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An acquired or heritable connective tissue disorder? A review of hypermobile Ehlers Danlos Syndrome

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ABSTRACT

Hypermobile Ehlers Danlos Syndrome (hEDS) is a multifaceted disorder that is difficult to diagnose and manage primarily due to the unknown causes. Research on hEDS continues to evolve but tangible progress will be realized when the growing body of evidence compliments clinical practice. This critical review of the literature aims to stimulate lateral thinking about the pathogenesis, diagnosis and management of hEDS. The current international classification of Ehlers Danlos Syndrome introduced stricter diagnostic criteria for hEDS, which bore a blanket category (*hypermobility spectrum disorders*) for conditions presenting with symptomatic joint hypermobility, but do not match the hEDS diagnostic criteria. One would argue hEDS is another all-encompassing classification for heritable connective tissue disorders and or acquired musculoskeletal conditions without a definitive molecular basis. As scientific research progresses to accommodate validated and or annulled hypotheses, the plethora of unknowns in hEDS continue to challenge healthcare outcomes and care experiences.

1. Introduction

Ehlers Danlos Syndrome is the overarching term for a range of heritable connective tissue disorders, deriving its designation from dermatologists Edvard Ehlers and Henri-Alexandre Danlos (Beighton and Beighton, 1986). The updated international classification of Ehlers Danlos Syndromes (Malfait et al., 2017) distinguishes 13 subtypes, but this paper focuses on hypermobile Ehlers Danlos Syndrome (hEDS) that manifests as a multifactorial condition.

Presumed to be a heritable disorder of connective tissue, diagnostic criteria for hEDS are based on clinical characteristics (Malfait et al., 2017), which present unprecedented challenges for subjective interpretations. Benefits from treatment are predictive without sound benchmarks and limited understanding of the condition leads to gratuitous investigations, wrong therapies and inappropriate referrals (Castori and Voermans, 2014). Hypotheses in research initiate further work to annul or qualify thoughts, but the last two decades of joint hypermobility research have witnessed numerous theoretical propositions without ensuing studies to support assumptions made (Kumar and Lenert, 2017). The growing body of evidence presents a plethora of unknowns, raising questions about what hEDS constitutes.

One of Edvard Ehlers's professional tenets was undertaking in-depth investigations to demarcate symptoms, classify, mark and define disorders based on cause(s) instead of coining illnesses as rare or isolated cases and thus under recognised (Beighton and Beighton, 1986). Several scholars have followed suit to discern hEDS but speculations, inconclusive results and emphases of unknowns embody the literature about its pathogenesis and etiology (Tinkle et al., 2017). Classified as a heritable connective tissue disorder (HCTD), there are no biomarkers to substantiate this presumption, given the absence of reproducible classification of any pathogenic variant in any gene despite using next generation sequencing (Forghani, 2019; Syx et al., 2015). Familial diagnoses present distinct manifestations within and between families (Castori et al., 2014; Colombi et al., 2015). This negatively affects how evidence is embedded in clinical practice to improve health outcomes and care experiences. As scientific research on hEDS continues to evolve, actual progress will be realized when the evidence compliments clinical practice. This critical review of the literature aims to stimulate lateral thinking about the pathogenesis, diagnosis and management of hEDS.

1.1. Pathogenesis of hEDS

Like other HCTDs, hEDS is characterized by connective tissue laxity and fragility that heighten predisposition to tissue rupture due to weak tensile loading causing injuries. The sequela is contingent on defects in gene expression and the gravity of the mutation in the extracellular matrix (Kazkaz and Grahame, 2018), which are unknown for the case of hEDS. Prior to amalgamating joint hypermobility syndrome (JHS) and hEDS as one clinical condition (Malfait et al., 2017), debates dwelt on

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whether JHS and hEDS were distinct conditions with overlapping characteristics but a similar genetic defect base (De Paepe and Malfait, 2012; Castori et al., 2010; Castori and Colombi, 2015). The undisclosed conflict of interest surrounding all work that led to the 2017 international classification of the Ehlers-Danlos syndromes is noteworthy. Patient Support Groups funded and organized the international symposium held in New York in 2016, where the consortium agreed to merge JHS and hEDS into a phenotypic entity based on existing literature and the group's professional experience (Bloom et al., 2017). The current literature does not offer gold standard evidence and the involvement of a small group of professionals in critical decisions promotes the hegemony and tunnel vision of eminence-based medicine. Edvard Ehlers and Henri-Alexandre Danlos involved real EDS cases during debates at different fora to affirm precision of clinical observations (Beighton and Beighton, 1986).

