Functional Movement Disorder Gender, Age and Phenotype (FMD GAP) study: A systematic review and meta-analysis of 4889 individual cases

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.

Abstract

Background

Functional movement disorder (FMD) is a common presentation of functional neurological disorder (FND). Patients present with diverse phenotypes such as tremor, weakness, and gait disorder. Our current understanding of the basic epidemiological features of FMD such as age of onset and gender is limited to small case series and unclear. We aimed to examine the relationship between age of onset, phenotype, and gender in FMD in a systematic review and meta-analysis of published and unpublished individual patient data (IPD).

Methods

Electronic searches of PubMed were conducted with a hand search of reference lists for studies of people with FMD reporting individual age of FMD onset and gender (M/F). Unpublished IPD were collected through a research network. We planned to describe the distribution of FMD age of onset and how this varied by gender and motor phenotype. A one-stage, IPD meta-analysis was performed using multilevel mixed-effects linear regression, including random intercepts for country and data source.

Findings

Published and unpublished IPD were combined for a total of 4889 individual FMD cases, 72.6% of whom were female. The mean age of FMD onset was 39.6 years (SD 16.1). Females had a significantly earlier age of onset. Mixed FMD (23.1%), tremor (21.6%), and weakness (18.1%) were the most common phenotypes. Compared to tremor (40.7 yrs), the mean age of onset of dystonia (34.5 yrs) and weakness (36.4 yrs) were significantly younger, and gait disorders (43.2 yrs) had a significantly later age of onset. The interaction between gender and phenotype was not significant.

Interpretation

FMD occurs across the life span but peaks in mid-life with varying effects of gender on age of onset and phenotype. The data supports 'lumping' FMD as a unitary disorder based on epidemiological characteristics and overlap but that there is also value in 'splitting' where relevant into individual phenotypes.

Funding

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Research in context

Evidence before this study

Functional movement disorder (FMD) is a subtype of functional neurological disorder (FND), in which neurological symptoms arise as a result of communication dysfunction in the nervous system. Patients with FMD can manifest a wide range of symptoms of altered movement including tremor and weakness. FND is encountered across all neurological sub-specialties depending on the presenting symptom. These distinct neurological features likely arise from common underlying mechanisms, representing different phenotypes of a unitary syndrome. The largest case series in FMD to date contains 410 patients, with many more published case series dedicated to a particular phenotype and its basic epidemiology is uncertain. For this reason, although FND is a commonly seen condition, it is not known whether different FMD phenotypes are associated with different ages of onset or if certain phenotypes exhibit gender differences. To answer these questions, we aimed to collect a large, simple dataset of gender, age of onset, and phenotype of published and unpublished FMD cases. We conducted a systematic review across all FMD phenotypes and combined it with data shared from an international group of FMD specialists to produce an individual patient meta-analysis of 4889 cases. We searched PubMed for studies from 1968 to 2019 using the following three key words: "functional", "psychogenic" or "conversion"; in combination with any of: "motor", "movement", "gait", "tremor", "dystonia", "weakness", "tic", "facial", "paralysis", "paroxysmal", "jerks", and "parkinsonism." This search was supplemented by reviewing the reference lists of eligible studies and previous reviews. After removing duplicates and ineligible studies, we included 1432 individual patient cases in our systematic review and meta-analysis. 3457 more unpublished cases were shared from our study group.

Added value of this study

This is the largest epidemiological dataset of functional movement disorders by a factor of ten. We included all phenotypes of FMD and also compared the results to a large dataset of functional seizures. We examined the distribution of age of onset of the total sample and within the most common phenotypes of FMD (tremor, dystonia, weakness, gait disorder, mixed, parkinsonism, and facial spasms), and if the distribution is modified by gender. To formally evaluate the association with gender and phenotype, a one-stage individual patient data meta-analysis was performed with age of symptom onset as the dependent variable in a multilevel mixed-effects linear regression model. Our results show that FMD can occur across the lifespan but peaks in mid-life, with a second peak in late adolescence. Dystonia and weakness have an earlier age of onset than other phenotypes, with myoclonus and parkinsonism being a little older. FMD more commonly occurs in women, regardless of phenotype. Compared to patients with functional seizures, people with FMD present later with a different population and gender distribution.

Implications of all the available evidence

Our findings support 'lumping' FMD as a unitary disorder based on epidemiological characteristics and overlap but that there is also value in 'splitting' where relevant into individual phenotypes.

Introduction

Functional movement disorder (FMD) is a common presentation of functional neurological disorder (FND). Patients present with a variety of symptoms of altered movement, including tremor, jerks, dystonia and gait disorders, often displaying combinations of multiple phenotypes. Although heterogeneous, patients with different forms of FMD share many clinical features including comorbid chronic pain, fatigue, and cognitive symptoms and aetiological risk factors.(1)

Despite the prevalence of FMD, an understanding of the basic epidemiology of the condition is limited. Large-scale epidemiological data are lacking as a result of the heterogeneity in presentation, as the majority of studies are smaller case series describing specific FMD phenotypes. It is not known whether different FMD phenotypes are associated with different ages of onset – for example whether functional parkinsonism is more common in older individuals – or if certain phenotypes exhibit gender differences, for example the reported higher incidence of functional axial myoclonus in males.(2) There is evidence that gender ratios may vary by age of onset in other forms of FND. In the largest case series of FND to date of 698 subjects diagnosed with functional seizures, the mean age of onset in women was significantly younger than in men, yet the onset was approximately equal between genders at the extremes of life.(3)

Characterizing such basic epidemiological data in a large sample can provide clues to underlying risk factors for developing FMD and possible underlying neurobiological mechanisms. In addition, framing FMD as a single entity with multiple presenting phenotypes enables the combination of a large number of cases for group-level analysis, affording the power to detect patterns in the larger group and individual phenotypes.

