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An Investigation of Headaches in Hypermobile Ehlers-Danlos Syndrome

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Abstract

Ehlers-Danlos Syndrome is a group of heritable connective tissue disorder with a variety of subtypes. This review focuses on different types of headache in Hypermobile Ehlers-Danlos Syndrome (hEDS). Although there are various neurological manifestations that could present as headaches in hEDS, this report will discuss the prevalence and presentation of migraine, idiopathic intracranial hypertension, dysautonomia, craniocervical instability, temporomandibular joint dysfunction, and Chiari malformation in patients with hEDS. Although the exact etiology and pathophysiology of various types of headache seen in hEDS is not known. One of the limitations of the study is lack of enough observational studies to establish a causal association between the various types of headache discussed and hEDS. In addition to discussing previous research on these topics, this review summarizes areas in need of further investigation.

Abbreviations

EDS: Ehlers-Danlos Syndrome; cEDS: classical Ehlers-Danlos Syndrome; hEDS: hypermobile Ehlers-Danlos Syndrome; vEDS: vascular Ehlers-Danlos Syndrome; kEDS: kyphoscoliosis Ehlers-Danlos Syndrome; IIH: Idiopathic Intracranial Hypertension; TMJ: Temporomandibular Joint; POTS: Postural Tachycardia Syndrome; CCI: Craniocervical Instability; CM: Chiari Malformations

Introduction

The Ehlers-Danlos Syndrome (EDS) are a rare group of connective tissue diseases with a variety of subtypes associated with it. The syndromes are thought to be a result from a defect in the synthesis or structure of collagen that leads to skin hyperextension, joint hypermobility, and fragile tissues [1]. There are various subtypes of EDS that vary slightly and the classification of subtypes has changed as of 2017 as EDS is an ever-evolving field with new data emerging [2]. This paper will be referring to the subtypes as established by the 2017 International Classification of the Ehlers-Danlos Syndromes [3]. There are 13 different EDS subtypes with a rare 14th subtype that was found in 2018; however, the hEDS subtype still does not have a genetic mutation assigned to it [2,4]. This paper's purpose is to discuss neurological complaints that can be seen in some EDS subtypes.

Classical EDS (cEDS): cEDS inheritance is autosomal dominant and is thought to be related to mutations in COL5A1 and to lesser extents, COL5A2 and rare COL1A1 mutations [3,5]. This mutation is thought to affect type V collagen [5]. Typically this leads to skin hyperextension, widened atrophic scars, and joint hypermobility [1].

Hypermobile EDS (hEDS): hEDS inheritance is thought to be autosomal dominant and may be related to mutations in COL5A3, but may also have environmental or hormonal factors as well [1,6]. The exact cause of hEDS and any distinct mutations are unknown, but research is ongoing [7]. Typically, patients complain of recurrent joint dislocations, chronic joint and limb pain, general joint hypermobility, hyperextensibility, and smooth or velvety skin [1]. This subtype often affects more females than males with a ratio as high as 9:1 [6]. It should be noted that this subtype may affect multiple systems of the body. hEDS could present with muscle pain and spasms, fatigue, neuropathic pain, headaches, and Temporomandibular Joint (TMJ) disorder [6].

Vascular EDS (vEDS): vEDS could be caused be an autosomal dominant *COL3A1* gene mutation that leads to defective secretion of abnormal collagen III or to a lesser extent a rare *COL1A1* gene mutation [1,3]. In addition to genetic testing, some criteria to diagnose this vEDS subtype includes visible veins under thin skin, easy bruising, and fragility or rupture of arteries, intestine, or the

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uterus, and a characteristic facial appearance [1]. Additionally, this subtype is related to organ rupture or carotid artery dissections [7]. It is imperative for patients diagnosed with vEDS to seek appropriate preventative care because possible complications include vascular issues related to childbirth and surgery or procedures such as colonoscopy, which could result in higher mortality of this variant compared to other EDS subtypes [6].

Kyphoscoliosis EDS (kEDS): kEDS is thought to be due to deficiency in a collagen-modifying enzyme called Lysyl Hydroxylase [1]. This type of EDS is autosomal recessive and clinically appears with generalized joint laxity, progressive scoliosis and hypotonia at birth, rupture of the ocular globe, and fragile sclera [1]. Typically kEDS associated with mutations in *PLOD1* or *FKBP14* genes [3,6].