Although gene-environmental interaction has not been fully explored in hEDS, Tinkle et al. (2009) suggested the blurred distinction between hEDS and JHS was due to clinical evolution stimulated by age or environmental activity. Not far from this intimation, Castori et al. (2011) identified a sex influence on how hEDS manifests, presuming higher incidence among females than males. Castori et al. (2011) recruited a convenient sample of six (n = 6) males and forty-four (n = 44) females to compare symptom prevalence across sexes. Indeed, the majority of primary research published constitutes samples of more females than males (Tinkle et al., 2017). This trend has led to the assumption that a female fetus is more susceptible to a genetic predisposition to hEDS (Castori, 2012), which contravenes distinguishing hEDS as an autosomal dominant trait. For undefined reasons, a female conceptus is more likely to develop hEDS than a male conceptus. On the other hand, evidence supporting hEDS as an autosomal dominant trait is also debatable due to inconsistences registered in the hypermobility assessment tools used (Castori and Colombi, 2015). Questions henceforth arise relating to what constitutes hEDS.

Researching the impact of sex on health transcends the occurrence or absence of a Y chromosome to discern biological, physiological and social aspects and their effects (Institute of Medicine (US) Committee et al., 2006). Whilst the literature briefly cites a reproductive perspective (Castori, 2012, 2013), I have not come across research investigating the role of the reproductive system in the pathophysiology of hEDS. For example, testosterone has positive effects on sensory awareness of pain (Vincent and Tracey, 2008) and disproportionate levels of testosterone in sexes could modulate health seeking behaviors amongst people diagnosed with hEDS. The fluctuation of hormone serum range for controlling immune and inflammatory functions during late luteal and or menses in females may equally have an impact on symptomatology and clinical evolution of hEDS.

Compelling evidence identifies the role of sex hormones in modulating the brain gut axis resulting symptomatic disorders such as migraine headaches, chronic pelvic pain and fatigue (Mulak et al., 2014; Heitkemper and Jarrett, 2008), more common in females than males (Castori et al., 2010). Similarly, the influence of sex differences on innate immunity and response to conditions associated with chronic pain is well evidenced (Castori et al., 2010a; Sorge and Strath, 2018; Bartley and Fillingim, 2016). Testosterone known for its anti-nociceptive functions (Bartley and Fillingim, 2016; Craft, 2007), explains the effects of lower levels of androgens in females on thresholds for sensory awareness of pain (Bartley and Fillingim, 2016; Cairns and Gazerani, 2009). Thus, deductions about female fetuses being more receptive to a mutated gene than their male counterparts require better empirical evidence than a headcount of service users in hypermobility clinics. The hEDS research community is yet to witness a study following systematic and non-sex biased sample recruitment to offer a balanced reflection of characteristics and factors that underpin variances in clinical expression.

1.2. Diagnosing hEDS

Delayed diagnoses are resource intensive due to multiple healthcare consultancies and erroneous therapies (Castori, 2012). The introduction of stricter diagnostic criteria for hEDS (Malfait et al., 2017) is marginally helpful since diagnostic accuracy using clinical definitions is still contingent on physicians' experience of undertaking similar assessments. Evidence of a plausible relationship between the mutation of Tenascin XB and hEDS (Petersen and Douglas, 2013) is currently untenable because the statistical correlation in the originating study was not significant (Zweers et al., 2005). Besides, traditional statistical modelling does little to detect complex genetic and environmental structures of multifaceted conditions (Institute of Medicine (US) Committee et al., 2006). In the same vein, a few people diagnosed with hEDS and a definitive genetic mutation on Tenascin XB have illustrated symptoms similar to classical EDS (Kaufman and Butler, 2016). The sole focus on isolating Mendelian patterns without exploring the impact of environmental influences on how hEDS manifests may deter useful results in deciphering the multifactorial condition.