We therefore planned collection of a very large dataset of epidemiological data on FMD from 1) a systematic review and individual patient data (IPD) meta-analysis using published data and 2) with unpublished data from individual researchers. We hypothesized that women present with FMD symptoms at a younger age than men and that there would be gender differences among FMD phenotypes, which may be partly explained by differing age of onset.

Methods

Study design

An individual patient data (IPD) meta-analysis was performed including published and unpublished cases of patients diagnosed with FMD. The study was coordinated, and data were collected and managed, by the host site, the University of Toronto, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(4) The study was approved by the Research Ethics Board of the University Health Network, Toronto, Canada.

Eligibility criteria and phenotypic characterization

Inclusion criteria were applied at the study level. Studies were considered eligible if they contained individual patient data that satisfied three minimal criteria: 1) diagnosis of FMD classified as either "documented," "clinically established," or "probable;"(5,6) 2) age of FMD onset (either explicitly stated or derivable from comparing age and symptom duration entries), and 3) sex/gender were reported. We chose to use the term "gender" as we relied on patient self-report. Presenting phenotype, either from a results table or if a particular phenotype was the topic of the paper, was a secondary criterion.

FMD phenotypes were classified into the following ten categories, based on the most common FMD presentations: tremor, dystonia, gait disorder, weakness, jerks/myoclonus, mixed, facial symptoms, parkinsonism, other, and unknown/not documented. "Mixed" was included as a phenotype to encompass cases in which there was more than one phenotype present at onset, for example a mixed hyperkinetic phenotype e.g. tremor and a gait disorder, dystonia and facial symptoms, or weakness and gait disorder. "Facial symptoms" encompassed facial dystonic spasms/pulling. "Other" was included as a catch-all category for other distinct phenotypes. Inclusion of the "unknown/not documented" accommodated IPD which lacked phenotype characterization. Adults and children were considered eligible. Only reports written in English were included. FMD had to be the primary diagnosis and reports of patients with co-morbid neurological or "overlay" conditions were excluded.

Study identification and search strategy

Published data were collected from an advanced search on PubMed from 1968 to 2019 using the following three key words: "functional", "psychogenic" or "conversion"; in combination with any of the following key words: "motor", "movement", "gait", "tremor", "dystonia", "weakness", "tic", "facial", "paralysis", "paroxysmal", "jerks", and "parkinsonism." Titles that included the key words "seizure", "epilepsy", or "epileptic" were excluded to remove reports of dissociative/psychogenic seizures. All titles using the term "functional" unrelated to FMD or movement disorders were removed. The search was expanded by including all relevant references. Furthermore, additional records were identified through hand search, using the above-mentioned keywords, by one of the investigators, in order to increase the likelihood that no relevant studies were overlooked. The results from the systematic review were combined with the results from the hand search, removing all duplicates. Papers were then excluded if they were missing the requisite variables of interest (sex/gender or age of FMD onset), only group-level data was available and not IPD, or any cases where a "possible" level of diagnostic certainty was recorded. Individual corresponding authors of papers only reporting group-level data were contacted and asked if they wished to share their published data in IPD format.

Data sharing

Unpublished data were shared from experts in the field via an initial invitation to the Movement Disorders Society FMD Study Group

(https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Study-Groups/FunctionalMD-Study-Group.htm) Members were invited to contribute de-identified, unpublished data from their personal or research databases in compliance with their own institutional research ethics boards. All patients were required to have been diagnosed by neurologists with movement disorders training and derived from neurological settings. See Supplementary Methods for details of individual datasets that contributed to this analysis.

Outcomes

The outcomes of interest were the distribution of the age of FMD onset and whether this exhibited gender differences and/or differed by FMD phenotype, and whether gender moderated any differences between phenotypes.

Statistical analysis

Descriptive statistics were reported using means (SD) or frequencies (%), where appropriate. Histograms of age of symptom onset were generated for the entire sample, for each of the six main FMD phenotypes, and split by gender. A Doornik–Hansen omnibus test was used to assess multivariate normality of age of onset, which was repeated for males and females separately. To formally evaluate the association with gender and phenotype, a one-stage IPD meta-analysis was performed with age of symptom onset as the dependent variable in a multilevel mixed-effects linear regression model. Gender (male versus female) and phenotype (tremor; dystonia; gait; weakness; jerks/myoclonus; mixed; other/unknown) were included as fixed effects, whereas country (28 levels) and data source (109 levels) were included as random effects, to account for between-source heterogeneity. An interaction term between gender and phenotype was included in a second model to test for potential moderating effects, *i.e.* to detect if the effect of gender on age of onset differs by phenotype. We also planned a comparison of age of onset and gender with the largest sample of dissociative seizures, a distinct subtype of functional neurological disorder.(3) All statistical analysis was performed using Stata version 16.0 (StataCorp, Texas).