EDS presents with various neurologic manifestations ranging from headaches, hypermobility, chronic joint pain, neuropathies, and fatigue. Headache is one of the most common and disabling forms of pain in hEDS [8,9]. Chronic recurrent headache may constitute neurologic presentation in EDS in the absence of known structural, congenital, or acquired central nervous lesions that correlate to their symptoms [10]. Types of headaches in EDS include migraine, Idiopathic Intracranial Hypertension (IIH), muscle tension, craniocervical instability, cervical spine disorder, TMJ disorder, carotid dissection, and other possible conditions [9]. Generally, headaches are more commonly related to hEDS and vEDS subtypes and migraines seem to have a higher prevalence in hEDS compared to other forms of headache [6,11]. This paper will focus on headaches in hEDS patients.

Materials and Methods

This is a narrative literature review to evaluate the investigation of headache in Ehlers-Danlos syndrome. In this study, we evaluated three popular search engines which include: PubMed, ScienceDirect, and Google Scholar. We limited our search to "Ehlers-Danlos Syndrome" and "Headache" keywords in all the search engines. Articles that search engines offer are listed according to relevant to the research topic. The search results with most recall, precision and importance to the topic were highly preferred, as was recent articles. However, we made expectations for articles greater than 10 years old if we felt their topic was relative to our review article.

Discussion

Migraine

Migraine is a chronic debilitating neurologic condition that can begin in childhood or adolescence and last throughout ones' life [12]. There is a female predominance with migraine [13]. Migraine headaches are common neurologic manifestation of hEDS that can occur with or without aura, although the pathophysiology of migraines in hEDS patients is not well understood [8]. Bendik et al. [13] found that migraine prevalence in patients with Joint Hypermobility Syndromes (JHS) is up to three times higher than patients without JHS. Puledda et al. [8] showed that patients with hypermobility type EDS had more severe migraines than age matched control migraine patients. These patients were diagnosed earlier in life with migraines and more frequently than patients without this diagnosis. Puledda et al. [8] study demonstrated that "migraine has a very high impact on quality of life". This impact of quality of life could affect psychological health which makes it important in truly understand the full scope of the impact of headaches on hEDS patients. Additionally, early diagnosis and preventative therapy may be key in reducing negative symptoms of living with this syndrome.

Bulbena et al. [14] noted that there is a "high prevalence of psychiatric conditions among individuals with hypermobile type of Ehlers–Danlos syndrome (JHS/hEDS)". Anxiety is seen as a complaint in patients with hEDS [14]. Some comorbid conditions associated with hEDS can present with symptoms similar to anxiety; "therefore, a thorough workup is warranted to rule out dysautonomia" [2].

In our search, we found multiple case studies regarding correlation between migraines and unspecified EDS subtypes. Three of these case studies included young, female patients with migraine and EDS. For example, Kumar et al. [1] reported a case on a 28-year-old Caucasian female who suffered from migraines and unspecified EDS. Di Palma and Cronin report on a 27-year-old female with cEDS that suffered from migraines without aura [15]. Additionally, Walter reported on a 15-year-old female diagnosed with EDS and had migraines three times a week with photophobia, phonophobia, nausea, and vomiting but denied any visual changes, numbness, tingling, weakness, or focal deficits [5]. Although these three cases are not specific to hEDS, the common factor is that these three women all had EDS and developed migraine at an early age. This commonality demonstrates a common neurologic characteristic of EDS and is an area of research that requires further investigation.

Idiopathic intracranial hypertension (IIH)

Idiopathic Intracranial Hypertension (IIH) is a condition characterized by raised Intracranial Pressure (ICP), and its diagnosis is established when an opening pressure measured during a lumbar puncture is elevated >20 cm H_2O in non-obese patients or >25 cm H_2O in obese patients [16]. IIH is more common in females with female to male ratios ranging from 15:1 to 4:1 and obesity being an added risk factor [10]. Neurological signs seen in patients with IIH include papilledema, enlarged blind spot, visual field defects, sixth nerve palsy, transient visual obscurations diplopia, tinnitus and intracranial noises [16,17].

There are multiple theories surrounding the pathophysiology of IIH. One theory is that the increased intracranial pressure is due to excess CSF production [18,19]. Other theories argue that IIH is due to obstruction of veins that drains blood from the brain leading to increase venous sinus pressure [19,20]. Although the exact mechanism may not be known, some studies demonstrates the role of elevated levels of GH, somatostatin, and IGF-1 in raising intracranial pressure [21,22]. According to a prospective study by Katz et al. [23] somatostatin receptor types 1 and 2 in human Choroid Plexus (CP) and Arachnoid Granulations (AGS) may be involved in cerebrospinal fluid production and absorption and may as well play a role in increased intracranial pressure seen in IIH.

