ZEBRAS OF MEDICINE:
PROVIDING PROPER CARE FOR PATIENTS BY ACCURATELY DISTINGUISHING BETWEEN EHLERS-DANLOS SYNDROME AND FIBROMYALGIA

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Abstract

Ehlers-Danlos syndrome (EDS) and fibromyalgia (FM) are two syndromes that are largely misdiagnosed and underdiagnosed. A lack of readily available tests and poor awareness of both disorders among medical professionals make patients greatly reliant on the ability of a clinician to recognise EDS or FM. While patients present with similar symptoms in both syndromes, including chronic pain, fatigue and depression, facets such as hypermobility should raise suspicion for EDS in a clinician. The rise in evidence for EDS and FM as comorbidities further complicates this story. This review outlines the difficulties clinicians face in diagnosing EDS and FM. It aims to provide an overview of the differences and similarities between EDS and FM in terms of clinical presentation, diagnosis, and treatment options. Elucidating these could contribute to improved care and treatment for both patient groups.

Introduction

Ehlers-Danlos syndrome (EDS) is a broad term for a group of heritable disorders affecting the connective tissue [1]. Classically, these disorders are mostly characterised by hypermobility of the joints and hyperextensibility of the skin. However, other symptoms such as extreme fatigue, chronic pain, cardiovascular symptoms, gastrointestinal problems, and neurological issues also often present themselves [1]. While 13 subtypes of EDS exist, the most enigmatic subtype is hypermobile EDS (hEDS). With a prevalence of 1 in 10000 to 1 in 15000, hEDS is considered the most common form of EDS, which is estimated to affect 1 in 5000 individuals [2]. In contrast to the other 12 subtypes, hEDS is not yet associated with specific genetic mutations. Therefore, hEDS is only presumed to be heritable, and it is actually classified as a multi-faceted disorder based on clinical characteristics. Additionally, EDS patients experience a wide range and onset of symptoms [2]. Because of this, the diagnosis of EDS is appreciably complicated for many patients.

This difficulty in diagnosing EDS presents itself in many ways. On average, patients have to wait 14 years for an accurate diagnosis, at least in part due to poor awareness of the condition amongst medical professionals [3, 4]. This average is highly skewed by female patients, whom doctors on average take 16 years to diagnose with EDS, compared to 4 years for male patients [4]. Women are likely diagnosed later because their symptoms are written off as common complaints or psychological issues [4]. Additionally, 56% of EDS patients received at least one misdiagnosis before their correct EDS diagnosis. Having a misdiagnosis also increases the time to reach a correct EDS diagnosis from 8 years to about 20 years [4]. One patient describes her experience as follows:

> One day I counted that I had received 32 incorrect diagnoses before the correct one. They ranged from "you have nothing" to "it's all in your imagination" to very severe ones, like cancer. Some doctors told me I could live a normal life, others told me I was going to die. ([4], p. 137)

One of the most prevalent misdiagnoses for EDS is fibromyalgia (FM). This is a common chronic pain disorder, likely affecting between 2 and 4% of the population [5]. Aside from widespread chronic pain, the primary symptoms include fatigue and cognitive difficulties. One study with 57 participants found that 26% of FM patients also fit the criteria for hEDS [6]. Additionally, hEDS may explain some or all of the symptoms that were previously assigned to FM. FM in itself is also an underdiagnosed disease, with as many as 3 in 4 patients remaining undiagnosed (data on file. Decision Resources report 2009. Pfizer, New York, NY). Many FM patients experience negative mental health outcomes as a result of the invalidation of others, which could be further exacerbated by the delay in FM diagnosis for many patients [7]. The time to reach an FM diagnosis averages 6.42 years, resulting in delayed treatment, decreased psychological health, and possibly sub-optimal care [8]. Many factors have been found to influence this delay, with comorbidities, the age of the patient, and the age of the physician being a few of them [8]. A survey of experienced physicians described that the majority of the physicians in question reported difficulties in diagnosing FM, with the main causes being inadequate training in and knowledge of FM [9].

As one can imagine, the tumultuous road to a diagnosis has severe consequences for EDS and FM patients. Prolonged feelings of hopelessness and isolation due to a lack of a proper diagnosis add to the psychological burden already imposed on patients due to their physical symptoms. Roughly 38% of EDS patients described harmful psychological consequences of the delayed diagnosis. Additionally, the delayed diagnosis was responsible for more general deleterious consequences in 86% of these patients [4]. A previous misdiagnosis in FM patients was associated with prolonged disease duration, possibly due to a delay in the correct treatment options [10]. Many commonalities exist between EDS and FM. However, a differential diagnosis is needed to provide proper treatment to patients. Therefore, this review aims to outline the differences and similarities between EDS and FM. Moreover, the possibilities of EDS and FM as co-morbidities will be briefly discussed and the treatment options for both disorders will be compared.

