Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Hypermobile Ehlers-Danlos Syndrome: A Prodromal Subtype of Functional Movement Disorders?

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ABSTRACT: Background: The phenotypic diversity of functional movement disorders (FMD) is considered a reflection of its many etiological subtypes. Ehlers-Danlos syndrome (EDS), a joint hypermobility syndrome, also has variable phenotypes, which may include functional symptoms.
Objectives: To determine the prevalence of combined diagnoses of FMD and EDS.
Methods: We searched our Electronic Medical Records for patients carrying diagnostic codes for EDS and FMD. Further data extraction was done through chart review.
Results: Of 11,621 patients evaluated from January 1, 2016 to May 1, 2022, 16 carried a diagnosis of EDS, of which 9 (56.3%) were also diagnosed with FMD. Conversely, a diagnosis of FMD was documented in 190 (1.6%), of whom 16 (8.4%) were diagnosed with EDS. In all EDS-FMD cases, the diagnosis of EDS preceded the onset and diagnosis of FMD.
Conclusions: The co-occurrence of FMD and EDS is beyond chance, suggesting association. EDS may represent a prodromal subtype of, and share common pathophysiologic features with, FMD.

Functional movement disorder (FMD) is a common syndrome with a diverse phenotypic range and pathophysiology. Up to 20% of referrals to a movement disorder specialty clinic represent FMD.[1,2] Several models have been used to explain the development of FMD, supported by functional magnetic resonance imaging and other modalities.[3–9] Psychiatric, neurologic, and somatoform comorbidities are often seen in patients with FMD—anxiety, PTSD, depression, and migraine, as examples.[10,11] Ehlers-Danlos syndrome (EDS) is a joint hypermobility syndrome recognized by joint hypermobility, skin hyperextensibility and widespread tissue fragility.[12] While EDS can be suspected clinically, it can be molecularly defined by identifying pathogenic *COL5A1* or *COL5A2* mutations.

Of 13 described EDS subtypes, 12 require molecular testing for a confirmatory diagnosis. Only the hypermobile EDS subtype has a currently unknown genetic basis and remains a clinical diagnosis. Hypermobile EDS has been reported to include a range of neurologic and somatoform symptoms such as sleep disturbances, fatigue, functional gastrointestinal problems (such as irritable bowel syndrome [IBS]), widespread pain, anxiety, depression, postural orthostatic tachycardia syndrome (POTS), fibromyalgia, and small-fiber neuropathy. Painful fixed dystonia, a recognized FMD, has been reported in EDS.[13] We aimed to explore the frequency of EDS and FMD diagnoses in the same patients.

Methods

Our single center specialty clinic cohort was created utilizing our electronic medical record's "Slicer Dicer" (Epic Systems Corporation, Verona, WI, USA), analyzing the records of five Movement Disorder specialists from January 1, 2016 to May 1, 2022 to obtain the medical record numbers of patients with ICD codes for "functional movement disorder" or "conversion disorder with motor symptom or deficit" or "conversion disorder with mixed symptom presentation" and "Ehlers-Danlos syndrome." Individual chart review was performed for further data extraction and

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TABLE 1 *Ehlers-Danlos syndrome patient demographics, clinical characteristics, and genotype*

Patient	Age (yr)	Gender	FMD	Genotype	Comorbidities
1	35	F	Tics	*COL5A1* Classical EDS	Fibromyalgia, chronic pain, migraine, depression, anxiety, insomnia, POTS, Chiari I
2	19	M (transgender female to male)	Tremor *Functional speech (stutter)*	*ALDH18A1* (associated with Cutis Laxa (AR) and Spastic Paraplegia 9A (AD)) (Not EDS)	Fibromyalgia, Chronic Pain, Depression, Anxiety, Insomnia
3	23	F	Chorea, Dystonia Post COVID-19 infection	*NOTCH1* VUS (Adams-Oliver syndrome) (not EDS)	Chronic pain, migraine, depression, anxiety, POTS
4	36	F	Astasia-Abasia, Tremor	Neg WES	Chronic pain, Migraine, depression, anxiety, PTSD, insomnia, IBS, *Visual snow phenomena*
5	39	F	Tremor	Neg WES	Migraine, Fibromyalgia, Depression, Anxiety, Insomnia, POTS, IBS
6	42	F	Dystonia	Neg HCTD panel; FXTAS negative	Chronic pain, Migraine, Anxiety, Insomnia, POTS
7	19	F	Dystonia	Not tested	Chronic pain, Depression, Anxiety, PTSD, Insomnia
8	71	F	Myoclonus, Dystonia *Functional weakness*	Not tested	No pain, mood, or sleep disorder endorsed.
9	46	F	Tremor	Not tested	Fibromyalgia, chronic pain, Insomnia, IBS
10	32	F	*Functional weakness*	Not tested	Fibromyalgia, chronic pain, migraine, depression, anxiety, insomnia, IBS, POTS
11	29	F	None	*COL1A1* VUS Classical EDS	Chronic pain, Migraine, Insomnia, IBS, POTS
12	23	F	None	*COL1A2* VUS Cardiac valvular EDS	Generalized Dystonia Chronic pain, Migraine, depression, Anxiety
13	50	F	None	*SMAD3* mutation (Loeys–Dietz syndrome), *POLG1* mutation (not EDS)	Fibromyalgia, chronic pain, migraine, depression, anxiety, insomnia, POTS
14	64	F	None	Neg WES	Cervical Dystonia, Chronic pain
15	35	F	None	Neg WS	Fibromyalgia, Chronic pain, Migraine, Depression, Anxiety, Insomnia, POTS
16	38	F	None	Not tested	Chronic pain, Migraine, Depression, Anxiety, Insomnia

