Ehlers-Danlos Syndrome Type III: Hypermobility Type

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Abstract

Ehlers-Danlos Syndrome (EDS) is a relatively rare disorder characterized by irregularities in the chemical make-up of the body’s connective tissues. EDS Type III is a disease which affects loose, areolar connective tissues due to an abnormality in a fibrous protein collagen III; mutations of collagen III are associated with type III and IV EDS. EDS Type III is categorized as EDS hypermobility type because of the presence of hypermobile joints, musculoskeletal troubles, dislocations and subluxations. Haploinsufficiency involving the elimination or inactivation of a TNXB allele causes a decrease in the production of protein tenascin-X which causes phenotypical alterations of collagen fibers in connective tissues. When connective tissue is deficient in tenascin-X collagen III has a significant decrease in the collagen fiber length, number of fiber branches, and relative collagen density which translate into EDS Type III. Signs and symptoms of EDS Type III include soft, smooth or velvety skin, pain, joint hypermobility, subluxations and dislocations, and hematological symptoms. EDS Type III causes a several additional complications to the body including cardiovascular problems, gastrointestinal difficulties, oral/dental irregularities, and obstetric/gynecologic complications. A diagnosis can be made based on molecular genetic analysis or clinical observation of the signs and symptoms including, less so, the additional complications. Treatment and is centered on joint strengthening and pain management. Currently there is no prognosis for EDS Type III, nor are their preventative measures to avoid contracting this disease.

Keywords:
Ehlers-Danlos Syndrome, hypermobility, connective tissue disease, haploinsufficiency, collagen III, tenascin-X, TNXB, joint disorders
Ehlers-Danlos Syndrome Type III: Hypermobility Type

Ehlers-Danlos Syndrome (EDS) is a relatively rare disorder, occurring in less than 1 in 20,000 people though EDS hypermobility type (III), is thought to be the most common type of the approximately ten types of EDS (UW Medicine, 2011; NIH, 2001).

The different types of EDS are characterized by irregularities in the chemical composition of the body's connective tissues like the skin, muscles, ligaments, and visceral and parietal linings. EDS Type III is a disease which affects loose, areolar connective tissues (Derrickson & Tortora, p. 128, 2009) due to an abnormality in collagen III, a fibrous protein found in many connective tissues including loose areolar. Mutations of collagen III are associated with type III and IV EDS (LifeSpan Bio Incorporated, 2011). According to King, “... studies of the skin in the Ehlers–Danlos syndrome frequently reveal abnormal heterotypic collagen fibrils containing collagen types I, III, and V, indicating that the syndrome is a disorder of the collagen fibril (2001).” EDS Type III is categorized as EDS hypermobility type because of hypermobile joints, musculoskeletal troubles, dislocations and subluxations (Aurlia, Jurassic & Rocco, 2001). Generally considered the least severe type of EDS, Type III can cause much pain and discomfort, as well as additional complications (Levy, 2010).

The biochemical etiology of EDS Type III is generally unknown; however, molecular genetic research and genetic testing are proving insightful and encouraging for potential advancements and treatments. According to Berk, Bretcher, Kaiser, Krieger, Lodish, Ploegh, & Scott, “Haploinsufficiency requires both alleles [in diploid organisms] for normal function, and removing or inactivating a single allele in such a gene leads to a mutant phenotype (p. 167, 2008).” Haploinsufficiency of a TNXB allele has been associated with EDS hypermobility type because of the consequential deficiency of the collagen III protein tenascin-X (Levy, 2010). The
tenascin proteins share at least three structurally similar extracellular-matrix proteins including tenascin-C and tenascin-X, which are expressed in the [connective] tissues affected in the Ehlers–Danlos syndrome (King, 2011). Because of haploinsufficiency involving a TNXB allele there is likely a correlation in the decreased production of tenascin-X which causes the mutant phenotype, which in this case presents as EDS Type III.

The signs of EDS Type III include, according to Levy, soft, smooth or velvety skin, which is sometimes extra elastic, and the presence of pain. Pain associated with EDS Type III can be myofacial, neuropathic, or chronic, though separate from the acute pain of dislocations or subluxations. Symptoms include: 1) joint hypermobility, subluxations and dislocations which tend to be acutely painful and spontaneous, yet yield minimal lasting trauma; 2) hematological symptoms (easy bruising). Additionally, degenerative joint disease is a commonality amongst EDS Type III sufferers (2010).

According to Derrickson & Tortora, normal areolar connective tissue consists of collagen, elastic, and reticular fibers in a semifluid ground substance of fibroblasts, macrophages, plasma cells, adipocytes, and mast cells. It is located in the subcutaneous and dermal papillary regions of the skin, parts of mucous membranes, and around blood vessels, nerves, and body organs (2009). Refer to the appendix for connective tissue images: Figure 1 includes a photograph and diagram of normal areolar connective tissue, and Figure 2 portrays a visual comparison normal connective tissue and tissues with tenascin-X deficiency. When the connective tissue is deficient in tenascin-X collagen III has a significant decrease in the collagen fiber length, number of fiber branches, and relative collagen density (as described in Figure 2); this is due to the molecular genetic etiology of EDS Type III (Bristow, Mecham, Schalkwijk, Steijlen, van Kuppervelt, van Vlijmen-Willems, & Zweers, 2004).
The occurrence of EDS Type III causes several additional complications to the body. The main concerns are: cardiovascular problems; gastrointestinal difficulties such as functional bowel disorders, gastroesophageal reflux, gastritis, and gastroparesis (delayed gastric emptying); oral/dental irregularities like a high, narrow palate and dental crowding; obstetric/gynecologic complications include complicated pregnancy by premature rupture of membranes or rapid labor and delivery (Levy, 2010).