The updated classification of EDS includes flexible cut off points on the Beighton score to compensate for changes in joint movement in hEDS (Malfait et al., 2017). However, the stricter diagnostic framework does not incorporate means of controlling for implicit nor explicit influences on joint movement and hence leaving room for diagnostic error. The stricter diagnostic criteria for hEDS introduced a blanket category (*hypermobility spectrum disorders [HSDs]*) for conditions presenting with symptomatic joint hypermobility, but not matching the hEDS diagnostic criteria (Castori et al., 2017; Castori and Hakim, 2017). One would also argue that hEDS is an all-encompassing category for progressive heritable connective tissue disorders and or acquired musculoskeletal conditions without a molecular basis. Table 1 identifies the some of the pitfalls in the new hEDS diagnostic criteria.

Aggregate propositions in the literature blur certitude about the heritable nature of hEDS and its pathophysiology. For example, the HSDs category is an exclusionary diagnosis for hEDS, but HSDs are likely to revert to asymptomatic joint hypermobility or mutate to hEDS (Castori and Hakim, 2017). Moreover, generalized hypermobility, a characteristic that must be met for an accurate diagnosis of hEDS is typically congenital but can also be acquired (Castori et al., 2017). While such prepositions may not be entirely inaccurate, it would help to distinguish unique numerators for acquired or heritable joint hypermobility to qualify the supposed syndromic temperament of hEDS.

Some scholars introduce hEDS as a metamorphosis of joint hypermobility underpinned by variable expression at different life stages (Castori and Colombi, 2015; Castori et al., 2017). Although hEDS is a presumed heritable connective tissue disorder, it is likely to remain passive as asymptomatic joint hypermobility until exposed to activators yet to be defined (Castori et al., 2017). Fig. 1 illustrates the following statement plus similar emphases in the literature (Castori and Colombi, 2015; Castori et al., 2017): "HSD is not always a permanent diagnosis and may change into asymptomatic joint hypermobility in case of complete resolution of symptoms or into hEDS (or, perhaps, other genetic disorders)" [Castori and Hakim, 2017 p.645]. I am inclined to conclude that hEDS is not a phenotypic entity, but a nomenclature for a range of health conditions whose expression is modulated by gene-environment risk factors.

Adapted from the hierarchical stratification of joint hypermobility. (Castori and Colombi., 2015. *Generalized joint hypermobility, joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type. Am. J. Med. Genet. Part C Sem Med. Genet. 169(1), pp. 1–5)*

Stratifying joint hypermobility in a hierarchical order (Castori and Colombi, 2015) illustrates clinical evolution to other undetermined HCTDs at the highest level of the hierarchy. This implies a hEDS diagnosis is not conclusive until clarity about a yet undiscovered, defective gene(s) is obtained or not. Until then, the joint hypermobility research community oscillates in knots of uncertainties.

Table 1
Perceived shortfalls in the diagnostic criteria for hEDS.