EDS, Ehlers-Danlos syndrome; HCTD, Heritable Connective Tissue Disorders; FXTAS, Fragile X Tremor Ataxia Syndrome; POTS, Postural Orthostatic Tachycardia Syndrome; VUS, variant of unknown significance; WES, whole exome sequence.

removal of extraneously "sliced" charts. All FMD diagnoses were made by a Movement Disorder specialist. All included patients with EDS carried this diagnosis with or without genetic confirmation. Age, gender, ethnicity, and movement disorder phenotype (if present) was recorded. Comorbidities extracted included: migraine, fibromyalgia, other chronic pain, depression, anxiety, insomnia, irritable bowel syndrome, POTS, and the presence of other neurological symptoms.

Results

During the study period, of a total of 11,621 patients evaluated. A diagnosis of EDS was documented in 16 (0.13%), of whom 9 (56.3%) were also diagnosed with FMD and one additional patient with functional weakness. A diagnosis of FMD (or prior conversion disorder terminology) was documented in 190 (1.6%), of whom 16 (8.4%) were also diagnosed with EDS. The diagnosis of EDS preceded the onset and diagnosis of FMD in all 16 patients with combined EDS and FMD. The prevalence of FMD in EDS patients compared to the clinic population overall suggests a significant association ($X^2 = 297.35$; $p < 0.00001$). All 16 EDS patients were female sex at birth (1 patient was transgender female to male); 11 (68.8%) were white, non-Hispanic; and their mean age at diagnosis was 37.5 years (range 19–71).

FMD phenomenology among EDS patients included tremor, dystonia, chorea, myoclonus, tics, and gait disorders; 3 patients had mixed movement phenotypes: dystonia with chorea, dystonia with myoclonus and functional weakness, and astastia-abasia/ataxia with functional tremor. One EDS patient had functional weakness without a movement disorder. Dystonia, as an isolated movement disorder, or as a mixed phenotype, was the most common FMD phenomenology seen in 3 of 9 FMD patients. Common comorbidities included chronic pain or fibromyalgia (15/16), anxiety (12/16), insomnia (12/16), depression (11/16), migraine (10/16), POTS (7/16), and IBS (5/16). EDS patient demographics, clinical characteristics, and molecular testing results are summarized in Table 1.

Pathogenic variants associated with EDS were detected in 1 patient (*COL5A1*) whereas variants of unknown significance (VUS) in COL1A1 and COL1A2 were ascertained in one patient each. The remaining 13 patients carried a diagnosis of EDS without genetic confirmation; 5 of these 13 were never tested. Mutations not associated with EDS were incidentally found by WES in 3 patients: *ALDH18A1*, *SMAD3*, and *NOTCH1* VUS. The patients with *COL5A1* and *ALDH18A1* mutations had functional tics and functional tremor, respectively. The *COL5A1* patient, with classical EDS, was the only genetically defined EDS patient with FMD. The *NOTCH1* VUS patient had a mixed functional phenotype with chorea and dystonia. The *COL1A2* VUS patient had generalized dystonia deemed organic by their movement disorder specialist. The *SMAD3* and *COL1A1* VUS patients did not have FMD. The *SMAD3* patient was referred for botulinum toxin consideration for migraine and the *COL1A1* VUS patient was referred for neck pain to rule out cervical dystonia; both had been previously diagnosed with POTS and IBS.