Results

Systematic review and data selection

The overall IPD selection process is summarized in **Figure 1**. See the Supplementary Results for a detailed description of the systematic review process. The total dataset consisted of 4889 individual FMD cases gathered from the systematic review and hand-search (n=862), shared published group-level data (n=570), and shared unpublished databases (n=3457). In total, 1432 individual FMD cases from published sources were included in the dataset.

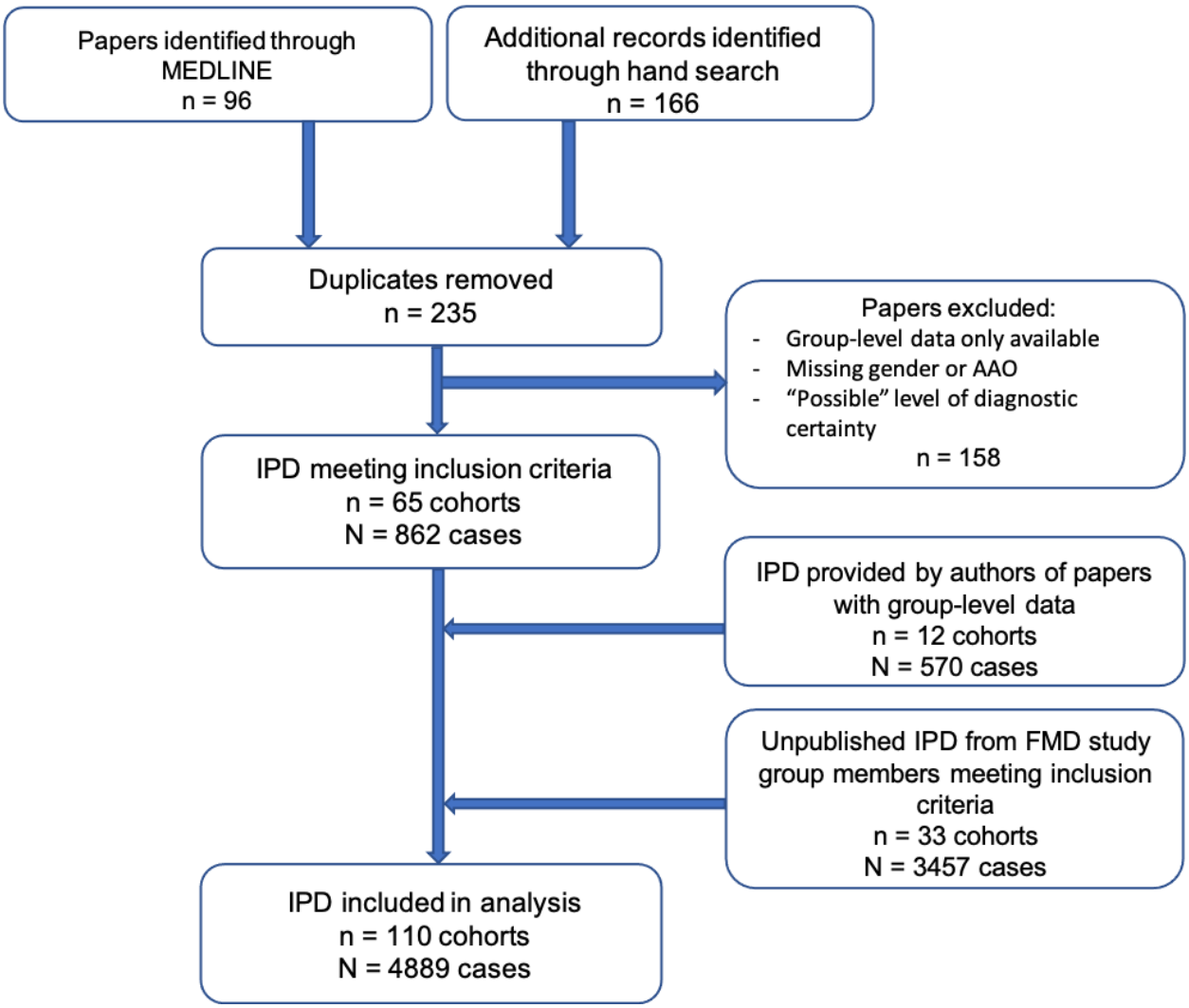

Figure 1. Data selection process including published and unpublished individual patient data. AAO, age of onset; FMD, functional movement disorder; IPD, individual patient data.

Data characteristics

A complete summary of the descriptive statistics is provided in **Table 1**. The cohort comprised 3549 (72.6%) female patients. The mean age of symptom onset was 39.6 years (median 39.7). Phenotype frequency ranged from 23.1% to 1.4%, the most prevalent phenotypes being mixed, followed by functional tremor (21.6%), and the least prevalent phenotypes being facial symptoms and parkinsonism. There were 479 (9.8%) entries of IPD missing phenotype characterization.