Criterion	Shortfall
GJH is considered a prerequisite for the diagnosis of hEDS and GJH is a constitutional trait strongly influenced by acquired and inherited conditions (e.g., sex, age, past-traumas, co-morbidities, etc.), some minor adaptations to the cut-off of five should be considered for the diagnosis of hEDS. The committee on behalf of the International Consortium on the Ehlers–Danlos Syndromes proposes _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. This may vary from other types of EDS but such types have confirmatory testing. Assessment of other joints should be considered for patients with lower Beighton scores. However, similar concerns about age, gender, and environmental influences as well as measurement methodology and reliable cut-off values, limit such analysis as too subjective in the determination of GJH. Therefore, the use of such measurements cannot be factored into a diagnostic algorithm at this time. Obviously, more information regarding the assessment methodology (ies) in the determination of GJH is needed (p.17)	This criterion acknowledges the influence of genetic and environmental aspects in the development of joint hypermobility. These aspects should be recognised across the entire diagnostic criteria for hEDS. How does time influence the development of other features that may only become apparent with age? The variation noted for other EDS types introduces a bias against a condition without confirmatory tests. The diagnostic criteria lack a systematic approach to their development. Sex, age, past-traumas, co-morbidities etc. would have, not essentially similar, some form of effect on other EDS types with confirmatory testing. The proposed cut off values are approximate, subject to observer variation and would not yield reproducible results within variable environmental contexts. No means are incorporated in the diagnostic criteria to adjust for possible variations.
Two or more of features A-C (A and B; A and C; B and C; A and B and C) **A**: systemic manifestations of a more generalized connective tissue disorder (a total of five must be present) (p.18–19). **B:** positive family history, with one or more first degree relatives independently meeting the current diagnostic criteria for hEDS (p.18). **C**: Must have at least one musculoskeletal complications (p.19).	Meeting features A&C presents fluidity around feature B, especially for people without perceptible acquired connective tissue disorders. A&C initiates the likelihood of hEDS being an acquired connective tissue disorder, which is glossed over throughout the diagnostic criteria. Feature A encompasses a range of possible manifestations, some of which are listed with limitations. I will only tackle a few, bearing in mind that, particularly age and sex affect the development of nearly all manifestations listed under feature A. **Unusually velvety skin*:*** There are no reliable tools to evaluate disparity emanating from demographic features (age, sex, and ethnicity). Castori and Colombi, 2015 suggest a positive mucocutaneous necessitates combination of prominent features but the confirmatory total of five may constitute any of the listed 12 features, some of which may not be clear cut (e.g. unusually soft or velvety skin, mild skin hyperextensibility). Manifestations that cannot be sharply defined are not excluded in the contribution towards the suggested total of five. **Mild skin hyperextensibility**: Evaluation of this clinical manifestation is based on random assessment of range of extensibility (Castori and Colombi, 2015). *"… extensibility of more than 1.5* cm *is "positive." If extensibility > 2.0* cm *is present especially in combination with other cutaneous features … consider other EDS types as possible alternative diagnoses (p.18)*. The probability of observer variation for estimated extensibility between 1.5 cm and 2.5 cm is humanly high. ***Bilateral piezogenic papules of the heel***: The research on which this indicator is inclined (Kahana et al., 1987) investigated painful piezogenic pedal papules. The lack of emphasis of pain introduces a case of cherry picking data. If attributable to a connective tissue disorder, 34.5% (10/29) of an adult sample with an EDS diagnosis and painful piezogenic pedal papules does not present practical significance to affirm the correlation. Piezogenic pedal papules are common across all age groups in a healthy population including children without connective tissue disorders (Kahana et al., 1987; Van Straaten et al., 1991). The association of piezogenic pedal papules with conditions underpinned by connective tissue disorders is currently anecdotal pending scientific evidence. ***Mitral valve prolapse (MVP).*** Inclusion of this manifestation although it is usually not clinically significant in people with hEDS confounds the 'stricter' element of the diagnostic criteria for hEDS. The random inclusion of infrequent features also widens the diagnostic spectrum, lengthening the process of delineating hEDS.
All [3] must be met: (p.19). Absence of unusual skin fragility, which should prompt consideration of other types of EDS Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired connective tissue disorder (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 towards a diagnosis of hEDS in this situation. 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., myopathic EDS, Bethlem myopathy), other HCTD (e.g., other types of EDS, Loeys–Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g., OI).	The exclusion criteria in totality rely on health professionals' widespread knowledge of medicine, which is neither the case in specialist nor general medicine. This resource intensive activity does not advance the diagnostic process which still calls for a multitude of consultancies with specialist. The exclusion criteria appear to defend the inclusion of a wide range of components overlapping with other HCTDs in 'stricter' diagnostic criteria. hEDS may present with some of the clinical symptoms of the myriad of listed and non-listed but comparable categories of health conditions, but hEDS is not any of these. The exclusion criterion suggests hEDS embodies a range of conditions yet to be segregated.
Inheritance- autosomal dominant	A definite diagnosis of a HCTD relies on molecular confirmation. This information is unknown for hEDS.
Clinical diagnosis	Depends on subjective interpretations liable to diagnostic error.

