
  - Thin, translucent skin
  - Atrophic ("cigarette paper") scars (although mildly atrophic scars are sometimes seen in EDS, hypermobility type, especially in areas subject to physical stress, such as extensor surfaces and the abdominal wall)
  - Molluscoid pseudotumors

**Minor diagnostic criteria** are supportive of but not sufficient to establish a diagnosis of EDS, hypermobility type:

- Positive family history of EDS, hypermobility type (or family history of joint laxity), without significant skin or soft tissue fragility, in a pattern consistent with autosomal dominant inheritance
- Recurrent joint dislocations or subluxations
- Chronic joint, limb, and/or back pain
- Easy bruising
- Functional bowel disorders (functional gastritis, irritable bowel syndrome)
- Neurally mediated hypotension or postural orthostatic tachycardia
- High, narrow palate
- Dental crowding

The sensitivity and specificity of examination for joint hypermobility is dependent in part on the individual's age, gender, and medical history.

- Young children (especially age  $\leq 5$  years) tend to be very flexible and are therefore difficult to assess.
- Women are, on average, more flexible than men.
- Older individuals tend to lose flexibility, and post-surgical or arthritic joints often have reduced range of motion. A history of former joint laxity or clinical demonstration of substantial laxity in

multiple joints is sometimes accepted in lieu of a positive Beighton score in such cases, if the family history and other minor criteria are strongly suggestive.

## **Testing**

The biochemical etiology of EDS, hypermobility type is unknown in most cases.

## **Molecular Genetic Testing**

**Genes.** Heterozygous mutation in *TNXB* is associated with EDS, hypermobility type in a small subset of individuals. However, skin hyperextensibility, easy bruising and other hematologic manifestations are not part of this phenotype (see Genotype-Phenotype Correlations).

**Evidence for locus heterogeneity .** A mutation in *TNXB* is not identified in most individuals with a clinical diagnosis of EDS, hypermobility type. Thus, the etiology and genetic locus/loci are unknown in the vast majority of cases.

**Clinical testing.** See Table 1.

**Research testing.** Serum tenascin-X protein testing is available on a research basis only.

Table 1. Summary of Molecular Genetic Testing Used in Ehlers-Danlos Syndrome, Hypermobility Type

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method <sup>1</sup>	Test Availability
<i>TNXB</i>	Sequence analysis	Sequence variants <sup>2</sup>	Unknown <sup>3</sup>	Clinical Testing
	Deletion / duplication analysis <sup>4</sup>	Partial-, whole-gene, and contiguous gene deletions <sup>5</sup>	Unknown	

Test Availability refers to availability in the GeneTests™ Laboratory Directory. GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests™ Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory.

GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene
2. Only a few mutations have been identified; see Molecular Genetics, Pathologic allelic variants.
3. Among a cohort of 80 individuals with hypermobility type EDS without family history of autosomal recessive tenascin-X-deficient EDS, biochemical deficiency of tenascin-X was found in six (7.5%), with confirmation of a mutation in *TNXB* in two (2.5%). All six of these individuals had typical joint laxity and many had soft skin, but all lacked easy bruising or mildly hyperextensible skin [Zweers et al 2003]. Among another cohort of 16 individuals with EDS, hypermobility type and normal serum



tenascin-X levels, one definite pathologic mutation and one suspected pathologic mutation were detected [Zweers et al 2005].

4. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment. See CMA.

5. Some had congenital adrenal hyperplasia as a result of contiguous gene deletion involving *CYP21A2* (see Genetically Related Disorders).

**Test characteristics.** Information on test sensitivity, specificity, and other test characteristics can be found at [www.eurogentest.org](http://www.eurogentest.org) [Mayer et al 2012].

Information on specific allelic variants may be available in Molecular Genetics (see Table A. Genes and Databases and/or Pathologic allelic variants).

### Testing Strategy

**To confirm/establish the diagnosis in a proband.** The diagnosis of EDS, hypermobility type is based entirely on clinical evaluation and family history (see Clinical Diagnosis). *TNXB* sequencing or quantitative serum tenascin-X analysis could be considered in persons with joint laxity in the absence of easy bruising or skin hyperextensibility. Testing of other EDS-associated genes, especially *COL3A1*, is sometimes useful when there is clinical diagnostic uncertainty regarding the specific EDS type (see Differential Diagnosis).

**Prenatal diagnosis and preimplantation genetic diagnosis (PGD)** for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*<sup>TM</sup> chapters any clinical uses of testing available from laboratories listed in the GeneTests<sup>TM</sup> Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

### Genetically Related (Allelic) Disorders

An autosomal recessive form of Ehlers-Danlos syndrome has been described in individuals with tenascin-X deficiency resulting from compound heterozygous or homozygous *TNXB* mutation/deletion [Bristow et al 2005]. Clinical features include 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*.

Some, but not all, carriers of this autosomal recessive form of EDS have joint laxity and soft skin typical of EDS, hypermobility type, but do not manifest skin hyperextensibility, easy bruising, or other hematologic manifestations [Zweers et al 2003].

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Ehlers-Danlos syndrome (EDS), hypermobility type, 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 pharmacologic, mechanical, 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 [Roman et al 1989]. 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, tilt-table testing to help confirm postural orthostatic tachycardia and/or neurally-mediated hypotension. It is sometimes appropriate to rule out adrenocortical insufficiency.
- If irritable bowel syndrome is suspected, consideration of 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) at any age if height loss greater than one inch is documented or x-rays are suggestive of osteopenia. Women should have their first study no later than menopause. It is unclear if or at what age men without height loss or abnormal x-rays should have a screening DEXA.
- If a history of severe or prolonged bleeding is present, consideration of hematologic evaluation for von Willebrand disease, thrombocytopenia, or other bleeding diathesis. Although pathophysiologically unrelated, these conditions may coexist with hypermobility type EDS and exacerbate the hematologic manifestations.
- For individuals with significant pain and/or fatigue, screening for and correction of other potential causes, including (but not limited to) vitamin D deficiency, vitamin B<sub>12</sub> deficiency, folate deficiency, iron deficiency, celiac disease, or hypothyroidism
- If there is suspicion of Chiari malformation, consideration of cerebral MRI, possibly with CSF flow studies
- Medical genetics consultation if there is uncertainty about the diagnosis or for assistance in evaluation and management

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### **Suggested Reading**

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