Discussion

In our cohort, FMD was commonly associated with EDS, with features diagnostic of FMD consistently emerging after the onset of those leading to the diagnosis of EDS. Furthermore, the prevalence of the co-occurrence between FMD and EDS phenotype/genotype is significantly greater than the prevalence of FMD in the overall movement disorder patient cohort, even as our clinic's FMD prevalence (1.6%) was below the range of other published rates seen in movement disorder specialty clinics (2–20%).[1] This emphasizes the strength of the association of FMD with EDS diagnosis ($X^2 = 297.35$; $p < 0.00001$), even excluding the patient with functional weakness in the calculation. Carrying the diagnosis of EDS may be associated with a pathophysiology overlapping with FMD and suggest that the EDS phenotype can manifest in the prodromal stage of FMD—before any movement disorder semiology become recognizable at the bedside.

Genetically confirmed EDS types do not classically have neurologic manifestations. However, comorbid migraine[14] and epilepsy[15] have been reported among hypermobile and molecularly defined EDS patients. Hypermobile EDS is characterized by chronic widespread pain, and many additional features beyond the diagnostic criteria have been described including anxiety, depression, sleep disturbances, fatigue, functional gastrointestinal disorders, fibromyalgia and other somatization disorders, small fiber neuropathy, and POTS.[12,16–19] Miller and colleagues searched for hypermobile EDS in 91 patients with POTS and found 28 (31%) meeting clinical diagnostic criteria.[18] Cazzato et al evaluated 24 patients with EDS (20 with hypermobile EDS, 3 with vascular EDS, and 1 with classic EDS) for small fiber neuropathy.[17] All patients had small fiber neuropathy per skin biopsy and 23 of 24 had neuropathic pain. Kassavetis and colleagues recognized a disproportionate amount of joint hypermobility syndrome in the history of their patients presenting with a fixed dystonia.[13] Of 44 patients included in the study with fixed dystonia, 9 (32%) were found to have joint hypermobility syndrome. Rapid onset fixed dystonia is part of the diagnostic criteria for functional dystonia.[20]

Pain, psychiatric symptoms, and other somatic/somatization symptoms associated with EDS and the EDS phenotype may be factors driving the development of (or sharing a pathophysiology with) FMD in these patients. In support of this, chronic pain, including migraine and fibromyalgia, are common comorbidities in FMD, with pain reported in 42% of 410 patients in a multicenter study.[21] In fact chronic pain is a prominent comorbidity, and potential precipitating factor, across the spectrum of functional neurologic disorders including PNES and functional weakness.[22–24] In our cohort all but 1 patient had comorbid chronic pain syndrome, including migraine and/or fibromyalgia. Chronic pain may be common in both EDS and FMD. In EDS, particularly hypermobile EDS, pain may be a symptom of somatization or secondary to repetitive injury related to joint hypermobility. Pain related to EDS or an EDS phenotype may prime the brain for the development of FMD.

Carrying the diagnosis of EDS, as extracted from an ICD search, does not necessarily equate to an accurate diagnosis of EDS. Without genetic confirmation, only hypermobile EDS can be diagnosed with clinical criteria alone. It is this subtype which is most associated with somatic symptoms. Presenting with a myriad of somatic symptoms to a number of physicians of various specialties may increase the likelihood of being diagnosed with

EDS without genetic confirmation or formal criteria-based diagnoses. Nevertheless, patients who carry the diagnosis of EDS, even if a potentially forme fruste phenotype, have higher odds for a subsequent diagnosis of FMD. The personality traits that lead to "doctor shopping," health anxiety and subsequent preoccupation as well as interoceptive or somatic hypervigilance are potential predisposing factors for developing FMD.[10]

There are several limitations to this study. This was a single center study with 5 movement disorder's specialists. The number of FMD patients may be underestimated overall and within the EDS patient sample. It has been reported that after making a diagnosis of FND only 22.8% of neurologists code for FND after the consultation.[25] There is also the chance of misdiagnosis of functional versus other movement disorder, which could have skewed our data. The rate of misdiagnosis of FMD is reportedly low, occurring in 4% of 1466 patients included in a meta-analysis of 27 studies.[26] A larger sample size from a more diverse pool of patients and physicians would be ideal to corroborate our findings.

In conclusion, a diagnosis of FMD was disproportionally prevalent among patients who carried a diagnosis of EDS. EDS may be a risk factor for the development of (or, through pain or other pathways, share commont pathophysiological mechanisms with) FMD. Alternatively, somatoform disorders with chronic pain underpinning the diagnosis of EDS (particularly hypermobile EDS, even if not meeting full diagnostic criteria) may be present in the "prodromal" phase of FMD. Future studies should investigate the genetic and phenotypic factors of those whose EDS increases the later expression of FMD and what about this group differ between age-matched controls.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

JM: 1A, 1B, 1C, 2A, 2B, 3A.

DP: 1C, 2C, 3B.

AJE: 1C, 2C, 3B.

Disclosures

Ethical Compliance Statement: Informed patient consent was not necessary for this work. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work.

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