Table 1: Descriptive summary statistics of the total FMD sample

	n (%)	Age of onset Mean (SD)	Gender Female (%)
Total Sample	4889 (100.0)	39.6 (16.1)	-
Gender			
Female	3549 (72.6)	39.1 (15.9)	-
Male	1340 (27.4)	41.0 (16.5)	-
Phenotype			
Mixed	1127 (23.1)	42.1 (16.3)	848 (75.2)
Tremor	1056 (21.6)	40.7 (16.6)	752 (71.2)
Weakness	887 (18.1)	36.4 (13.4)	647 (72.9)
Dystonia	578 (11.8)	34.5 (14.8)	453 (78.4)
Gait	405 (8.3)	43.2 (18.4)	284 (70.1)
Jerks/myoclonus	221 (4.5)	39.7 (18.7)	140 (63.3)
Facial symptoms	67 (1.4)	37.3 (12.6)	56 (83.6)
Parkinsonism	69 (1.4)	45.0 (13.1)	36 (52.2)
Other/unknown	479 (9.8)	40.3 (15.8)	333 (69.5)

Almost half (42%) of the dataset came from the United States. The majority of the remainder of cases were from the United Kingdom, Europe, Australia, Mexico, and Canada. Countries in Africa, Asia, and South America were under-represented. The geographic distribution of the sample can be seen in **Figure 2** and Supplementary Table 4.

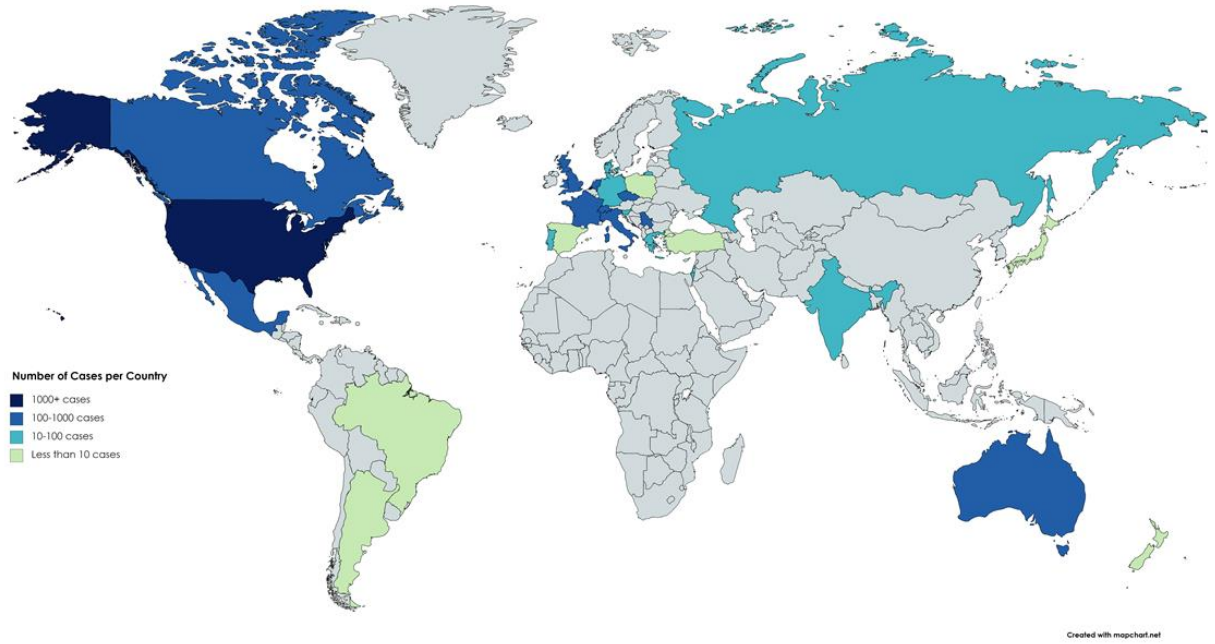

Figure 2: Geographical distribution of the total dataset, published and unpublished cases.

Whole sample

The distribution of the age of onset of the entire sample is presented in **Figure 3A**. The data approached a bimodal distribution with peaks between the ages of 16-22 and 35-45. The Doornik–Hansen test for multivariate normality indicated the data was significantly different to the normal distribution, which holds for males and females separately despite there being less skewness in the male group.