Zebras of Medicine providing proper care for patients by accurately distinguishing between Ehlers-Danlos syndrome and Fibromyalgia
- Robbin Kramer

Clinical presentation

EDS is a heterogeneous group of disorders with a common thread of symptoms, namely joint hypermobility, skin hyperextensibility and tissue fragility. However, the different EDS subtypes each also present with their own symptoms as classified in 2017 [1]. The presentation of the five most common and clinically relevant subtypes is summarised in Figure 1. Classical EDS is distinguished from other EDS-like disorders primarily by the presence of skin fragility, atrophic scarring, and soft "doughy" skin [11]. Classic-like EDS is comparable to classical EDS but is generally associated with mild muscle weakness instead of atrophic scarring [11]. EDS also contains two cardio-vascular subtypes, namely cardiac-vascular EDS and vascular EDS. Patients with these forms of EDS often experience progressive cardiac-valvular issues and arterial rupture at a young age respectively [11]. Lastly, hEDS generally presents with the least severe clinical symptoms of the subtypes, but severe skeletomuscular complications do occur [2]. Next to that, hEDS patients often suffer from extraarticular symptoms like fatigue, cardiovascular issues, bone mass issues, neurologic and spinal issues, psychological issues, and gastrointestinal symptoms [12]. These symptoms more often than not result in chronic pain problems in hEDS patients. While the frequency and degree of this pain vary, many hEDS patients report daily musculoskeletal pain [12].

Psychological aspects of all EDS types frequently include anxiety and depression [13]. The chronic pain that EDS patients experience, combined with the delayed diagnosis, likely contributes to this. One of the factors that complicates the recognition of EDS, and thereby can delay the diagnosis, is that hypermobility and flexibility are often confused. Hypermobility refers to the laxity of someone's ligaments that surround a joint, whereas flexibility refers to one's ability to lengthen muscles [14]. Unlike muscles, once ligaments are stretched, they cannot return to their original length. Hence, the problem with ligament laxity in EDS. Patients with hypermobile joints can actually present with muscle stiffness and muscle spasms due to the overactivity of the muscles to correct for the laxity in the joints [15]. Patients suffering from FM on the other hand, present with chronic widespread pain as their primary symptom. Here, chronic pain is defined as pain lasting more than 12 weeks despite treatment. Widespread pain is defined as pain in the axial skeleton, both above and below the waist and on both sides of the body [16]. Based on current literature, FM is thought to be the result of perturbances in the processing and regulation of pain in the brain [16-19]. Together with this widespread chronic pain, the other two primary symptoms of FM are fatigue and cognitive difficulties sometimes described as fibro-fog. As a result of the pain, other symptoms such as sleep disturbance, fatigue, concentration issues, and depression also frequently arise [5]. The sleep disruptions may result in abnormal neurotransmitter levels, further exacerbating the pain amplification [20]. Further key symptoms that could raise suspicion for FM in combination with the main triad include muscle tenderness, joint stiffness, and irritable bowel syndrome [19].

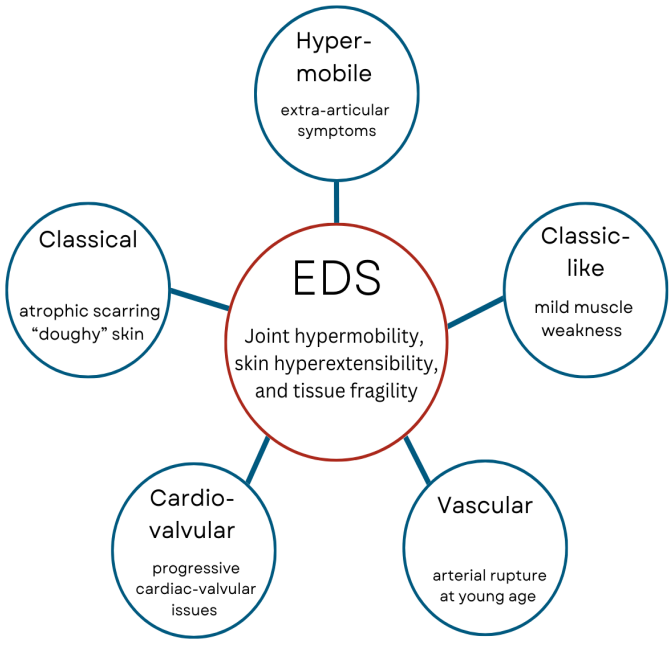

Figure 1 *- Overview of the clinical presentation of the most prevalent EDS subtypes.*

