The Under-considered Comorbidity Between Ehlers-Danlos Syndrome and Epilepsy: a Literature Review

The need of additional research and information on the connection between connective tissue disorders and neurological symptoms is strongly highlighted by the majority of the experts in the field of multiple specialties, who are looking for better ways to diagnose, treat, and support patients showing these symptoms (Cortini, & Villa, 2018; Verotti, Spartà et al., 2014; Savastava et al., 2011; Verotti, Monacelli, et al. 2014; Henderson et al., 2017; Castori & Voermas., 2014; Ünalp et al., 2022; Kim et al., 2016).

The purpose of this literature review is to synthesize present studies and research on the neurological manifestations of Ehlers-Danlos syndrome (EDS), with a particular focus on the comorbidity of epilepsy, first recorded in 1972 (Cortini, & Villa, 2018). This correlation between the two disorders is still highly uncertain, and attributed to various symptoms, malformations, or malfunctions found in individuals with EDS. This literature review is thus presented in an active medical discussion, with strong and present effects on patients around the world.

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) is a group of genitive connective tissue disorders characterized by joint weaknesses that causes hypermobility, fragile and elastic skin, and easily-ruptured blood vessels—which is usually paired with repeating bruising (Savastava et al., 2011). Different variations of EDS are reported in medical literature, such as classic EDS or vascular EDS, in which the blood vessel fragility is more prominent, and can lead

to serious ruptures of arteries, namely the aorta, and hollow organs, such as intestines and the uterus (Sakka et al,. 2017).

The most common type of EDS is hypermobile Ehlers-Danlos syndrome (hEDS), which is accompanied by a 50% chance of passing the genetic mutation that causes the syndrome to each of a patient's children (Mayo Clinic, 2022). Frequently recorded complications include: joint dislocations or subluxations (partial dislocations), early-onset arthritis, and high-blood pressure related to the fragility of blood vessels (Mayo Clinic, 2022). Additional secondary symptoms can be proneness to injury, as well as longer healing periods, due to the fragility and elasticity of skin (Mayo Clinic, 2022).

The weakness of joints and other connective tissues can lead to instability, curvature of bones, and quick degeneration, as well as involuntary movement and malformations of the brain and/or spinal cord that can affect neurological function (Henderson et al., 2017). Lesser-known symptoms and complications are also likely to arise when EDS affects the development and functioning of the brain.

A multidisciplinary syndrome

The different varieties of Ehlers-Danlos syndrome (EDS) are being studied and assessed mostly by rheumatologists and geneticists, but part of the medical community is starting to push further the neurological study of the connective tissue disorder, because of the multiple neurological manifestations that can go undiagnosed without the presence of a trained neurologist (Castori & Voermans, 2014; Savastava et al., 2011). As such, Savastava et al. (2011), call for EDS to be considered a "multidisciplinary pathology with a

consequent multidisciplinary approach" (p. 370). If such an approach were to be taken, neurologists would be consulted in the initial phases of diagnosing Ehlers-Danlos syndrome in a way that would have the potential to significantly improve the quality of life of individuals with EDS who are presenting with neurological manifestations that are currently often ignored, until they become too concerning and dangerous.

The neurological manifestations reported in EDS patients can be divided into more common and known ones, and those that require extensive research to be completely understood. Common manifestations, which are still not to be underestimated, are chronic pain, migraines, and headaches. Additional known, but less understood, comorbidities include cerebrovascular disorders, intracranial hypertension, tethered cord syndrome, movement disorders, epilepsy, and brain malformations and lesions such as periventricular heterotopia, plexopathy, polymicrogyria, and Chiari I malformation (Savastava et al., 2011; Henderson et al., 2017; Castori & Voermans; 2014; Sakka et al,. 2017).

Conditions such as chronic pain syndrome, headaches, and migraines are often overlooked both by medical professionals and patients, as they tend to be considered insignificant, or not relevant enough to justify further examination and testing—especially when considering the elevated cost of medical support.

