

REVIEW ARTICLE

The Ehlers–Danlos Syndromes

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hEDS

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ABSTRACT: An Osteopathic Family Physician will encounter hypermobile patients. Hypermobility is a symptom of many of the subtypes of the Ehlers Danlos Syndromes (EDS). With the updated classification system (the 2017 International Classification of the Ehlers-Danlos Syndromes) it is important for the osteopathic family physician to become familiar with the EDS patient. The classification system identifies 13 subtypes of EDS.¹ Of these 13, 12 have a recognized genetic basis. Hypermobility EDS (hEDS) has a clinical diagnosis criteria checklist (Figure 1, page 29). There is opportunity for the osteopathic family physician community to help diagnose and treat the EDS population. This article seeks to have the osteopathic family physician become familiar with the Ehlers-Danlos Syndrome, and provide an overview of all of the subtypes of EDS, including hEDS and discusses signs, symptoms, and risks associated with the syndrome.

BARRIERS TO TREATMENT

During the course of a career, the osteopathic physician will encounter a patient with hypermobility. It is important for the osteopathic family physician to become familiar with the difference between hypermobility and Ehlers Danlos Syndrome (EDS). Hypermobility may be localized to a specific joint or can be generalized throughout many joints. Based on the accompanying symptoms, the osteopathic family physician can become familiar with when to differentiate between the hypermobile patients verses the patient with EDS. This article seeks to introduce all of the subtypes of EDS and the symptoms that the patient may present to the osteopathic family physician with.

The Ehlers Danlos Syndromes are a type of connective tissue disorders that have certain defining features.¹ EDS has recently been reclassified into 13 subtypes, (the 2017 International Classification of the Ehlers-Danlos Syndromes) and includes a type, which is diagnosed clinically.¹ In 2018, an EDS spectrum connective tissue disorder was identified by a genetic mutation found in four individuals.² This subtype is due to an AR mutation in the AEBP1 gene, and these patients have joint hypermobility, skin elasticity, osteoporosis and poor wound healing.² The importance of identification of a specific type of EDS is imperative, as there are a multitude of risks, some life threatening, that need proper surveillance.¹ This article seeks to give the family physician an overview of each type of EDS, so that the osteopathic family

physician can become familiar with each subtype and learn when to look for EDS in the hypermobile patient.

CLASSICAL EDS

Classical EDS (cEDS) is thought to be of an Autosomal Dominant (AD) pattern of inheritance is associated with skin issues and hypermobility (major criteria) as well as minor criteria (including but not limited to easy bruising, soft skin, hernias, or family history).¹ Skin is especially fragile and “wound healing is poor.”³ The Beighton score (which measures joint hypermobility on a 9 point scale) for patients with cEDS is “5 or greater.”⁴ This type of EDS is diagnosed clinically and by genetic testing. The “pathologic variant in COL5A1, COL5A2, or (less commonly) COL1A1” is seen.³

CLASSICAL-LIKE EDS

Classical-like EDS (clEDS) patients typically have mutations in the TNXB gene, in an autosomal recessive (AR) manor.¹ The mutations seen in the TNXB gene are varied and their symptoms are usually more severe than seen in the hypermobile EDS (hEDS) subtype.⁵ clEDS patients present with manifestations of skin issues and hypermobility, and this subtype can be challenging to differentiate from hEDS.

CARDIAC-VALVULAR EDS

Patients with cvEDS typically present with “severe progressive cardiac-valvular problems”¹ as well as musculoskeletal and skin issues. Cardiac-valvular EDS (cvEDS) has an Autosomal recessive inheritance pattern.¹ “The biallelic COL1A2 mutations result” in

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absence of a collagen chain. This subtype of EDS is considered rare.⁶ “Absence of confirmatory genetic findings does not exclude the diagnosis as specific types of mutations may go undetected by standard diagnostic molecular techniques.”¹¹

VASCULAR EDS

Vascular EDS (vEDS) is inherited in an AD pattern of inheritance and is thought to be caused by a mutation in the COL3A1 or COL1A1 gene, which affects collagen.¹ “vEDS is typified by a number of characteristic facial features (eg, large eyes, small chin, sunken cheeks, thin nose and lips).”⁷ It is important for clinicians to recognize a vEDS patient, as proper surveillance needs to be followed. vEDS patients are at risk for arterial or organ rupture.⁸ vEDS patients may present with aneurysms or bleeding issues.⁸ Since vEDS is a rare disease with serious co morbidities and complications, genetic testing is recommended.¹⁰ “Absence of confirmatory findings does not exclude diagnosis, as specific types of mutations may go undetected by standard diagnostic molecular techniques.”¹¹ The importance of working with a Geneticist and Cardiovascular specialist in these cases are imperative.