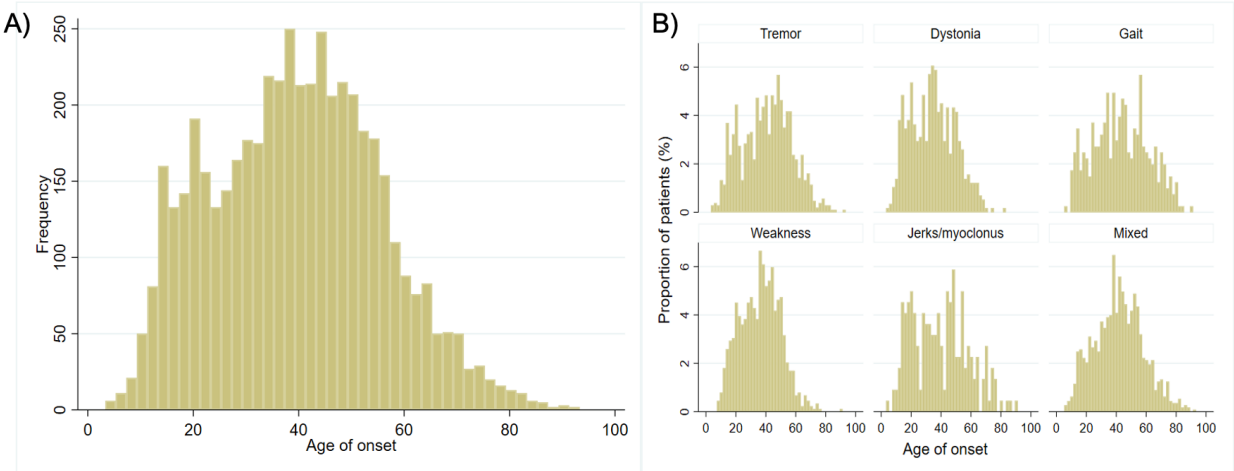

Figure 3: Histogram of FMD age of onset for the whole sample (n=4889) (3A) and separated by the six main presenting FMD phenotypes (3B).

Gender differences

When controlling for FMD phenotype (and heterogeneity between data sources within countries), males demonstrated a significantly older mean age of onset as compared to females (41.0 yrs vs. 39.1 yrs) (**Table 2**). Females represented greater than 64% of the sample across all age groups, with a tendency for more cases in the younger age groups (age 10-50) (**Figure 4A** and **4C**). By comparison, the age of onset of dissociative seizures in females produced a very different distribution with a clear early peak in late adolescence, tapering into adulthood. This is in contrast to a similar frequency across the lifespan in males (**Figure 4B**).(3)

Table 2: One-stage IPD meta-analysis multilevel mixed-effects linear regression model for age of symptom onset

	Coefficient (95% CI)	p-value
Phenotype		
Tremor (ref)	-	-
Dystonia	*-4.31 (-5.98, -2.65)	<0.001
Gait	*3.21 (1.39, 5.03)	0.001
Weakness	*-3.74 (-5.34, -2.13)	<0.001
Jerks/myoclonus	0.95 (-1.27, 3.17)	0.403
Mixed	0.32 (-1.05, 1.69)	0.650
Other/unknown	-1.10 (-3.18, 0.98)	0.300
Gender		
Female (ref)	-	-
Male	*1.67 (0.72, 2.63)	0.001

*Statistically significant at the p<0.05 level

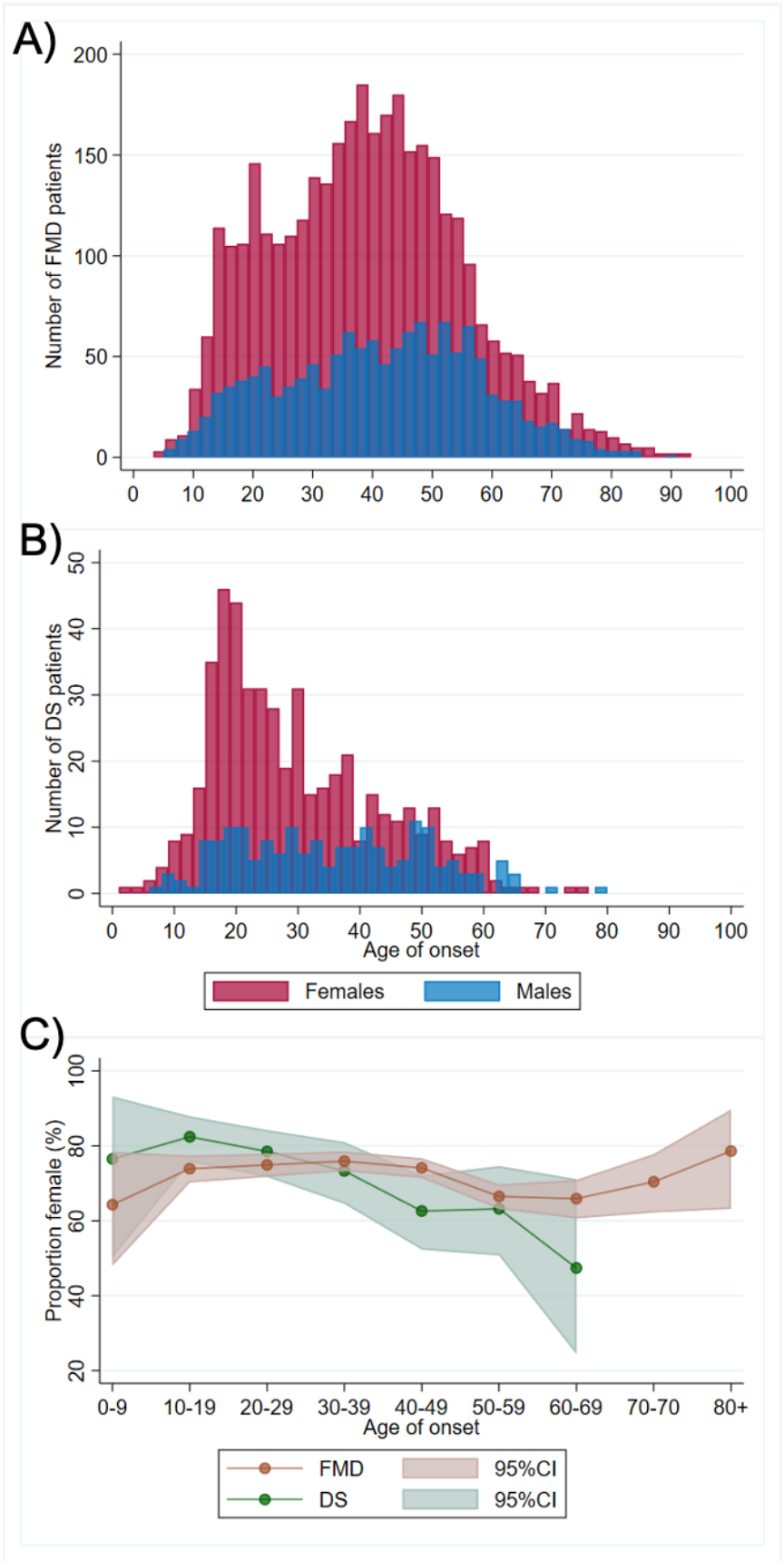
A)
Number of FMD patients
0
50
100
150
200
0
10
20
30
40
50
60
70
80
90
100
B)
Number of DS patients
0
10
20
30
40
50
0
10
20
30
40
50
60
70
80
90
100
Age of onset
Females
Males
C)
Proportion female (%)
20
40
60
80
100
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-70
80+
Age of onset
FMD
95%CI
DS
95%CI