This tendency of undermining patient's experiences, whether because of ignorance or bias, is becoming a topic of mainstream discourse under the term of "medical gaslighting". The debate taking place majorly online, is thought to be a force

towards a desire for self-improvement from physicians, and can hopefully direct the medical community towards better practices in all specialties (Ng, et al., 2024)

Ehlers-Danlos syndrome and epilepsy

One of the neurological manifestations of Ehlers-Danlos Syndrome (EDS) is epilepsy in various forms. Epilepsy is the fourth most common brain disorder in the world and it presents with unprovoked recurring seizures—a manifestation of excessive electrical activity within neurons that alters the exchange of communication between brain cells (Epilepsy Foundation, n.d.). While epilepsy isn't always paired with physical impairments or daily disabling effects, different patients experience the disorder in personal ways, including but not limited to those who are unable to work or drive, and 1 in 1,000 people diagnosed with epilepsy who experience sudden unexpected death in epilepsy (SUDEP) (Epilepsy Foundation, n.d.).

The disorder is linked to a variety of causes such as genetics, brain trauma, autoimmune disorders, metabolic issues, or infectious diseases. Different causes and different elements of an individual's experience can lead neurologists to diagnose different types of epilepsy, such as sleep-related epilepsy, photosensitive occipital lobe epilepsy, eating epilepsy, and many more (Epilepsy Foundation, n.d.). However, it is often hard to know the exact cause, and many patients never receive an accurate source to their symptoms and are solely diagnosed with a generalized seizure disorder (Epilepsy Foundation, n.d.). As previously mentioned, one of the known and recorded connections to Epilepsy is Ehlers-Danlos syndrome (EDS).

A study by Savastava et al. (2015) reports the case of a 1 year old girl diagnosed with Ehlers-Danlos syndrome (EDS) and suffering from afebrile seizures. While seizures in infants might be common and inconsequential when high fevers are present, afebrile seizures are signs of underlying seizure disorders and further examination on brain matter and function was recommended to the patient.

The girl showed signs of periventricular heterotopia (PH), a condition where neurons of the brain fail to migrate in the optimal position during early stages of development because of collagen malfunctions; these neurons instead form nodules and lumps, which are often discovered after a first seizure is witnessed (MedlinePlus, 2020).

Periventricular heterotopia (PH) is recognized in multiple research studies as a possible cause of the comorbidity of EDS and epilepsy, as it is connected to collagen, which as a form of connective tissue is not entirely functional in EDS patients (Castori & Voermans, 2014; Cortini, & Villa, 2018; Sakka et al,. 2017; Savastava et al., 2011; Savastava et al., 2015; Verotti, Spartà et al., 2014; Verotti, Monacelli, et al. 2014).

In Savastava's case (2015) the study posed new questions as the patient showed unilateral PH, rather than the previously reported bilateral PH. The newly-found report is once again a reason to further investigate the neurological aspects of EDS.

Periventricular heterotopia (PH) is however not the only connection between EDS and epilepsy, as proven by Verotti, Monacelli, et al. (2014) in their study comparing EDS patients with and without PH showing symptoms of epilepsy. While the study does recognize a stronger connection and medication resistance when PH is present, the existence of EDS patients without PH does call for a more detailed understanding of the

comorbidity (2014). Verotti, Monacelli, et al.'s study (2014) connects the comorbidity to a "disruption in the link between the extracellular matrix and cytoskeleton with consequent malformations of the vessels and brain parenchyma" (p. 821). In other words, the supporting components of brain tissue (extracellular matrix) and the collagen proteins that shape cells (cytoskeleton) are not able to link in the correct matter; this disruption causes vessels and brain tissue including neurons and support cells (brain parenchyma) to develop in an abnormal way.

An additional structural malformation found in the linkage of Ehlers-Danlos syndrome and epilepsy is polymicrogyria—a condition in which the brain presents with irregular folds (giry) on its surface—as reported by Sakka et al. (2017). The case study of a 20 year old man with EDS experiencing seizures, appears to be one of the few cases reported in literature of polymicrogyria, EDS, and seizures, so it is hard to objectively determine the validity of Sakka et al'. findings (2017). It is however worth noting that the study (Sakka et al., 2017) brings to light an increasing trend of epileptic manifestations of Ehlers-Danlos syndrome: whether it be because of more efficient diagnosis of EDS, or because of actual changes in epidemiology, is another question that needs additional research to be answered.