ARTHROCHALASIA EDS

Arthrochalasia EDS (aEDS) is an AD genetic disorder, thought to be caused by a mutation in the COL1A1 or COL1A2 gene.¹ The main features of this disorder are hypermobility, skin issues, congenital hip dysplasia, and muscle weakness.¹¹ “In addition to fragility of skin and joint laxity that are observed in other forms of EDS,” patients usually have distinct facial features.¹¹ “As patients get older the hypotonia decreases and the facial features become less distinct.”¹¹

DERMATOPARAXIS EDS (DEDS)

Dermatoparaxis EDS (dEDS) is an AR genetic disorder involving the ADAMTS2 gene.¹ Patients with this rare subtype of EDS present with extremely lax skin.¹ Some features seen in dEDS patients include a swelling on the forehead at birth, skin fragility, ocular issues, and umbilical hernia.¹² Patients with dEDS are also at risk for “visceral complications due to connective tissue fragility.”¹²

KYPHOSCOLIOTIC EDS (KEDS)

Patients with Kyphoscoliotic EDS (kEDS) have genetic mutations in PLOD1 or FKBP14 genes in an AR fashion.¹ These patients present with skin fragility, hypermobility and kyphoscoliosis.¹³ The kyphoscoliosis can be severe, causing organ compromise.¹³ Patients with genetic variations in the FKBP14 gene can also have hearing impairment.¹

BRITTLE CORNEA SYNDROME (BCS)

Patients with BCS have an AR pattern of inheritance and present with ocular issues.¹ The genes affected in this subtype are usually ZNF469 or PRDM5.¹ Sometimes a blue sclera is seen, and ocular

issues could be serious (including potential for ocular rupture or blindness).⁶ Hearing impairment and hearing loss can also be seen in patients as well.⁶

SPONDYLODYSPLASTIC EDS (SPEDS)

Patients with the rare subtype spEDS, have inherited a probable AR genetic variant in B4GALT7, B3GALT6, or SLC39A13.¹ Two major criteria, (i.e., short stature muscle hypotonia, and bowing of limbs plus characteristic radiographic abnormalities) and three minor criteria (skin hyper extensibility, pes planus, motor or cognitive delay, and osteopenia are suggestive for spEDS.¹⁴ “Confirmatory molecular testing is obligatory to reach a final diagnosis.”¹¹

MUSCULOCONTRACTURAL EDS (MCEDS)

mcEDS patients present with cranial facial features, and musculoskeletal features that are inherited in an AR fashion with a genetic basis in CHST14 and DSE.¹ Contractures and finger/hand characteristics are seen.⁶ Cardiovascular, urological, ophthalmological and auditory issues are also seen in mcEDS patients.⁶ This is in addition to the cutaneous symptoms seen in the EDS. Absence of these confirmatory findings does not exclude the diagnosis of mcEDS, as specific types of mutations may go undetected by standard diagnostic molecular techniques.”¹¹

MYOPATHIC EDS (MEDS)

Patients with myopathic EDS (mEDS) have “muscle weakness, hypotonia, myopathy, and connective tissue symptoms.”⁶ mEDS is caused by defects in genes for collagen or affecting the muscles and is thought to have a genetic basis in the COL12A1 gene possibly AR or AD in inheritance pattern.¹ Many patients report severe hypotonia or contractures.⁶ The skin scarring typical of EDS patients can also be seen. Absence of these confirmatory findings does not exclude the diagnosis, as specific types of mutations may go undetected by standard diagnostic molecular techniques.”¹¹

PERIODONTAL EDS (PEDS)

