Ehlers-Danlos Syndromes (EDS)
Part 1: Overview

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INTRODUCTION

Ehlers-Danlos Syndromes (EDS) are a group of genetic connective tissue disorders that are heavily connected to hypermobility spectrum disorder (HSD; Ehlers Danlos Society, 2024). The purpose of this resource is to highlight the etiology, prevalence, diagnostic workup, and cultural considerations regarding EDS. This resource is a brief overview intended to provide basic, introductory knowledge for clinicians learning about EDS.

COMMON SYMPTOMS

Symptoms of EDS often arise in childhood and become more severe into adulthood (Palomo-Toucedo et al., 2020). Some of the common symptoms of EDS can include:

- Joint instability and hypermobility
- Joint dislocations
- Partial joint dislocations (subluxations)
- Early osteoarthritis
- Weak muscles
- Skin hyperextensibility (stretchy & fragile skin)
- Widespread pain
- Migraine
- Generalized connective tissue fragility

SUBTYPES

EDS has 13 heterogeneous sub-types (Ehlers Danlos Society, 2024; Jeffrey et al., 2021).

- Arthrochalasia type (aEDS)
- Brittle Cornea Syndrome (BCS)
- Cardiac-valvular EDS (cvEDS)
- Classical EDS (cEDS)
- Classical-like EDS (clEDS)
- Dermatosparaxis type (dEDS)
- Hypermobile EDS (hEDS)
- Kyphoscoliotic EDS (kEDS-PLOD1)
- Myopathic EDS (mEDS)
- Musculocontractural EDS (mcEDS)
- Periodontal EDS (pEDS)
- Spondylodysplastic EDS (spEDS)
- Vascular EDS (vEDS)

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Most of the EDS sub-types are very rare, with hEDS being the most common. For that reason, this resource will focus mainly on the hEDS subtype.

ETIOLOGY

EDS is a genetic disorder inherited in an autosomal dominant pattern (50% chance of being passed on to each child). The causative variant(s) in the respective gene can be identified in 12 out of the 13 subtypes of this condition. A causative gene has not yet been identified for hEDS, although a genetic basis is suspected (Jones et al., 2022). Causative genes impact the body in diverse ways and are categorized according to shared characteristics. Some of these genes are linked to disorders affecting how collagen (a key protein in connective tissues) is structured and processed. Other genes are associated with issues involving how collagen folds and forms crosslinks. Additionally, certain genes can lead to problems with the structure and function of the myomatrix (the environment where muscle cells grow), disruptions in the production of glycosaminoglycans (important molecules in connective tissues), deficiencies in the complement pathway (a part of the immune system), or problems with processes that occur inside cells (Ehlers Danlos Society, 2024).

PREVALENCE

Joseph et al. (2018) report that the prevalence of all types of EDS is approximately one in 300 to 5000 births annually. cEDS has a prevalence of one in 20,000–40,000 births and vEDS has a prevalence of one in 100,000–200,000 (Ehlers Danlos Society, 2024). hEDS is more prevalent and represents 80%–90% of all EDS cases (Jones et al., 2022). Research by Demmler et al. (2019) estimates that one out of every 500 people is affected by HSD or hEDS. Females are affected at a higher rate. The exact reason for this gender disparity is not fully understood, but there is a connection between joint hypermobility and sex hormones, which may be the underlying cause. Functional voice and throat problems, including dysphagia, dysphonic vocal quality, reduced pitch range, vocal fatigue, and difficulty with projecting the voice, have a higher prevalence in those with EDS than in the general population (Hagberg et al., 2004; Hunter et al., 1998; Lam et al., 2021). hEDS is associated with the following comorbidities: chronic fatigue (Hakim et al., 2017a), autonomic disorders (Hakim et al., 2017b), postural orthostatic intolerance (POTS; Chuchin & Ornstein, 2023), Chiari malformation Type I (CMI; Henderson et al., 2017), atlantoaxial instability (AAI; Henderson et al., 2017), craniocervical instability (CCI; Henderson et al., 2017), tethered cord syndrome (TCS), functional neurologic signs (Fernandez et al., 2023), movement disorders (Henderson et al., 2017), temporomandibular disorder (TMD; Mitakides & Tinkle, 2017), Mast cell activation disorder (MCAD; Seneviratne et al., 2017), increased sensitivity to allergens, respiratory problems, gastrointestinal problems (Fikree et al., 2017), anxiety, sleep disorders (Gaisl et al., 2017), and reduced quality of life (QOL; Jeffrey et al., 2021).