These three similar hypotheses can be summarized by stating that epilepsy can be caused by different forms of structural abnormalities of the central nervous system, whether it be periventricular heterotopia, disruption in collagen proteins, and other alterations to the development of the nervous system. Consequently, the comorbidity with EDS is explained by all of these abnormalities being connected to irregularities of

different sorts of connective tissues and blood vessels—the parts of the body most affected by Ehlers-Danlos syndrome. As a matter of fact, Savastave et al. (2015) attribute the comorbidity to different organs and systems—including the nervous system—being particularly weak and failing structurally because of the elasticity of collagen found in connective tissue.

While these theories are accepted by many, Castori and Voermans (2014) call attention to the fact that the existing literature is not nearly enough to make such claims. The connection between epilepsy and Ehlers-Danlos syndrome can be attributed to structural and developmental abnormalities, but only partially—as other mechanisms and causes may be present, but still unknown because of the little amount of research done on this comorbidity.

Similarly, Verotti, Monacelli, et al. (2014) recognize that the data found in their study and similar ones is likely to be affected by the unknown amount of individuals diagnosed with EDS, but have asymptomatic periventricular heterotopia, those who present unknown neurological conditions, and all of those people who remain undiagnosed.

Ehlers-Danlos syndrome and other neurological manifestations

As previously discussed, epilepsy is not the sole neurological manifestation of Ehlers-Danlos syndrome (EDS). While this literature review focuses on epilepsy, it is still important to note and better explain the additional neurological disorders linked to EDS in order to gain an informed understanding of the condition. These neurological manifestations are also worth noting because of their highly debilitating effects on

patients, such as motor delays, coordination disorders, higher risks of neuronal injury, tremors, and spasms—which significantly reduce the quality of life of individuals with EDS who are already facing daily pain and fatigue. The conditions analyzed by Henderson et al. (2017) are reported to be particularly hard to detect and diagnose with standardized tests, requiring instead specialized studies that not all physicians are familiar with.

An example—intracranial hypertension—is described by Henderson and a team of members of the International Consortium on the Ehlers-Danlos Syndromes in a study to share with other medical experts at the EDS International Symposium (2017). The study researches neurological and spinal manifestations of EDS, focusing on epidemiology, etiology, clinical findings, treatments, and areas needing further investigation. For instance, intracranial hypertension is a condition in which the pressure surrounding the brain is particularly high due to the "excess cerebrospinal fluid (CSF) production, reduced CSF absorption, excessive brain water content, and increased cerebral venous pressure leading to reduced CSF reabsorption" (p. 197). Intracranial hypertension can cause intense sensitivity to light, and significant changes in vision, with 10% of patients reaching complete blindness (Henderson et al., 2017). Additional symptoms that can strongly affect quality of life based on their severity include headaches, nausea, vomiting, and tinnitus—a condition in which patients experience ringing in their ears, a noise that can be so loud it incapacitates the ability to hear external sounds and can result in hearing loss (Henderson et al., 2017; Mayo Clinic, 2022).

A different study, by Castori and Voermans (2014) delineates similar findings in regard to neurological aspects of Ehlers-Danlos syndrome. They heavily focus on

cerebrovascular diseases, highlighting the connection between EDS and its blood-vessel fragility with strokes, aneurysms, spontaneous brain bleeds, and tearing of cervical arteries. Vascular EDS can especially be the cause of strokes even in younger patients, who usually would not be considered at risk (Castori & Voermans, 2014). Because of these risks, EDS should be tested for whenever vascular concerns arise. Regardless of the clear signs in molecular testing that can easily identify the presence of vascular EDS, patients often face serious consequences because Ehlers-Danlos syndrome is not taken into consideration and thus goes undetected (Castori & Voermans, 2014).

Cerebrovascular manifestations in patients with EDS should also be regarded more seriously because of the dangers that can rise during treatment. The fragility of blood vessels can be severely impactful on how a condition can be treated, and often physicians opt for more conservative methods that lower the risk of fatal bleeds (Kim et al., 2016). While these methods may be effective, Kim et al.'s study (2016) claims that they are often not the treatments that best fit patients with connective tissue disorders and must be updated as soon as possible.

