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Hypermobile Ehlers-Danlos Syndrome: Clinical Description and Natural History

FOR NON-EXPERTS

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Hypermobile type Ehlers-Danlos syndrome (hEDS) is the most common subtype of the Ehlers-Danlos syndromes (EDS) and possibly the most common of all hereditary disorders of connective tissue (HDCT). The new EDS classification system replaces the diagnosis of Ehlers–Danlos syndrome Type III/ Ehlers–Danlos syndrome Hypermobility Type (EDS-III / EDS-HT) and joint hypermobility syndrome (JHS).

Many people who were previously assigned a diagnosis of EDS-III, EDS-HT, or JHS will meet the criteria for hEDS; some will instead be classed as having Hypermobility Spectrum Disorders (HSD). The new criteria for hEDS are stricter now, intended for a more consistent and targeted identification, in the hopes of aiding a greater understanding of the cause(s) and course (natural history)

of the disorder. With stricter criteria there is a greater chance of finding the specific reasons why and how disease comes about. With greater understanding comes a better chance of positive changes for those with hEDS: fostering highly targeted research, achieving successful disease management, and ultimately maximizing quality of life for people with hEDS.

hEDS is mainly identified by generalized joint hypermobility (GJH), additional joint issues, and obvious skin signs, which are less severe than those seen in Classic EDS (cEDS) or Vascular EDS (vEDS). hEDS is more than "just GJH" plus a few items from a checklist of findings. In order to best understand the nature of hEDS, people with hEDS and those caring for them must become familiar with the disorder.

Prevalence of hEDS: "It is common, representing up to 1–3% of the general population."

Current estimates indicate as many as two million people in the UK, ten million in the USA, 17 million in Europe, and 255 million worldwide have hEDS. While the new classification is more selective, hEDS is recognized by the International Consortium on the Ehlers-Danlos Syndromes as common — specifically, representing up to 1–3% of the general population.

Genetics: We have a lot to learn about the underlying genetics of hEDS.

At present, no single gene mutation causing hEDS has been identified. hEDS is likely to be caused by many different genetic changes. With the stricter classification of hEDS and more in-depth genetic studies, additional hEDS-related genes should be identified. Identification of genetic causes for hEDS may lead to it being further broken down into specific named hEDS subtypes, or perhaps lead to hEDS being redefined or replaced by multiple new specific EDS types, in a manner similar to how classical-like EDS (clEDS) has been defined as a new EDS type due to the genetic cause being identified.

hEDS has a roughly 50% chance of being passed on to each child (autosomal dominance), but other patterns of inheritance may explain this disorder in certain families. hEDS inheritance is somewhat difficult to analyze, as hEDS may be mild during much of life, or compared to close relatives with the disorder, or may even appear to "skip" a generation. This may be in part because JH is heavily influenced by age, gender, and weight. The reason for a perceived excess of females remains poorly understood, but may come down to sex hormones having a greater influence upon

JH. The best way to describe hEDS is as an autosomal dominant disorder influenced by age and gender, with symptoms more common in females.

Natural History: What happens to people with hEDS?

If a person has hEDS, it will likely affect them in different ways throughout their lifetime, and the person may be diagnosed with many other conditions known to occur in those with hEDS. For example, three disease phases were proposed in a 2010 study: a "hypermobility" phase, a "pain" phase, and a "stiffness" phase. Alternatively, existing studies have led to speculation that there is a natural transition from EDS-HT to GJH with age.

Existing studies show that children with hEDS who experience pain will be more likely to have pain limited to lower limbs (*e.g.*, "growing pains") and pain caused by repetitive tasks such as handwriting in the school setting. Children with hEDS may have poor coordination. The "pain" phase is often accompanied by diagnosis with fibromyalgia or other long-term (chronic) pain conditions and perhaps chronic fatigue, typically starting in the second to fourth decade and accompanied by chronic pain, headaches, digestive system disorders, among others. The "stiffness" phase is seen in only a few persons, and, unfortunately for them, the symptoms of the "pain" phase may persist and escalate, functionality may overall be significantly reduced.