Periodontal EDS is characterized by severe periodontal disease, as well as hypermobility and skin issues.⁶ These type of patients were found to have bone loss even after restorative surgery for patients’ periodontal disease.¹⁵ The severe periodontal disease seen in this disorder starts in childhood or adolescence.¹⁶ The disease is passed AD and in the C1R or C1S genes.¹ Specific craniofacial features including long, prominent nose, short philtrum and triangular face has been observed.¹⁶

HYPERMOBILE EDS (HEDS)

hEDS, “probably the most common EDS subtype”,¹⁷ has a criteria associated with diagnosis as per the 2017 International Classification of the Ehlers-Danlos Syndromes (EDS)¹ (see Figure 1). No distinct genetic mutation has been found to cause this type, as of publication. Research is ongoing on the genetic basis, and is

thought to have an AD form of inheritance.¹ Many patients with hEDS present with joint hypermobility, skin issues, fatigue and chronic pain.¹⁷

Many patients with hEDS can also have a variety of comorbidities.¹⁸ Along with hypermobility, there could be chronic pain, cardiovascular issues, psychological issues, bone mass issues and GI symptoms.¹⁸ Since there is a variety of symptoms the osteopathic family physician should become familiar with the presentation.

For the osteopathic family physician who sees pediatric patients, hEDS and hypermobility may be difficult to diagnose for children, as children are typically more flexible and hypermobile than adults.¹⁸ It is particularly important to rule out a HCTD in children, as some of the signs and symptoms of hEDS overlap with other connective tissues disorders.¹⁸

Since there are many systems that the hypermobile patient may present with, it is important the osteopathic family physician become familiar with EDS. There is a chance that the osteopathic family physician may be the first provider the EDS patient contacts. Due to the diverse nature of the EDS and hEDS in particular, a multidisciplinary approach to the EDS patient including Primary Care, pain management, Cardiology, Physical Therapy, Occupational Therapy, Psychology, and Geneticist (if applicable) is needed.¹⁷ Since EDS affects many systems of the body, and there is currently no genetic basis of hEDS it is important for the osteopathic family physician to become familiar with the Ehlers Danlos Syndromes as they may be the first one to recognize some of the signs, symptoms and co-morbid conditions seen in this condition. The osteopathic family physician may also be the one in contact with a geneticist to assist in the identification of a specific subtype. The importance of the diagnosis and proper surveillance for the EDS patient is imperative. With further research, the osteopathic family physician can be helpful in treating an EDS patient. Literature and education is needed for providers to become aware of this condition and this article seeks to be an introduction for the osteopathic family physician to all the EDS subtypes.

AUTHOR DISCLOSURES:

No relevant financial affiliations or conflicts of interest.

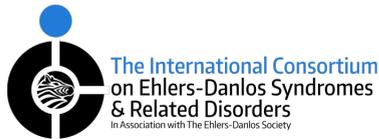
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FIGURE 1:

Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)¹⁹

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Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across
all disciplines to be able to diagnose EDS



Patient name: _____ DOB: _____ DOV: _____ Evaluator: _____

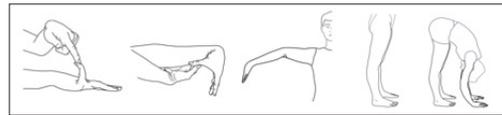
The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 **and** 2 **and** 3.

CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ≥6 pre-pubertal children and adolescents
- ≥5 pubertal men and women to age 50
- ≥4 men and women over the age of 50

Beighton Score: ____/9



If Beighton Score is one point below age- and sex-specific cut off, two or more of the following must also be selected to meet criterion:

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

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five must be present)

- Unusually soft or velvety skin
- Mild skin hyperextensibility
- Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- Bilateral piezogenic papules of the heel
- Recurrent or multiple abdominal hernia(s)
- Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- Dental crowding and high or narrow palate
- Arachnodactyly, as defined in one or more of the following:
 - (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- Arm span-to-height ratio ≥1.05
- Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- Aortic root dilatation with Z-score >+2

Feature A total: ____/12

Feature B

- Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

Feature C (must have at least one)

- Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- Chronic, widespread pain for ≥3 months
- Recurrent joint dislocations or frank joint instability, in the absence of trauma

CRITERION 3 – All of the following prerequisites MUST be met

1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired CTD (e.g. Lupus, Rheumatoid Arthritis, etc.), 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.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g. Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g. osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

Diagnosis: _____