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.

Keywords Hypermobile Ehlers Danlos Syndrome, joint hypermobility, connective tissue disorder, diagnosis, management

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 & 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. Malfait et al. (2017) underscored the “dire need for a better clinical definition of the hypermobile type of EDS and its delineation from other hypermobility disorders” (p. 9). However, authors did not disclose the conflict of interest surrounding the consensus to

absorb joint hypermobility syndrome into Ehlers Danlos Syndrome hypermobility type as a phenotypic entity with neither consistent evidence nor patient involvement. Patients' Support Groups funded and organized the international symposium held in New York in 2016, where the Consortium reached a consensus based on existing literature and the group's professional experience (Bloom et al., 2017). Edvard Ehlers and Henri-Alexandre Danlos involved real cases at different fora of EDS debates to affirm precision when based on clinical observations (Beighton & Beighton, 1986).

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 & 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 & Lenert, 2017). The growing body of research 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 recognized (Beighton & 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 following an overall lack 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.

Pathogenesis of hEDS

Like other HCTDs, hEDS is characterized by connective tissue laxity and fragility that heighten predisposition to tissue ruptures 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 & 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 whether JHS and hEDS were distinct conditions with overlapping characteristics but a similar genetic defect base (De Paepe & Malfait, 2012; Castori et al., 2010; Castori & Colombi, 201). Although gene-environmental interaction have not been fully explored in hEDS, Tinkle and colleagues (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 with distinguishing hEDS as an autosomal dominant trait. For undefined reasons, a female conceptus is deemed more likely to develop hEDS than a male conceptus. On the other hand, evidence supporting

hEDS as an autosomal dominant trait is debatable due to inconsistences registered in the hypermobility assessment tools used (Castor & 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, 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 & 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.

Although heterogeneous in presentation, gastrointestinal involvement is highly common in hEDS (Castori & Grammatico, 2015). 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 & Jarrett, 2008), which are more common in females than males (Castori et al., 2010). Similarly, substantial evidence exists about the influence of sex differences in innate immunity to conditions associated with chronic pain and pain experience (Castoriet al., 2010a; Sorge & …2.018), An introduction of testosterone in female mice facilitated use of microglia in the spinal cord to mediate chronic pain like the male mice instead of T cells (Sorget et al., 2015). Testosterone is known for its anti-nociceptive functions ((Bartley & Fillingim, 2016; Craft, 2007), which explains the effects of the lower levels of androgens in the female sex on the threshold for sensory awareness of pain (Bartley & Fillingim, 2013; Carins & 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 research following systematic and non-sex biased sample recruitment to offer a balanced reflection of characteristics and factors that underpin variances in clinical expression.

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 & Douglas, 2013) is currently untenable because the statistical correlation in the originating study was not significant (Zeweers et al., 2005). Besides, traditional statistical modelling does little to detect complex genetic and environmental structures of multifaceted conditions (Institute of Medicine, 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 & 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 gave rise to 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 & 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. 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 & 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 researchers present hEDS as a metamorphosis of joint hypermobility underpinned by variable expression at different life stages (Castori & 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 that are yet to be defined (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 & Hakim, 2017 p.645]. Figure 1 is one interpretation of Castori and Colombi (2015) and Castori et al. (2017) rationalization of the development of hEDS along the joint hypermobility spectrum.

Figure 1 Evolution of hEDS along the joint hypermobility spectrum

[Figure 1]

adapted from the hierarchical stratification of joint hypermobility. (*Castori, M. and Colombi, M., 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 & 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.

Symptoms in hEDS

Hypermobile Ehlers Danlos Syndrome is multifaceted in clinical presentation with a range of symptoms that can hardly be generalized (Scheper et at., 2015). The discussion here is not exhaustive but rather highlights a few examples of inconclusive areas in the literature. A wide spectrum of neurological, mucocutaneous, musculoskeletal and gastrointestinal complaints present uniquely in hEDS. For example, a study of clinical heterogeneity of hEDS observed common musculoskeletal complaints but widespread non-musculoskeletal clinical disparity attributing this to genetic variability or dysautonomia (De Wandele et al., 2013). Prepositions for clinical heterogeneity followed genetic relations without illuminating the role of environmental risk factors. A follow-on study established dysautonomia in hEDS highlighting peripheral sympathetic neuropathy and medication with autonomic side effects as likely causes for dysautonomia (De Wandele et al., 2014). The commonest types of dysautonomia in hEDS are thought to be neurocardiogenic syncope and postural orthostatic tachycardia syndrome (Tinkle et al., 2017). However, muscle weakness, a trait prevalent in hEDS is primarily found in familial dysautonomia with a known mutation of the IKBKAP/ ELP1 gene (Axelrod, 2004).

Muscle weakness, proprioception and physical activity in hEDS are not sufficiently understood perhaps due to cross-sectional and statistical methods used in discerning clinical evolution happening in female adults over time. 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 & Gandevia, 2012). A statistical control for physical activity in a study examining lower extremity muscle mass, muscle strength, functional performance and physical impairment still indicated very low muscle strength in hEDS attributed to abnormalities in the muscle extracellular matrix (Rombaut et al., 2012). Nonetheless there is continued

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).

Hypermobile Ehlers Danlos Syndrome is largely corelated with psychiatric disorders (Baeza-Velasco et al., 2015; Cederlöf et al., 2016) but descriptions of their triggers are weakly founded. For example, Pasquini et al. (2014) linked the high risk and prevalence of obsessive-compulsive disorder in hEDS with controlling parents. Whilst genes plus gene-environment interactions may influence personality (Moffit 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 (Moffit et al., 2006).

Managing hEDS

Hypermobile Ehlers Danlos Syndrome is characteristically a 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). Castori et al. (2013) contend both central and peripheral elements intrinsically underpin pain sensation in hEDS, but assessing and managing a subjective experience effectively is contentious without clear guidance. Pharmacology attests to high doses of opioids for pain management outside of clinical guidance to alleviate human suffering (Tennant, 2014). The highly recommended interdisciplinary management is beneficial to both physicians and patients (Castori et al., 2015; Bathen et al., 2013), but this is difficult to attain in fragmented systems of healthcare that people with rare conditions struggle to navigate (Simpson, 2016). Cherry- picking from existing pain control measures to suit individual needs (Castori et al., 2012) flags numerous uncontrolled trials, failing to benchmark and build on what works to improve healthcare outcomes. A humanization framework is a practical guide in enabling experiential understanding of individuals and their condition (Clark & Knight, 2017) however, short appointments and performance driven healthcare systems restrict deep involvement in care processes.

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. Molecular mechanisms involvement has become a quick and safe way to explain unclear domains in hEDS despite the lack of biomarkers to date. 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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