Conditions Often Occurring in Persons with hEDS

Pain: Yes, hEDS *CAN* cause significant pain!

Uneducated doctors all-too-often make emphatic statements such as, "Ehlers-Danlos syndrome cannot cause pain!" In fact, while hEDS does not necessarily cause significant pain for every person meeting diagnostic criteria, many with hEDS will develop significant pain for some portion of their lives. Any doctor who invalidates the fact that hEDS ***can*** cause significant pain may have a profoundly negative impact, not only upon the success of the relationship between clinician and patient, but also upon the quality of life of those with hEDS.

Health practitioners need to understand that the occurrence of significant pain for many persons with hEDS is well-supported in the literature and has logically proposed or proven cause. In fact, joint/muscle pain in two or more limbs (recurring daily, ≥ 3 months) and long-term widespread pain (≥ 3 months) are specifically considered as a part of the criteria for diagnosis of hEDS.

Skin and Connective Tissue: People with hEDS do *NOT* have to have profoundly stretchy skin!

Most notably, in hEDS, the degree of softness, stretchiness, fragility, bruisability, and poor wound healing of skin differs from "normal" subjects but is mild in comparison to other types of EDS. Clinicians who are not up to date on the classification of EDS types often expect that ***all*** EDS types demonstrate severe skin changes, such as those observed in persons with cEDS and vEDS. ***Mild*** skin stretchiness (rather than severe) is clearly considered as a systemic manifestation in the criteria for clinical diagnosis of hEDS.

Stretch marks are not inevitable in hEDS, however, they often appear in persons with hEDS during adolescent growth spurts and are not necessarily due to rapid weight gain. The absence of stretch marks should ***not*** argue against a diagnosis of hEDS. Other tissues which may fail in hEDS include the protective coverings around organs. Weakness in this connective tissue in hEDS often results in hernia (tissues or organs pushing through). Hernias may also be more likely in persons with hEDS who undergo abdominal surgery, such as laparotomy or C-section.

Fatigue: Chronic fatigue is one of the most common complications among persons with hEDS.

Chronic, debilitating fatigue is common in hEDS, and such fatigue has significant impact on mental and physical function and ultimately on quality of life. Those with hEDS will often meet the criteria for chronic fatigue syndrome (CFS). Under no circumstances should a diagnosis of CFS to a person who also meets criteria for hEDS mean that hEDS should be disregarded. hEDS is considered to be a specific cause of chronic fatigue, while CFS is considered a syndrome with unknown cause; in this case the diagnosis of CFS would more appropriately called into question.

Cardiovascular: While conditions of the heart and blood vessels can occur with hEDS, they are not usually life-threatening, but deserve individual consideration.

Heart and blood vessel conditions occurring in hEDS include heart valve and vessel dysfunction including mitral valve prolapse (MVP) and aortic root dilation. Problems with blood pressure and heart rate can also occur including postural orthostatic tachycardia syndrome (POTS), neurally-mediated hypotension (NMH), and orthostatic

intolerance. Those having blood pressure changes may also experience near-fainting or fainting episodes.

Gastrointestinal (GI) Disorders: Digestive system problems occur with high frequency in hEDS.

As many as 75% of people with hEDS are likely to encounter problems with the function of their digestive system in their lifetime. Problems can occur anywhere along the digestive system, including the mouth and throat (*e.g.*, chewing and swallowing) in addition to the functions of the rest of the GI tract. Disorders include poor movement of material along the tract, reflux, heartburn, abdominal pain, bloating, irritable bowel, diarrhea, constipation, or incontinence. Structural problems occur at a higher rate in those with hEDS than in the general population including hernias, internal organ displacement, and rectal prolapse. The relationship between all structural abnormalities and hEDS requires further study.

Dysautonomia: "Fight or Flight" and "Rest and Digest" function poorly for a majority with hEDS.

An extensive body of literature clearly indicates frequent problems with involuntary bodily functions (dysautonomia) in hEDS. Problems with involuntary body functions can lead to fatigue, dizziness, fainting, memory changes, poor concentration, reduced sweat production, changes in gut movement, bladder dysfunction, and/or certain psychological traits. Dysautonomia can be a devastating manifestation of hEDS, and, for some patients, it affects their quality of life more profoundly than joint instability, pain, or any other part of the disorder.

