Ehlers–Danlos Syndrome

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Ehlers-Danlos syndromes (EDS) are a group of connective tissue disorders which manifest with hyperextensibility of joints and skin, and general tissue fragility. While not a major criterion for clinical diagnosis, pain is a frequently endorsed symptom across subtypes of EDS. Similarly, in painful conditions, quality of life is known to be diminished. As such, EDS and related diagnostic heterogeneity is reviewed, and quality of life correlates of pain in pediatric samples are discussed.

Keywords: Ehlers-Danlos Syndromes ; Joint Hypermobility Syndrome ; Pain ; Pediatric ; Quality of Life

1. Introduction

The Ehlers–Danlos syndromes (EDS) encompass a heterogeneous group of incurable connective tissue disorders that are clinically characterized by skin hyperextensibility, joint hypermobility, subluxation and dislocation, and general tissue and vasculature fragility [1][2]. According to the most recent classification system, described by Malfait and colleagues, 13 subtypes of EDS are presently described. The hypermobility type (hEDS), followed by the classical type of EDS present most commonly, together accounting for over 90% of cases [3]. Presently, gene mutations and related genetic testing have been identified and utilized for diagnosis of the classical, arthrochalasia, kyphoscoliosis and vascular forms of EDS [4]. However, no genetic testing is available for hEDS, and the mutations and mode of genetic transmission remain poorly understood. Some theorize a sex-linked inheritance pattern, given that there are more female patients are diagnosed with hEDS than males, especially within hEDS [5][6]; however, underdiagnosis of male patients may also account for this imbalance. Given the lack of genetic testing, diagnosis of hEDS is based on clinical examination (e.g., classification delineated by Malfait and colleagues [7]) and family history [2]. With respect to the three most common forms of EDS (hypermobility, classical, vascular) focused on in the present review, all three present with proposed autosomal dominant inheritance, and share several diagnostic features. However, while major diagnostic criteria for vEDS are marked by severe cardiovascular and valvular consequences (e.g., arterial rupture at young age, uterine rupture during pregnancy, spontaneous colon perforation), cEDS is distinguished by skin hyperextensibility, scarring and generalized joint hypermobility, and hEDS is marked by generalized joint hypermobility, positive family history of hEDS, and the exclusion of diagnostic criteria associated with other forms of EDS [7].

Despite the heterogeneity of subtypes and associated symptoms, pain symptomatology is commonly endorsed across all subtypes of EDS [7]. There are numerous causes of pain in EDS, including hypermobility of joints, increased frequency of subluxation and dislocations of major and minor joints, injury to soft tissue and muscle pain, and prior surgical intervention [8]. Often, pain in EDS becomes chronic [9][10], leading to increased functional disability [3] and poorer psychological health [11] in adult patients [12].

However, while the onset of symptoms of EDS occurs as early as the first year of life [13], individuals with EDS often do not receive a diagnosis until adolescence or emerging adulthood [14] with delays of several years between symptom onset and intervention [15], making the study of symptomatology in pediatric populations challenging. As such, little is known about how the aforementioned pain symptomatology and diminished quality of life described in adults may generalize to pediatric and emerging adult populations. Yet, research that describes pain symptomatology and related interventions in this demographic group is crucial, given that findings from other pediatric populations highlight how the experience of chronic pain early in life is associated with poorer quality of life and continued chronic pain in adulthood [16]. Therefore, the present review aims to describe pain characteristics in pediatric and young adult populations with various forms of EDS, describing known interventions to manage such pain as well as the relationship between pain symptomatology and quality of life in the context of pediatric EDS.

Notably, given the relative lack of research in samples with pediatric EDS specifically, studies commonly include pediatric joint hypermobility syndrome (JHS) patients, as several experts consider JHS and hEDS to be clinically equivalent [17][18][19]. Like those with hEDS, individuals with JHS are diagnosed based on hypermobility criteria (e.g., Malfait classification) and on the presence of arthralgia (though, a “minor” rather than a “major” diagnostic criterion for hEDS) [19][20].