One theory is a possible association between hypermobile type of EDS and risk of potential development of IIH mediated primarily through the effects of insulin-like growth factor-1 [24]. According to Hulens et al. [16] IIH, Fibromyalgia and chronic fatigue syndrome share a variety of symptoms that may all be explained by same pathophysiology of increased intracranial pressure. These conditions share a strong female predominance and are frequently associated with EDS. Although large case series have suggested an association between EDS and IIH, we are yet to see a causal association in biomedical literature.

Dysautonomia

Dysautonomia is a disorder of autonomic nervous system due to a failure or overactivity of the sympathetic or parasympathetic component [25]. Dysautonomia is prevalent in hEDS, but the exact cause is currently unknown and probably multifactorial in origin. According to study by De Wandele et al. [26] the result points to peripheral neuropathy as one of the common underlying mechanism. The neuropathy hypothesis supports the high prevalence of sensory neuropathic symptoms and insufficient sympathetic vasoconstriction seen in Valsalva and tilt-table test. This also could explain why Postural Tachycardia Syndrome (POTS) occurs so frequently in hEDS and why EDS and POTS frequently coexist [27,28]. Although controversial, some authors have speculated that blood vessels of patients with hEDS have increased distensibility, allowing for more venous pooling during the upright posture [28]. Some of the symptoms and signs of dysautonomia seen in patient hEDS include tachycardia, lightheadedness, palpitations, presyncope, chest pain, and syncope [28].

Temporal mandibular joint (TMJ) disorder

TMJ disorder has been shown to be a common disorder in EDS patients [29]. Tinkle and colleagues noted that there is a link in TMJ disorder and generalized joint hypermobility in both adults and children [30]. However, Mitakides [29] argues there is limited literature regarding TMJ disorder specifically in EDS patients [30]. From this limited research, there is indications that it is more commonly found in women and that there are multiple types of headache that present with unilateral or bilateral TMJ disorder pain in patients with EDS [29,30]. According to Mitakides [29] the pathophysiology could be attributed to muscles of mastication (temporalis, masseter, internal pterygoid, and external pterygoid) that are often involved in this pain [29]. It is likely due to muscle spasticity triggered by stress, postural disorders, clenching of the jaw, ischemia, osteoclastic compression degeneration, trigeminal neurologic input, or a combination of these that lead to pain associated with TMJ disorder [29]. The treatment for TMJ disorder in EDS patients should be "conservative, focused, and highly informed", which is important because the oral mucosa in hEDS patients is often easily injured and can lead to painless bleeding [29,30]. Although there seems to be a clear indication of a relationship between generalized joint hypermobility and TMJ disorder, the link between hEDS and TMJ disorder related headaches requires further investigation.

Craniocervical instability (CCI)

Craniocervical Instability (CCI), which is defined as a loose ligament condition that can occur in EDS patients [10]. CCI can occur when the ligaments around the skull and spine do not restrict movement that can cause damage leading to nervous damage, including headaches [10]. Additionally, CCI may be related to Chiari Malformation (CM), as discussed in the next paragraph [31]. Henderson and colleagues state that surgery may be needed in severe headache cases where non-surgical options have failed [10]. There is limited knowledge on how common CCI is in EDS patients and there are no established guidelines for treating patients with CCI, which provokes the need for research in regarding the relationship between these two diagnoses [10].

Chiari Malformations (CM)

Chiari Malformations (CM) is a "group of anomalies characterized by descent of the cerebellar tonsils or vermis into the cervical spinal canal" [32]. CM can result from known etiology. A case study showed there may be a genetically determined small posterior fossa volume as the etiology of CM [33]. Although there is variability in clinical presentation, basic clinical symptoms include occipital headaches, balance and coordination problems, as well as other cerebral signs. Many of the symptoms may be due to obstructed CSF flow and scar tissue development in the cerebellar tonsils and the compression of the cerebellum and spinal cord [33]. There may be a correlation between CM and EDS [33]. Nagy et al. [33] showed a patient with CM who reported daily occipital headaches were also diagnosed with Human Growth Hormone deficiency and EDS.

Conclusion

Headache is one of the common neurological symptoms seen in patient with EDS. It is more common in patient with hEDS subtype of EDS. Patients with this disorder have a wide range of symptoms that could affect multiple organ systems. As described, there are many theories explaining the pathogenesis of the various types of headache in hEDS. Most literature showed female predominance of the various types of headaches discussed compared to males.

The importance of understanding hEDS relationships to various headache types could be key in improving diagnoses and treatment of this syndrome. This paper focuses on the various neurological symptoms and headache types that can present in patients with hEDS. The challenge is limited observational studies to establish causal association between the various types of headache and hEDS. There is a need for continued investigation into the relationship between hEDS and neurologic symptoms. By understanding the relationship between the various types of headache and hEDS, physicians will have a better understanding of EDS and improve clinical diagnosis and treatment of this syndrome.

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