Bone Density: Existing evidence does not clearly indicate that hEDS is expected to cause low bone density or increased risk for fragility fractures. Carefully designed research is needed.

While existing studies have suggested a link between various EDS types and conditions such as osteoporosis (low bone density) and osteopenia (low bone mineralization), those with EDS often have a significantly reduced level of activity, and, rather than any alteration in bone density or mineralization being directly attributable to EDS, alteration in bone density or mineralization should be considered to be a direct result of reduced activity. Bone health should not be ignored in hEDS.

Osteoarthritis: Yes, hEDS increases the susceptibility of joints to osteoarthritis.

Osteoarthritis (a breakdown of joints) has been described in the literature as a possible long-term consequence of JH for decades. Since JH is a hallmark feature of hEDS, and JH is recognized to cause osteoarthritis, then hEDS would logically be expected to predispose many of those with the disorder to osteoarthritis. By the same token, osteoarthritis is by no means universal for all persons with JH, so it should NOT be expected to be inevitable for all people with hEDS.

Headaches: hEDS may lead to severe or debilitating headaches for a multitude of reasons.

Headaches in general, as well as migraines in particular, are known to occur more frequently in persons with EDS than in the general population. Headaches in hEDS are considered to have many causes, with potential mechanisms including instability, strain, or muscle spasms in the neck, jaw joint dysfunction, and/or medication side effects. The headaches vary in type and severity among all persons with hEDS who have headaches. Some find headaches to be the most disabling manifestation of hEDS.

Temporomandibular Joint and Dental Issues: Dentists, Orthodontists, and Oral Surgeons may be the first to consider a diagnosis of hEDS.

A hypermobile jaw joint is more likely to show dysfunction than a non-hypermobile jaw. Those with hEDS and jaw joint dysfunction often have sounds, locking, dislocation, grinding teeth, and headaches in the temple.

Mouth manifestations of hEDS may include fragile gums which bleed easily, gum recession, gum disease, small or absent frenula (small connective flaps between the front gums and lips), pointed and deep teeth, shortened roots, abnormal enamel, tooth fractures, ineffective dental anesthesia, and rapid orthodontic correction (and rapid return without orthodontia).

Spine: It is difficult at times to determine whether a person with hEDS would benefit from surgery, and, even when surgery is necessary, it doesn't always solve everything.

People with hEDS may have neck pain, difficulty walking, numbness and tingling of the hands and feet, dizziness, swallowing difficulties, and changes in speech. These

people are more likely to have signs of looseness or instability around the head and neck. In many cases, these symptoms are not entirely attributable to head and neck dysfunction: symptoms may still persist after successful surgery.

Abnormal spine curvature is common in people with hEDS, in a large part due to a combination of structural and functional abnormalities in the supporting tissues of the spine. Conservative management will ideally allow avoidance of surgery.

Gynecologic Issues: Women with hEDS may experience heavy periods or painful intercourse.

Pelvic Dysfunction: It is unclear whether hEDS alone predisposes women to pelvic dysfunction or how much of a role childbirth plays.

While the existing literature suggests that pelvic floor problems including urinary incontinence or uterine, rectal, or bladder prolapse are common to hEDS, many studies did not control for childbirth history, and included various EDS types.

Pregnancy and Childbirth: No studies to date recommend against pregnancy and childbirth based simply upon a diagnosis of hEDS.

While some studies of women with EDS-III/EDS-HT and JHS suggest increased rates of infertility, pregnancy losses, and premature births, other studies did not. In the case of studies regarding premature birth, the study group included women with Classic EDS. One of the most thorough studies prior to the current EDS classifications suggested similar measures of fertility.

When it comes to how pregnancy affects symptoms of hEDS, it goes like this: some get worse, some don't change, and some get better during the pregnancy. When it comes to labor, rapid labor is thought to occur in more than 1/3 of deliveries. The most considerable complications related to labor and delivery thought to occur at a significant rate in women with hEDS include bleeding during or after birth, as well as abnormal scarring from C-section or episiotomy. In general, no studies to date recommend against pregnancy and childbirth based simply upon a diagnosis of hEDS in the absence of any other factors.