DIAGNOSIS

To receive a diagnosis of EDS, a patient must meet clinical criteria (Castori et al., 2017; Malfait et al., 2017). All 13 sub-types require the presence of hypermobility, hyperlaxity of the skin, and fragility of several tissues. The clinical criteria vary based on EDS sub-type and are outlined by Malfait et al. (2017). Referral to a geneticist who can perform diagnostic testing is recommended for specific sub-type level diagnosis. Tissue biopsy with electron microscope analysis to evaluate for classic abnormalities in the appearance of collagen can also be performed. When EDS is suspected, CT, MRI, and echocardiography can be used to evaluate common cardiovascular concerns such as mitral valve prolapse and aortic dilatation. MRI can also reveal white matter lesions consistent with the diagnosis of EDS. For the purposes of this resource, we will focus on the clinical criteria for hEDS. hEDS does not yet have a genetic etiology test available, so it relies on clinical diagnostics.

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A diagnosis of hEDS will be given to patients who meet all 3 of the following criteria:

1. Criterion 1: Generalized joint hypermobility (GJH)
    a. Assessed via the Beighton score
        i. Measures the movement in 9 joints
        ii. >5 out of 9 is considered the cut-off score for GJH
        iii. Malfait et al., 2017, propose cut-off scores of ≥6 for pre-pubertal children and adolescents, ≥5 for pubertal men and women up to the age of 50, and ≥4 for those >50 years of age for hEDS.
        iv. To find out more about the Beighton scale, visit The Ehlers-Danlos Society website.
2. Criterion 2: Two or more of the following features:
    a. A systematic manifestation of generalized connective tissue disorder (GCTD)
    b. Positive family history, with one or more first-degree relatives
    c. Musculoskeletal complications
3. Criterion 3: All of the following prerequisites:
    a. Exclusion of other types of EDS
    b. Exclusion of other heritable and acquired connective tissue disorders (e.g., lupus, rheumatoid arthritis)
    c. Exclusion of alternative diagnoses that may also include joint hypermobility (e.g., neuromuscular disorders, other HCTD, and skeletal dysplasias)

The Ehlers-Danlos Society (Ehlers Danlos Society, 2024) offers a free downloadable checklist of the diagnostic criteria for hypermobile Ehlers-Danlos syndrome (hEDS).

CULTURAL CONSIDERATIONS

Transgender and gender-affirming clinics have observed a notable trend in the prevalence of Ehlers-Danlos syndrome (EDS) among their patients, as highlighted by Najafian et al. (2022). A recent study revealed compelling statistics, indicating that 2.6% of adults undergoing gender-affirming surgery were diagnosed with EDS—a rate significantly higher than the assumed incidence of transgender and gender diverse (TGD) individuals and over 130 times the reported prevalence of EDS in the general population (Najafian et al., 2022). Moreover, Jones et al. (2022) documented that within their multidisciplinary clinic focusing on EDS, a striking 17% of individuals diagnosed with EDS identify as transgender or gender diverse (TGD). This proportion is markedly elevated compared to the national average of 1.3%, although the precise nature of this association remains unclear. These findings underscore the importance of further research and understanding of the intersection between EDS and gender diversity, potentially informing more comprehensive and inclusive healthcare practices within both transgender and EDS-focused clinical settings.

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In addition to the observed prevalence of Ehlers-Danlos syndrome (EDS) in transgender and gender-diverse individuals, recent studies by Kindgren et al. (2021) have highlighted significant associations between hypermobile Ehlers-Danlos syndrome (hEDS) and attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Their retrospective study found that within their cohort, 16% had a confirmed diagnosis of ADHD, with an additional 7% undergoing diagnostic investigation for ADHD. Notably, in the 15–16-year-old age group, 35% of individuals with hEDS had ADHD, and this percentage increased to 46% among those aged 17–18 years. Furthermore, ASD was verified in 6% of the children studied. Casanova et al., 2020, also establish a relationship between ASD and hEDS where they highlight similarities in phenotypes, neurobehavior, neuropathies, neuropathology, autonomic dysfunction, and immune dysregulation. These findings underscore the importance of further research into the relationship between hEDS and neurodevelopmental disorders, potentially leading to improved healthcare practices and support for individuals with these overlapping conditions.

The next section of this resource (Part 2) will focus on dysphonia assessment and treatment considerations.

HOW TO REFERENCE THIS RESOURCE:

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