	Ehlers Danlos	Commonalities	Fibromyalgia
	Inherited connective tissue abnormalities	No definitive evidence yet	Hypersensitivity to pain
	Joint hypermobility, skin hyperextensibility, tissue fragility (subtype specific symptoms)	Widespread chronic pain, fatigue, anxiety, depression, GI issues	"Fibro-fog"
	Beighton score, exclusion of other joint hypermobility disorders, (genetic testing)	Systemic manifestation of symptoms	Pain location and duration, fatigue, "fibro-fog", symptom severity
	Genetic counseling	Multidisciplinary approach to manage symptoms	More vigorous exercise, antidepressants

Figure 2 *- A summary of the commonalities and differences between EDS and FM in terms of the cause of disease, clinical symptoms, diagnosis, and treatment. The FM diagnostic criteria of the 2016 version are presented here as it is more well known and commonly used than the 2018 criteria.*

The clinical presentation of EDS and FM overlaps quite a bit (see Figure 2). The key symptoms of FM can also be found in many EDS patients. Moreover, the pattern of autonomic symptoms, such as gastrointestinal, neuronal and spinal issues, is also very similar for EDS and FM [1, 19]. However, some differences in clinical presentations between EDS and FM should point a clinician towards the right syndrome. Hypermobile patients may counterintuitively present with muscle stiffness and muscle spasms. Although this can obscure the underlying issues of the patient, thereby complicating the clinical presentation of EDS, hypermobility should be a clear sign of EDS. Furthermore, the additional cardiovascular and scarring issues that are present in non-hEDS subtypes should assist a physician in making the distinction between EDS and FM.

Diagnosis

The diagnosis of EDS largely relies on the ability of a clinician to recognise the pattern of symptoms described above. Following a suspicion of EDS, further evaluation is needed to determine whether these are indeed consistent with EDS. This evaluation should focus on the extent to which the patient's body is affected by the possible underlying pathology [15]. Tests such as a CT scan, MRI or echocardiography can be used to further evaluate the effect of the underlying pathology [15]. Ultimately, the clinical diagnosis can

be verified using molecular screening for most EDS subtypes [11]. Apart from hEDS, all subtypes have been found to have a basis in one or more genetic mutations. Nonetheless, the absence of these confirmatory genetic results does not rule out an EDS diagnosis. Specific types of mutations are likely to go undetected by the current diagnostic molecular techniques [11]. Alternative diagnoses should certainly be reviewed in the absence of EDS-specific mutations.

However, hEDS is not so easily diagnosed, as it remains a fully clinical diagnosis without genetic confirmation. To be diagnosed with hEDS, patients need to simultaneously meet all three of the following criteria. First, they need to present with generalised joint hypermobility, as assessed by the Beighton score [11]. This test measures the mobility in five joints and assigns a score from 0 to 9 to the total hypermobility of the patient. Nevertheless, patients that score low can still score positively for joint hypermobility after consideration of other joints [11]. The Beighton score should be considered mostly as a diagnostic screening tool since factors such as age, stretching exercises and ethnicity affect joint hypermobility. The second criterion for hEDS is the presence of at least two of the following features: systemic manifestations of a more generalised connective tissue disorder; a positive family history in first-degree relatives; and musculoskeletal complications (e.g. musculoskeletal pain and recurrent joint dislocations in the absence of trauma) [11]. The last criterion requires the exclusion of alternative connective tissue disorders or other diagnoses that could include joint hypermobility (e.g. Marfan syndrome or skeletal dysplasias) [11]. Other symptoms are also abundantly present in hEDS but lack the sensitivity or specificity to be included in the formal diagnostic criteria. These include fatigue, gastrointestinal disorders, anxiety, depression and sleep disturbances [11].

FM used to be a diagnosis per exclusionem, meaning it could only be assigned to a patient if all other possibilities for a different diagnosis were exhausted [21]. Instead, the diagnosis is now based on a set of clinical criteria, similar to hEDS (Figure 2). One of the reasons for this is the current understanding that FM can and does co-occur with other chronic illnesses [5]. Many updates have been made to the diagnostic criteria for FM in the last three decades. The most recent criteria, established in 2018 and 2016, defined the core features of FM slightly differently. They both consider the duration and location of pain, but the 2018 version includes fatigue as a core feature, while the 2016 version assigns a score to the spread and severity of the pain symptoms [22, 23]. Additional features in the 2018 version that should point towards FM include but are not limited to generalised soft tissue tenderness, cognitive symptoms, and stiffness [22]. Opinions vary on whether these diagnostic criteria can fully capture the diversity in FM presentations, partly because of the diversity in this presentation and the large group of undiagnosed patients [24]. Diagnosis of FM is currently not supported by laboratory testing or imaging studies. Therefore, these tests should primarily be used to evaluate alternative diagnoses.