2. Pain and Quality of Life in Pediatric EDS

Decreased quality of life, as measured by psychosocial, emotional, physical and school functioning has been relatively well documented in those with EDS, with diminished functioning noted in adult [21][22] and pediatric [23][24] populations alike. While many propose that this diminished quality of life is explained by the increased frequency and intensity of pain experienced by the population as compared to the general public [25], few lines of inquiry have directly assessed this theory. However, the little research which has examined this relationship provides evidence in support of the proposal. The authors refer you to Table 2 for a brief summary of the quality of life correlation of pain in hypermobility syndromes, which are expanded upon in more detail presently. With respect to emotional functioning, among children and adolescents with EDS, greater intensity of pain, as well as a greater number of pain sites was associated with greater anxiety and depression [26]. Similarly, among children with JHS for whom pain was a significant symptom (88%), only 35% indicated being able to attend school full time, suggesting that the ability to attend school is further diminished among children with EDS who endorse pain [27].

Similarly, deficits in physical functioning have been noted in pediatric JHS and EDS populations who endorse pain. Both the number of pain sites and pain intensity were positively associated with greater functional disability in children and adolescents with hEDS, and only 6% of children with pain symptomatology in the context of JHS reported completing activities in their school gym classes [27]. Further, children with JHS present with lower maximal exercise capacity, compared to age- and gender-matched control subjects, as measured by diminished peak maximal oxygen consumption [25]. Researchers propose that the relatively poorer aerobic fitness noted in children with JHS is due to their experience of musculoskeletal pain, which leads to inactivity and subsequent deconditioning [25]. The relationship between pain and physical functioning is further complicated by reports of pain exacerbation through activity in youth with JHS [15]. Notably, 81% of children and adolescents with JHS indicate that their pain is exacerbated by exercise, with 65% indicating pain immediately following activity, 59% reporting pain later in the evening and 50% indicating pain the following day [15]. Given the increase in pain following exercise, and that exercise (i.e., physical therapy) is the recommended modality to manage musculoskeletal pain in the context of hypermobility syndromes, providers should consider this when making recommendations to patients. Providers may ask about the prior exercise experiences of pediatric JHS and EDS patients and adjust their explanation of why physical therapy is recommended accordingly. Providers may need to explain that exercises can be adapted to manage pain and prevent injury to reduce the perception of exercise as potentially frightening or inaccessible. Moreover, such conversations would be crucial to addressing kinesiophobia (fear of pain, movement or re-injury) which may develop as a function of the chronic pain experienced by populations with EDS [23].

Although some research to date, as above described, has delineated a relationship between pain and metrics of quality of life in pediatric JHS and EDS, a greater examination of as-of-yet under-examined aspects (e.g., social functioning) is warranted. This line of inquiry is especially valuable, in light of recent findings which suggest that among the predictors of quality of life in pediatric EDS, greater pain, along with greater fatigue, presents as the strongest predictor of diminished quality of life [28]. Through horseshoe and elastic net regressions, when selecting from various demographic and disease variables, pain and fatigue emerged as the strongest predictors of every measure of quality of life (physical, emotional, social, school, and psychosocial functioning) among adolescents with hEDS [28]. As such, a greater examination of how pain impacts quality of life in pediatric EDS is warranted. Future research may be advised to consider how pain-related variables, such as the number of pain sites, duration of pain, and even qualitative description of pain relate to self-reported quality of life.

Table 2. Summary of Quality of Life Correlates of Pain in Pediatric Hypermobility Syndromes.

Quality of Life Correlate	Sample Demographics (N, Illness Group)	Authors and Key Finding
Emotional Functioning	N = 34, hEDS	Tran et al., in press [26]: Anxiety, R = .50, Depression, R = 0.48
School Functioning	N = 54, JHS	Mato et al., 2008 [27]: Only 35% attended school full time

Physical Functioning	N = 54, JHS	Mato et al., 2008 [27]: Only 6% of children completed gym class activities
	N = 32, JHS	Engelbert et al., 2006 [25]: diminished peak maximal oxygen consumption as compared to those without JHS associated pain (Cohen's d = 0.93)
	N = 125, JHS	Adib et al., 2005 [15]: 85% of children note exacerbation of pain with exercise

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