Figure 4: Histograms showing age of onset distribution by gender in (3A) the whole sample of this study (n=4889) compared to (3B) the previously published UK sample of dissociative seizure patients (n=669).(3) The percentage of female patients within each age bin are overlaid in both graphs(B). 3C shows the comparison of FMD (red) and dissociative seizure (green) patients displayed as percentage female with confidence intervals.

Phenotype differences

The mean age of FMD onset was significantly different across FMD phenotypes when controlling for gender and data source within country random effects (**Table 2**). Compared to functional tremor, the mean age of onset of functional dystonia and functional weakness were younger by 4.3 years (95% CI, 2.7-6.0 yrs, $p<0.001$), and 3.7 years (95% CI 2.1-5.3 yrs, $p<0.001$), respectively. Functional gait disorder presented with a significantly older mean age of onset, by 3.2 years (CI 1.4, 5.0, $p<0.05$). The distribution of phenotypes (including "other") followed the same trajectory regardless of the number of cases, with for some symptoms including gait and dystonia, an early peak in the adolescent/early 20's, and a second peak in mid-life (30-40s) (Figure 5).

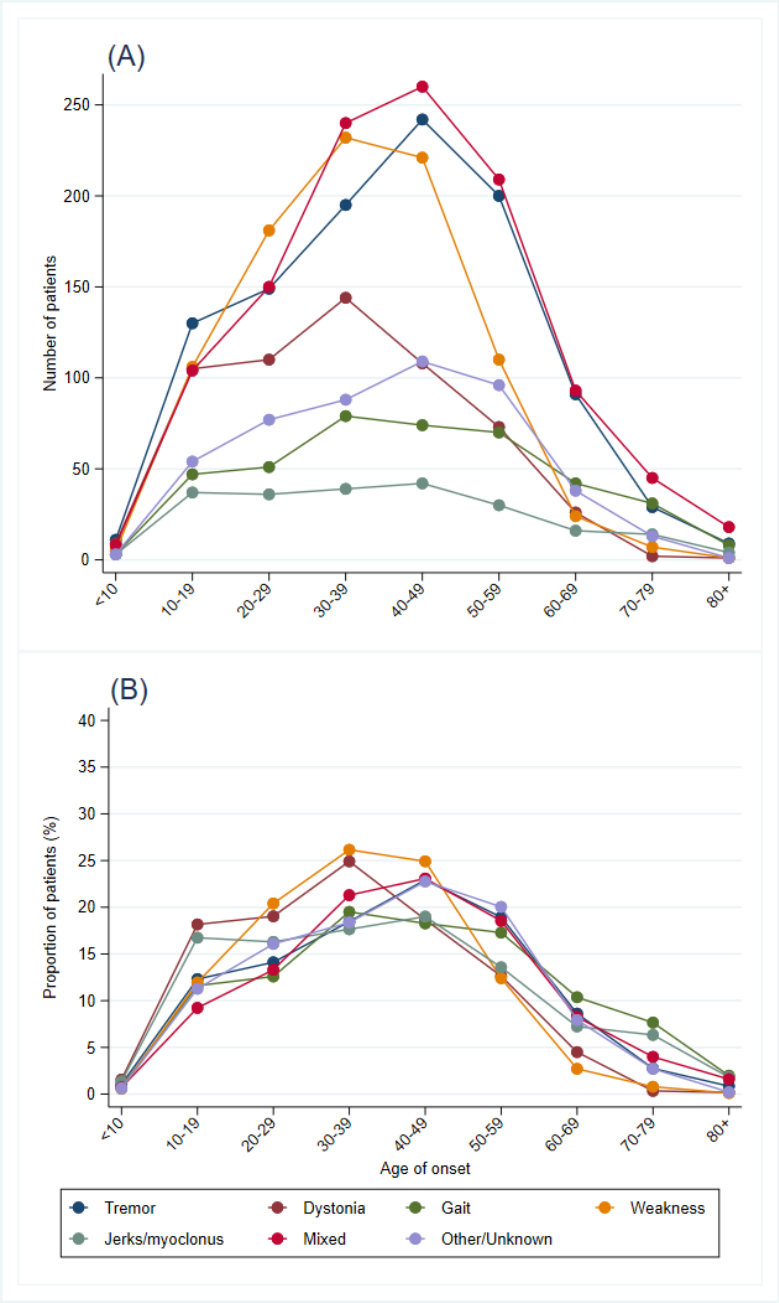

Figure 5: Connected dot plots showing age of onset in 10-year age bands by phenotype using (A) number of patients compared to (B) proportion of patients.

Gender and phenotype differences