Urinary System: hEDS may predispose children to urinary incontinence, urinary tract infections, vesicoureteral reflux, and voiding dysfunction.

Sleep Disturbance: Patients with hEDS may feel particularly tired.

People with hEDS often experience significant sleep deprivation. Going without healthy, restorative sleep can lead to any combination of significant health problems such as impaired immune response, poor muscle coordination, and higher perception of pain, as well as problems with memory and thought processes (*e.g.* "brain fog"), moodiness, depression, and anxiety. Some with hEDS carry formal diagnoses of additional conditions such as restless leg syndrome or sleep apnea.

Mast Cell Activation Disorder: Current understanding of mast cell activation syndrome (MCAS) in hEDS is limited.

Mast cell activation syndrome is an immune condition that can create allergy-like symptoms, up to and including anaphylaxis. More research is needed to see whether MCAS is a condition that occurs with greater frequency in hEDS than in the general population and how it affects a person with hEDS and the management.

Psychiatric: hEDS is not *in* the psyche, it is *in* the *connective tissue*, but it can affect the psyche.

Many with hEDS are assigned psychiatric diagnoses or frankly ignored when clinicians fail to recognize that they meet diagnostic criteria for hEDS. Clearly, this leads to a failure in attempts to effectively care for the person with hEDS. It is important to realize that psychological conditions (*e.g.* anxiety or depression) are common in chronic conditions including hEDS. Ignoring significant coexisting psychological problems will lead to suboptimal treatment.

Quality of Life: Studies to date consistently suggest that hEDS adversely affects quality of life.

Carefully designed studies have clearly demonstrated that quality of life is often measured or reported as lower in people with EDS than in the general population – in particular, people with EDS and associated secondary issues such as digestive system disorders, anxiety, depression, physical pain.

Management

Recognizing hEDS is only half of the battle. Diagnosis alone is not enough. As with any disorder, effective management of hEDS includes recognizing its complexity. A

body of evidence-based standards of care exists and includes the efforts of multiple healthcare practitioners. Management of hEDS must follow established standards of care and include treatment of both immediate and long-term issues as well as focusing on preventative care.

Clinicians, particularly surgeons and anesthesiologists, caring for a patient with hEDS should familiarize themselves with the management standards as they appear in the full publication (http://bit.ly/2017hEDS).

Key points for management of conditions in hEDS include:

- The approach should be holistic focusing on the complications, the desire(s) of the patient, quality of life and functionality, as well as psychological aspects.
- Results should not be expected overnight: It often takes months of routine toning exercise to stop deterioration, and it may take years before substantial reduction in pain is recognized. Fatigue, like pain, often responds to treatment such as exercise therapy but only very slowly.
- Use of multiple medications together, physical therapy, and complementary medicine is often more effective than as-needed use of one or two medications at a time. Some patients who continue to struggle to cope with their pain may need a broad pain management program. The overall goal should be to maintain adequate control of pain to a tolerable level, not to completely eliminate it.
- Management of psychiatric issues should include consideration of counseling and cognitive behavioral therapy, in addition to consideration of techniques such as distraction, hypnosis, and careful consideration of drug therapy.

Future Directions

While refinement of the diagnostic criteria of hEDS has been important, the search for genetic causes is crucial to identify, study, and ultimately treat patients with the disorder. hEDS is the only type of Ehlers–Danlos syndrome without a known molecular defect. In order to solve the puzzle and identify how hEDS comes about, tools such as a database registry will be imperative. Many further studies are urgently needed to better guide therapy. Studies could investigate physical therapy, pain management, imaging and measurements, and MCAS in the hEDS population.

Summary

It is particularly relevant to note that hEDS is thought to occur in about 1–3% of the general population, and thus every clinician should expect to encounter a significant number of patients with hEDS during the course of their practice. Further research is desperately needed, and hEDS must be on every clinician's radar. It is nothing short of negligent for clinicians to ignore these established standards of care for this disorder, as it has significant potential for negative impact on health-related quality of life.

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