EDS and FM as comorbidities

Increasing evidence supports the presence of EDS and FM as co-occurring disorders. Multiple studies have reported an association between hypermobility and FM which is significantly above that caused by chance [25-29]. For example, 81% of FM patients had joint hypermobility and 40% of children with joint hypermobility had FM in a study of schoolchildren in 1993 [25]. Additionally, a study by Alsiri et al. found a 68%-88.9% prevalence of concomitant hEDS and FM diagnoses [30]. The two disorders are thought to co-exist due to their similar pathophysiology [31]. For instance, the central sensitisation that is thought to underlie FM likely amplifies the joint pain that results from hEDS. Moreover, hypermobility scores have also been found to significantly predict symptom levels in FM patients [32]. An explanation for this could be that joint hypermobility plays a role in the pathogenesis of chronic pain in FM. On the other hand, dysautonomia, a dysfunction of the autonomic nervous system, has also been proposed as a key link between FM and hypermobility. Both EDS and FM patients have higher frequencies of dysautonomia than the general population, and it has been proposed to be causal for some of the syndromes' symptoms [31]. However, the association between FM and EDS is still imperfectly understood [29]. Further research is needed to distinguish between misdiagnosed patients and patients with FM and hEDS as comorbidities.

Treatment options

Unfortunately, neither EDS nor FM is currently curable. EDS and FM treatment focuses on managing symptoms and limiting disease progression, thereby improving a patient's quality of life (Figure 2) [15, 33]. The primary treatment for EDS is physical therapy to strengthen the muscles and joints and prevent joint dislocations. Additionally, EDS therapy aims to manage the pain, fatigue and psychological symptoms experienced by EDS patients. Furthermore, blood pressure medication is prescribed to patients diagnosed with an EDS type with cardiovascular involvement to reduce stress on the cardiovascular system [15]. The pain patients experience in EDS is managed by the use of over-the-counter medication. Stronger painkillers are generally only prescribed for acute injuries [34]. Unfortunately, medical interventions are often only partially successful in treating FM. Therefore, much of FM treatment involves lifestyle changes, such as stress management, sleep habits, and a balanced diet [33]. The medications that are prescribed for pain relief include over-the-counter painkillers, antidepressants, and anti-seizure drugs. These drugs have the combined benefit of treating the depressive symptoms, as well as the sleep disturbances and pain of FM patients [33]. In both EDS and FM, patients are often provided with opportunities to acquire self-management skills to recognise and act on upcoming symptoms [15, 33].

A major risk of misdiagnosing a disease is harming a patient by giving improper treatments. Much of the lifestyle changes that are prescribed to manage symptoms are similar for EDS and FM, so this seems to pose less of a risk here. However, there is a notable difference in physical therapy regimens for both syndromes. Moderate to high–intensity aerobic exercises, such as yoga, Nordic walking or swimming, are well-tolerated by many FM patients and even recommended to reduce pain and depression and improve physical function [35]. However, while physical therapy for EDS patients includes strengthening exercises, these patients often experience a higher degree of exercise intolerance than FM patients [31, 36]. This intolerance can result in an exacerbation of symptoms in EDS patients due to exercise. Therefore, the proposed treatment for FM could aggravate EDS symptoms if a patient is incorrectly diagnosed and assigned the wrong treatment.

Conclusion

As both FM and hEDS suffer from severe underdiagnosis and misdiagnosis, a proper understanding of these two disorders is essential. The differential diagnosis of FM and hEDS is limited, but some characteristics can discriminate between the two disorders. Joint laxity and skin extendibility should alert a clinician to the possibility of one of the many subtypes of EDS. Both disorders are diagnosed by assessing a group of clinical symptoms, which underlines the essentiality of sufficient physical examination and

history taking. While treatment for EDS and FM overlaps as well, some pharmacological treatments are not to be used interchangeably for both disorders. What further complicates this story is the likelihood of analogous pathophysiology in hEDS and FM. In conclusion, further research is needed into the pathogenesis of hEDS and FM, as this might lead to more sensitive and specific diagnostics and treatment. As of now, more clinicians should be alerted by the clinical presentation of both hEDS and FM to start reducing the number of misdiagnoses and underdiagnoses in both disorders.

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