These studies (Castori & Voermans, 2014; Kim et al., 2016) bring to light unrecognized comorbidities with EDS and concerning treatment methods, once again sharing with the medical community the urgency of improving the research surrounding Ehlers-Danlos syndrome. The connection between the majority of neurological manifestations and EDS remains often completely unknown or unclear (Henderson et al., 2017., Casori & Voermans, 2014). This lack of research and limited knowledge severely

limits the access to diagnosis, which can be deteriorating if not fatal, to all EDS patients; or even those with unknown and unspecified connective tissue disorders.

Female population

Additional research should also focus on the gender disproportion found in patients diagnosed with Ehlers-Danlos syndrome. Some of the literature analyzed in this review briefly alludes to the gender disproportion of EDS, mentioning that women are more likely to have the connective tissue disorder rather than men (Henderson et al., 2017; Verotti, Spartà et al., 2014; Verotti, Monacelli, et al. 2014).

Both of Verrotti's studies (2014) have significantly more female patients—25 v. 17, and 77.3%—while Henderson et al. (2017) mention EDS having a "predilection" for females, in the same way chronic headaches and migraines do (p. 196). Interestingly, the topic is never brought to attention, regardless of the intense stress on requiring additional research.

While it can be argued that these studies focus on neurological manifestations of Ehlers-Danlos syndrome, and thus shouldn't necessarily highlight the gender disparity, as studies based on the necessity of moving research forward, it is surprising that such a prominent factor is so easily overlooked. The misdiagnosing of EDS can lead to pain, fatigue, and other symptoms to worsen significantly, which has the ability to affect the quality of life of individuals, leading people to "[leave] their jobs, education, hobbies, and other activities as well as losing social and support networks, leading to anxiety, depression, and even suicidal ideation" (Robbins, 2022. p. 175).

Ehlers-Danlos syndrome and other forms of connective tissue disorders are found in women with a 3:1 ratio compared to men, but still women are diagnosed on average with a delay of 16 years compared to 4 years delays for men (Robbins, 2022). One of the theories as to why women tend to be more likely to have EDS is related to the “rapid growth associated with puberty or due to the increase of estrogen” (Robbins, 2022. p. 175).

However, this theory is loosely accepted, and additional research is certainly needed. Unfortunately, it is not surprising that a condition that mostly affects women is yet to be understood and is undermined by medical professionals in a field predominated by men. It is also of extreme importance to conduct studies including women, as EDS can have significant symptoms tightly related to the female reproductive system, and can worsen during pregnancy and labor with the possibility of causing serious and debilitating injuries (Robbins, 2022).

Conclusion

All in all, it is clear that the scientific community has made great steps toward a better understanding of Ehlers-Danlos syndrome and its connection to neurological manifestations such as epilepsy. A variety of different phenomena have been analyzed by a multitude of physicians, and hypotheses have been made. A series of conditions related to the process of proteins and collagen, and the weakness of connective tissues have been linked to an abnormal development of the brain and spinal cord.

The most notable malformations of the nervous system that have been found in many patients with EDS are periventricular heterotopia, polymicrogyria, and unspecified

abnormalities caused by the impossibility of correct connection between neuron cells and collagen (Castori & Voermans, 2014; Cortini, & Villa, 2018; Sakka et al,. 2017; Savastava et al., 2011; Savastava et al., 2015; Verotti, Spartà et al., 2014; Verotti, Monacelli, et al. 2014).

However advanced and revolutionary these studies may be, scientists are still far away from fully understanding the matter, and extensive additional research is needed in order to provide care to patients living with debilitating conditions. Some of the conditions that accompany EDS can be fatal, such as epilepsy or strokes, and it is imperative that researchers keep the conversation open to new discoveries.

Everyone, from patients to doctors, will benefit from future research and understanding of connective tissue disorders. Such chronic illnesses can be overlooked and cause underlying disabling conditions that deepen the mistrust in doctors and the fear of reaching out for help. When physicians are unable to diagnose chronic conditions, people can tend to rely on the internet for support, which can be additionally dangerous because of the wide spread of misinformation.

Doctors and researchers must come together to support patients of conditions that can have a varying spectrum of symptoms that cannot be recognized by a single specialist. In the case of Ehlers-Danlos syndrome, it should become customary to refer patients to neurologists in the early stages of diagnosis. With this approach, epilepsy and other dangerous neurological conditions can be preventively treated or avoided altogether.

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