Differences in ages of onset in relation to gender and phenotype are shown in **Figure 6**. Parkinsonism and jerks/myoclonus were seen more often in males, and parkinsonism tended to occur slightly older. Facial symptoms and dystonia occurred more often in females, with dystonia demonstrating the earliest age of onset. Tremor, gait disorders and mixed FMD

clustered together with overlapping confidence intervals. However, when including an interaction term between phenotype and gender into the multilevel mixed model, this was not significant (p=0.7566), which suggests one does not moderate the effects of the other.

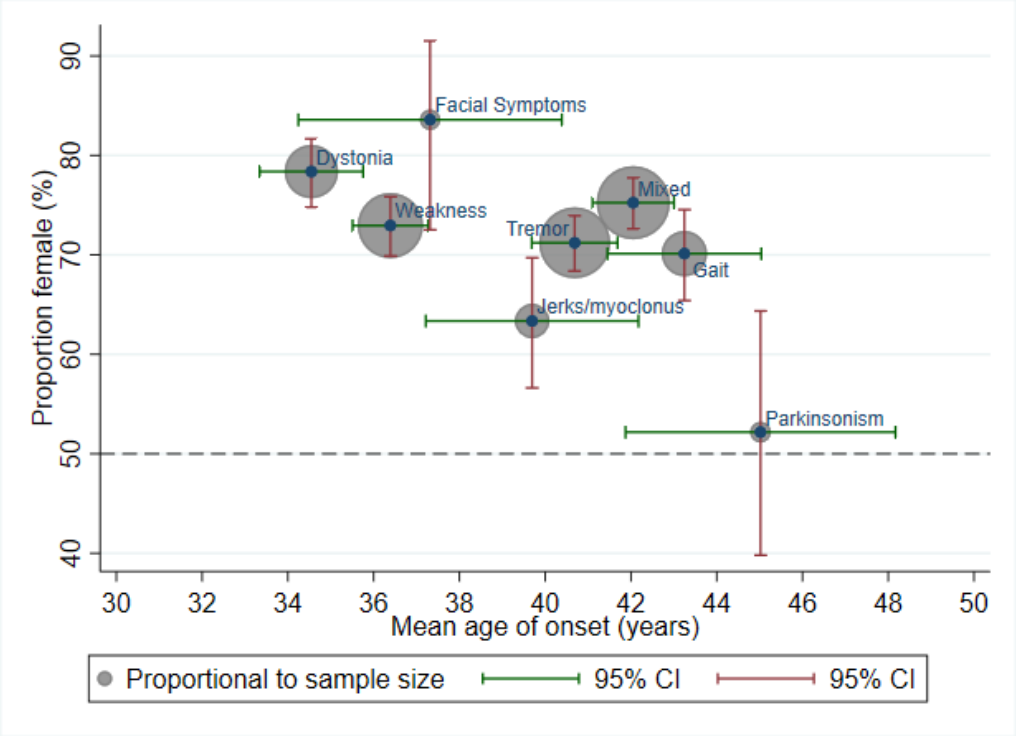

Figure 6: Mean age of onset compared to proportion of females by phenotype. The dashed horizontal line represents the point where the male:female ratio would be equal (50%).

Discussion

This large individual patient data meta-analysis of published and unpublished cases confirms previous studies demonstrating that FMD is more common in women, and symptom onset occurs in mid-life but provides much more fine-grained detail regarding the basic epidemiology of these disorders. The number of cases analysed is twelve times greater than the next largest study.(7) However, these results also demonstrate that FMD can be seen both as a single entity sharing common epidemiological characteristics, but also distinguishable phenotypes with somewhat different epidemiological features.