1.3. Symptoms in hEDS

Hypermobile Ehlers Danlos Syndrome is multifaceted in clinical presentation with a range of symptoms that can hardly be generalized (Scheper et al., 2015). The discussion here is not exhaustive but instead highlights a few examples of inconclusive areas in the literature. A wide spectrum of neurological, mucocutaneous, musculoskeletal and gastrointestinal complaints present uniquely in hEDS. A study of clinical heterogeneity of hEDS observed common musculoskeletal complaints but widespread non-musculoskeletal clinical disparity attributing this

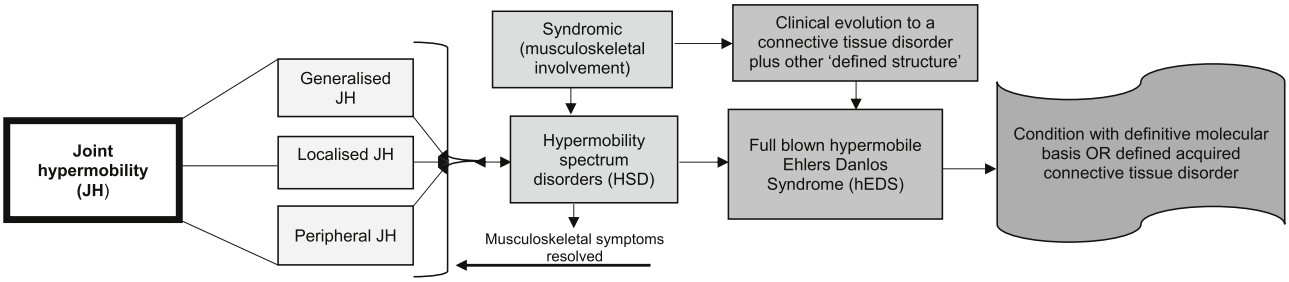

Fig. 1. Evolution of hEDS along the joint hypermobility spectrum.

to genetic variability or dysautonomia (De Wandele et al., 2013). Propositions for clinical heterogeneity followed genetic relations without illuminating environmental risk factors. A follow-on study established dysautonomia in hEDS highlighting peripheral sympathetic neuropathy and medication with autonomic side effects as likely causes (De Wandele et al., 2014). With humility, De Wandele et al. (2014) indicated the neuropathy hypothesis would explain the frequent occurrence of postural orthostatic tachycardia syndrome in hEDS, only if upheld true. As the neuropathy hypothesis pends validation, postural orthostatic tachycardia syndrome is deemed highly prevalent in females (Stiles et al., 2017). While understanding the role of sex hormones to autoimmunity in humans is under development, a trial introducing testosterone in female mice facilitated use of microglia in the spinal cord to mediate pain like male mice instead of T cells (Sorge et al., 2015). In light of sex differences, Wallis et al. (2017) presume a shared mechanism for neurological, gastrointestinal and immune disorder symptoms, usually considered separately. Is it time for the joint hypermobility research community to critically appraise other avenues to discerning the multilayers of hEDS?

The gap in longitudinal studies identifies the quality of evidence generated from cross sectional observations of clinical features that develop with age (Forghani, 2019). For example, Scheper et al. (2017) reported inconsistent results from a cross sectional study of the influence of proprioception on muscle strength and activity limitations. Muscle weakness and poor resistance affect movement and posture but the lack of strength in the muscles is due to anomalies instead of muscle waste (Proske and Gandevia, 2012). A statistical control for physical activity in a study examining lower extremity muscle mass, muscle strength, functional performance and physical impairment indicated very low muscle strength in hEDS (Rombaut et al., 2012). Nonetheless, subsequent research still involves associations of muscle weakness with muscle waste linked to pain and fatigue in hEDS (Scheper et al., 2017).