Diagnostic procedures for EDS Type III by professionals include genetic diagnosis, identifying the \textit{TNXB} gene and examining alleles to detect potential haploinsufficiency and therefore a tenascin-X deficiency (King, 2011). Alternatively, a trained physician familiar with EDS can provide a clinical diagnosis based on the signs and symptoms. In accordance to Levy, the major diagnostic criteria include:

- **Joint hypermobility**
  - 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°
  - Hyperextension of each knee greater than 10°
  - 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 forearm, where the upper limit of normal extensibility is 1-1.5 cm.
- **Absence of fragility or other significant skin or soft tissue abnormalities, which are suggestive of other types of EDS** (2010).

Minor diagnostic criteria are useful but not sufficient to diagnose EDS, hypermobility type. They include, “. . . a positive family history of EDS, hypermobility type or general joint laxity, recurrent joint dislocations or subluxations, chronic joint, limb, and/or back pain, easy bruising, . . . (Levy, 2010)” and the prior list of additional EDS Type III complications.
Treatment for EDS Type III varies for each individual. It is strongly recommended by the UW Medicine & Orthopaedics and Sports Medicine to make regular visits to an EDS specialist to keep potential signs, symptoms and current complications in check. Self-management of symptoms is important especially because of hypermobility to protect joints and reduce injury and pain. Individuals with EDS should have routine eye exams to screen for serious eye conditions and correct vision problems common with this condition. Exercise and physical therapy can help improve joint stability and help decrease the frequency of dislocations and/or subluxations. Surgery may be necessary for correction of fractures or dislocated joints (2011).

An important aspect of managing and treating EDS Type III (and other types) is effective, individualized pain management. According Levy, some options include: acetaminophen, 4000 mg/day, which is usually well tolerated; non-steroidal anti-inflammatory drugs like ibuprofen; cox-2 inhibitors like celecoxib (Celebrex); tramadol, a partial opioid agonist/antagonist; topical lidocaine or capsaicin; skeletal muscle relaxants like metaxalone (Skelaxin); tricyclic antidepressants like nortriptyline; serotonin/norepinephrine receptor inhibitors (SNRIs) like duloxetine (Cymbalta) can help with neuropathic pain as well as depression which is commonly associated with chronic pain or disease; selected anti-seizure medications like gabapentin (Neurontin) are effective for neuropathic pain as well; magnesium and/or potassium may reduce muscle tension and pain; opioids (morphine, oxycodone, fentanyl) are effective for myofacial and neuropathic pain, but are a last resort, and it is suggested that an extended release form be used with a short-acting form of the same medicine for breakthrough pain (2010). Additionally, as EDS is a chronic and debilitating disease, it is important to develop
strategies for coping with depression, anxiety, fear, or anger associated with the associated limitations (UW Medicine, 2011).

Currently, there is no prognosis for EDS Type III, nor are their preventative measure to avoid contracting this disease since it is currently established as a non-communicable, genetic disease (UW Medicine, 2011). Additionally, the research on the molecular genetics of EDS is just beginning as EDS becomes acknowledged by a larger medical and research community. For further research, insight and awareness please be referred to the Ehlers-Danlos National Foundation (www.ednf.org).
Figure 1: Normal areolar connective tissue. (Derrickson & Tortora, Table 4.4, p. 128, 2009)

Figure 2:
Normal and tenasin-X deficient connective tissue comparisons.

The normal human skin biopsy (A) shows the typical “candelabra-like pattern (2004)” of the elastic fibers. In the tenasin X deficient patients (B and C) have “grossly disturbed [candelabra-like patterns] indicating a significant decrease in the length, number of fiber branches, and relative collagen density in comparison to the controls. This indicates that there is a correlation between tenasin X deficiency and abnormal collagen (Bristow, Mecham, Schalkwijk, Steijlen, van Kuppervelt, van Vlijmen-Willems, & Zweers, M.C. 2004).
Glossary

*tenascin-X*—an extracellular fibrous protein found in collagen III and IV (Levy, 2010)

*TNXB*—gene that is responsible for the production of tenascin-X (King, 2011)

*haploinsufficiency*—the elimination of or inactivation of a single allele in a diploid gene which causes a mutant phenotype (Berk, Bretcher, Kaiser, Krieger, Lodish, Ploegh, & Scott (p. 167, 2008)).
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This website is reliable because it is made by the Southern Illinois University School of Medicine, intended for health professionals and researchers, and it was updated 2011.


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References


National Institute of Arthritis and Musculoskeletal and Skin Diseases, National