The onset of FMD occurs in mid-life, ranging from 35-55 years, although this probably underestimates pediatric and elderly cases.(8–11) A gender difference also has not been reported. In our sample, the age of onset of FMD was significantly younger in women by 1.7 years, similar to a previous study(12), but in both men and women the high standard deviation emphasizes that the onset occurs across the life span. Interestingly, this distribution differs substantially from dissociative seizures, another FND subtype. In that study, although the median age of onset was 28, the mode was much younger at 19 resulting in a skewed distribution (Figure 4) not seen in men who instead maintained a stable frequency of age of onset across the life span.(3) This pattern was distinct to that found in FMD, suggesting that the pathophysiology of these functional phenomena may not be identical . These results offer an interesting comparison between two well-described FND phenotypes which overlap phenomenologically but tend to be clinically managed in segregated pathways.(13) This analysis also raises the possibility that as well as shared predisposing and precipitating factors in FMD and dissociative seizures, there may be important differences which explain these different epidemiologies. For example, women as a group may experience disproportionate trauma or adverse life events at younger ages than men, predisposing them to developing dissociative seizures earlier in life; or the well-documented role of physical injury or illness in precipitating FMD (14) which may be less skewed towards younger age groups. Why certain individuals develop certain sub-phenotypes of FND is an important area of future study, and these results are useful for hypothesis generating.

Across the life span FMD occurs more commonly in women, who represent about three quarters of patients (73-75%), at the high end of previously published results.(15,16) Given the under-representation of pediatric and elderly cases in the sample we cannot be confident that this ratio is stable across the lifespan. Women are well-established to manifest higher rates of migraine, fibromyalgia, chronic fatigue syndrome, and other related functional disorders including irritable bowel syndrome.(17) This gender difference has been attributed to several factors including the higher reported incidence of anxiety, depression, and trauma in women, and that women are more likely to present to health services in general. Sex is a genetic modifier of disease pathophysiology, clinical presentation, and response to treatment. Gender influences on the behaviour of the community, clinicians, and patients is a social and psychological modifier of disease presentation, and a factor in determining how, when, and why a person accesses medical care as well as what diagnoses they receive.(17) These factors are of relevance to all of medicine, including FND. It should also be remembered that other

disorders such as multiple sclerosis and systemic lupus erythematosus are also much more frequent in women.

Mixed FMD was the most common phenotype, followed by tremor, weakness, and dystonia in keeping with other studies. Pediatric case series have also demonstrated tremor as the most common phenotype, followed by dystonia and myoclonus.(10) Patients with FMD commonly display multiple phenotypes, both at a cross-sectional point in time (for example at onset, as in this study) and over time.(18,19) Our results show that all phenotypes share the same distribution (Figure 5) which, together with the frequency of 'mixed' phenotype, further supports FMD as a unitary disorder. The geographical distribution of this sample was heavily weighted to North American and European cases, however transcultural studies have not shown significant phenotypic differences in FMD to date.(20,21)

Prior studies had found gender differences among FMD phenotypes, for example higher rates of dystonia in women (84%) (22), or axial myoclonus in men.(2) These results confirm that functional dystonia has a younger age of onset and is more often seen in women, and a higher proportion of men develop functional jerks and parkinsonism (Figure 6). Although the peak onset of FMD is between 34-44 years, dystonia and weakness tend to begin at the lower end of the range compared to a cluster of hyperkinetic FMD and gait disorders with onset over age 40.

The most significant limitation of this study is that two thirds of the IPD was shared from unpublished databases. We relied on each individual contributor to ensure that the data were accurate in terms of the age of symptom onset and phenotype, and an assumption that diagnostic clinical criteria were applied correctly. Although these cases were drawn from movement disorder specialists with a clinical interest in FMD, phenotypic characterization can be challenging in this population. However, "mixed", "other" and "unknown" categories, behaved as the more readily diagnosable phenotypes (e.g. tremor), suggesting that diagnosis in these categories was as reliable. Although we collected the largest dataset to date in FND, these data are drawn from clinic-based samples (many of which are from subspecialty movement disorders clinics) and may not reflect population-level epidemiological data. There was an underrepresentation of pediatric and elderly cases, and data in these age groups is less certain. The cases are heavily weighted to the North American and European centers and developed countries we did have. A post-hoc analysis using developed/developing country as a covariate in the main regression model did not impact the outcome.

In summary, FMD occurs across the life span but peaks in mid-life with varying effects of gender on age of onset and phenotype. This large dataset indicates that there is support for 'lumping' FMD as a unitary disorder based on epidemiological characteristics and overlap but that there is also value in 'splitting' where relevant into individual movement disorder phenotypes. This study provides a precedent for international data-sharing collaborations which is an effective and efficient way to synthesize data across sub-phenotypes in functional disorders.

Author contributions

S.C.L. – Conceptualisation, data curation, methodology, project administration, supervision, data validation, writing (original draft, review, editing)

M.C.P. – Data curation, project administration, data validation, writing (original draft, review, and editing)

T.E. – Data curation, project administration, writing (original draft, review and editing)

E.J.R. – Formal analysis, writing (original draft, review and editing)

J.S. – Conceptualisation, methodology, supervision, data validation, writing (original draft, review, editing)

FMD-GAP Study Group – Data sharing

Declaration of interests

All authors declare that there are no conflicts of interest.

Data sharing

Sharing the deidentified dataset and the protocol will be considered on a case-by-case basis after Article publication.

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