Causes of severe pain predominant in hEDS present another area of contention (Voermans et al., 2010; Scheper et al., 2015). Agreement about pain activation is more around joint hypermobility and dislocations particularly of the knees, ankles and shoulders but peripheral neuropathy, muscle cramps and tendinitis add to propositions for pain triggers (Rombaut et al., 2010. Whist pain in most conditions related to joint hypermobility could be as a result of trauma from excess joint movement, it is anticipated that the pain is independent of causes of the initial joint condition (Castori et al., 2013; Scheper et al., 2017) The complexity of understanding pain and its severity emanates from an interplay of various malfunctions within and around a diagnosis of hEDS (Scheper et al., 2015) which are not unfortunately fully understood.

Hypermobile Ehlers Danlos Syndrome is largely correlated with psychiatric disorders (Baeza-Velasco et al., 2015; Cederlöf et al., 2016) but descriptions of their triggers are weakly founded. Pasquini et al. (2014) linked the high risk and prevalence of obsessive-compulsive disorder in hEDS with controlling parents. Whilst gene plus gene-environment interactions may influence personality (Moffitt et al., 2006), the causal factor here is too constricted to explicate biochemical chains and how these could be delineated from environmental influences in context of a presumed autosomal dominant disorder. It is not clear whether the resultant psychiatric disorder is a response of gene expression to the controlling environment or whether the controlling trait follows genetic determinism. Pasquini et al. (2014) also associated perfectionism to healthcare professionals' lack of understanding of hEDS, which is a reductionist view to feelings of frustration, humiliation and resentment resulting from shortcomings in practitioners' person-centered practice (Berglund et al., 2010; Knight, 2015). Bulbena et al. (2017) posit a possible role of dysautonomia and fatigue on mental wellbeing in hEDS, which can easily be misdiagnosed as psychiatric disorders such as anxiety, depression and panic attacks. Although not all genetic outcomes are obtained through the environment, exploring measured gene-environment interactions is useful in understanding complex health conditions (Moffitt et al., 2006).

1.4. Managing hEDS

Hypermobile Ehlers Danlos Syndrome is a characteristically systemic condition that causes complex and lengthy experiences specifically in the management of pain and fatigue affecting individuals' quality of life (Knight, 2015). Inadequate effect of drug treatment and poorly controlled medication or physical therapy exemplify practice in managing hEDS (Castori et al., 2014). Evidence of causes of severe pain is inconclusive and the challenges for physicians are overwhelming since usual pain relief measures are often ineffective (Chopra et al., 2017). Assessing and managing a subjective experience effectively is contentious without clear guidance. The literature proposes numerous methods for the effective management of hEDS. Pharmacology attests to high doses of opioids for pain management outside of clinical guidance to alleviate human suffering (Tennant, 2014). Cherry-picking from existing pain control measures to suit individual needs (Castori, 2012) flags numerous uncontrolled trials, failing to benchmark and build on what works to improve healthcare outcomes. Interdisciplinary management would be beneficial to both physicians and patients (Castori and Colombi, 2015; Bathen et al., 2013), but it is difficult to attain in highly fragmented systems of healthcare that people with complex conditions struggle to navigate (Simpson, 2016). A humanization framework is a practical guide in enabling experiential understanding of individuals and their condition (Clark and Knight, 2017) however, short appointments and performance driven healthcare restrict deep involvement care processes.

Pain and fatigue carry the bulk of symptoms in hEDS but the lack of evidence on effective management means overall condition management is experimental and this varies widely along the medical hierarchy of competence.

2. Conclusion

As scientific research develops to accommodate validated and or annulled hypotheses, the plethora of unknowns in hEDS continue to challenge healthcare outcomes and experiences of care. The literature

about hypermobile Ehlers Danlos Syndrome is crowded with uncertainties and thus condition management is mostly predictive. The hierarchical stratification of joint hypermobility implies people diagnosed with hEDS are yet to receive another diagnosis. The task for future research is to explore environmental influences and control for anatomical variations in phenomenon examined, particularly if sex is a contributing factor.

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Conflicts of interest

The author has no conflict of interest to declare.

Appendix A. Supplementary data

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