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Opinion

Narrow Diagnostic Criteria and Diverse Disease Manifestations: How an Emphasis on the Highly Visible Symptoms of Hypermobile Ehlers Danlos Syndrome May Delay Diagnosis

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Hypermobile Ehlers Danlos Syndrome (hEDS), is an inheritable connective tissue disease caused by abnormal collagen organization and production, consisting of diverse genetic and phenotypical variants. Clinical descriptions of hEDS are frequently limited to joint hypermobility and skin elasticity, but the generalized tissue fragility experienced by hEDS patients can result in the perturbation of multiple organ systems and intracellular processes. Patients with hEDS are primarily diagnosed by means of a clinical exam known as the Beighton scoring system. The Beighton exam is used to determine whether or not a patient's joints are hypermobile, a phenomenon where joints extend beyond normal ranges of motion. The Beighton scoring system is a modification of the Carter and Wilkinson scoring system (1964), both of which intend to identify hypermobility through a functional assessment of tissue laxity by examining the range of angular motion in isolated joints [1]. The Beighton test can be completed in a matter of minutes, without the use of sophisticated diagnostic equipment; yet, despite the accessibility of this diagnostic tool, patients with hEDS often suffer for years before discovering the origin of their unexplained chronic pain. A mean average of 14 years elapses between the first clinical manifestations of compromised connective tissue and reaching diagnosis, with 56% of hEDS patients being initially misdiagnosed and 86% of patients experiencing deleterious consequences due to diagnostic delay [2]. The discovery of compromised connective tissue, and its impact on multiple organ systems, frequently provides a unifying diagnosis for seemingly unrelated symptoms. Identifying an underlying connective tissue disease also provides patients and their care team with information that significantly informs healthcare decisions, as compromised connective tissue may increase the risks associated with surgical procedures, pregnancy, and certain forms of exercise. Patients with hEDS may be sent to a geneticist to eliminate differential diagnoses, but, ultimately, arriving to the diagnosis of Hypermobile Ehlers Danlos Syndrome is based off of the Beighton scoring system and concordant pain. But if the Beighton test is such a simplistic and widely available diagnostic tool, why must patients circulate the healthcare system for years before being given a diagnosis.

Ehlers Danlos Syndrome (EDS) is a group of inheritable connective tissue diseases, consisting of thirteen subtypes [3]. Each subtype of EDS is caused by a mutation in one of the many genes that produce and organize collagen, which bundles with other proteins into fibers that form connective tissue. Connective tissue binds and supports organs, joints, and the nervous system, and collagen plays a crucial role in the elasticity and tensile strength of this widespread tissue [4]. Alterations to the production and organization of collagen consequentially affects multiple organ systems, yet the description and categorization of EDS heavily relies upon an narrow sample of the patient experience, acknowledging highly visible symptoms (e.g., significant hypermobility in specific joints) while neglecting symptoms of low visibility that nonetheless have a specific impact on quality of life [5].

Hypermobile Ehlers Danlos Syndrome (hEDS), is the third and largest subtype of Ehlers Danlos Syndrome (EDS). It is also the only subtype that is still awaiting an identifiable gene mutation, meaning that hEDS patients must heavily rely on the Beighton scoring system and clinical diagnoses based primarily on symptoms [6]. As aforementioned, the Beighton test is a revision of the Carter and Wilkson's scoring system, both of which examine the angular rotation of a joint's normal motion to determine persistent generalized joint laxity [7]. Diagnostic criteria that only recognizes the visible symptoms of a complex condition, consequentially neglecting the reality of the condition's diverse manifestations, results in patients not receiving a diagnosis until their symptoms become debilitating or highly visible.

The Beighton scoring system may therefore only provide a diagnosis of construct validity for hEDS patients presenting with hypermobility in isolated joints. hEDS is almost exclusively understood as a condition that causes joint hypermobility and skin fragility, and while these symptoms are indeed experienced by those affected by hEDS, they are a narrow sample of the patient experience. Many patients struggle with gastrointestinal and cardiovascular symptoms for years prior to an identifiable change in joint alignment, and may receive several subsequent diagnoses, such as Postural Tachycardia Syndrome (POTS), Mast Cell Activation Syndrome (MCAS), and dysautonomia [8]. According to a patient reported survey by Zeitoun, et al. 79.3% of patients with a confirmed EDS diagnosis suffered from Gastro Esophageal Disease (GERD) and 48% reported symptoms congruent with Irritable Bowel Syndrome (IBS) [9].

A 2017 study of 35 adult EDS patients confirmed the high prevalence of autonomic and cardiovascular dysfunction, with 48.6% of patients having Postural Orthostatic Tachycardia Syndrome (POTS) and 31.4% having orthostatic intolerance (31.4%); [10] and a 2015 patient reported survey revealed that 66% of patients with confirmed diagnoses of POTS and EDS reported symptoms suggestive of Mast Cell Activation Syndrome (MCAS) [11]. Despite the high prevalence of comorbidities among hEDS patients, they are often excluded from the clinical and diagnostic criteria for connective tissue diseases. These symptoms are frequently misdiagnosed and poorly managed, as the scope of compromised connective tissue is often limited to joint related issues. Symptoms with low visibility are excluded from major diagnostic criteria, despite the fact that the diverse disease manifestations of hEDS may stem from a shared etymology; in the case of Hypermobile Ehlers Danlos Syndrome, seemingly unrelated symptoms affecting multiple organ systems may be the result of altered collagen production and organization.

The current diagnostic criteria for hEDS precludes the possibility of a timely diagnosis, as it lacks the sensitivity to accurately determine the degree and distribution of compromised connective tissue. The Beighton scoring system may proficiently identify benign joint hyper mobility in isolated joints, but it is limited to the visible and "shocking" symptoms of hEDS, such as severe joint dislocations and skin fragility. The diagnostic criteria for hEDS should reflect the scope of connective tissue, which is an integral part of multiple organ systems and physiological processes. Patients should not have to wait until they begin to experience highly visible symptoms to receive the dignity and care that accompanies an accurate diagnosis.

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