Clinical Correlates of Functional Motor Disorders: An Italian Multicentre Study

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ABSTRACT

Background: Functional motor disorders(FMDs) are abnormal movements that are significantly altered by distractive maneuvers and are incongruent with movement disorders seeing in typical neurological diseases.

Objective:1) to describe the clinical manifestations of FMDs, including non-motor symptoms and occurrence of other functional neurological disorders (FND);2) to report the frequency of isolated and combined FMDs and their relationship with demographic and clinical variables.

Methods: For this multicentre, observational study, we enrolled consecutive outpatients with a definite diagnosis of FMDs attending 25 tertiary movement disorders centres in Italy. Each subject underwent detailed clinical evaluation with definition of phenotype, number of FMD (isolated, combined) and assessment of associated neurological and psychiatric symptoms.

Results: Out of 410 FMDs (71% females; mean age 47±16.1 years) the most common phenotypes were weakness and tremor. People with FMDs had higher educational level than general population, and frequent non-motor symptoms, especially anxiety, fatigue and pain. Almost half of FMDs patients had associated other FND, such as sensory symptoms, non-epileptic seizures and visual symptoms. Subjects with combined FMDs showed a higher burden of non-motor symptoms and more frequent other FND. Multivariate regression analysis showed that diagnosis of combined FMDs was more likely to be delivered by a movement disorders neurologist. Also, FMDs duration, pain, insomnia, a diagnosis of somatoform disease and treatment with antipsychotic were all significantly associated to combined FMDs.

Conclusions: Our findings highlight the need for multidimensional assessment in patients with FMDs, given the high frequency of non-motor symptoms and other FND, especially in patients with combined FMDs.

Functional motor disorders (FMDs) are abnormal movements that are significantly altered by distractive maneuvers and are incongruent with movement disorders seeing in typical neurological diseases.[1] FMDs include disorders characterized by either poverty of movement (weakness and slowness) or hyperkinesia (tremor, jerks, and dystonia).[2]

Stressful life events[3, 4] have been associated to FMDs, but a clear psychological causation may be also absent.[5, 6]Accordingly, in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-V)[7], psychological stressors preceding the onset of symptoms are not needed for the diagnosis of functional neurological disorders (FND), but positive symptoms and signs should be taken into account.[2] Yet, inclusionary approach to FND diagnosis, at least in the movement disorders field,[8] is limited.

Despite being largely misunderstood and underestimated, FMDs are very common[9, 10] and negatively impact on quality of life and working life.[11, 12] Knowledge on their clinical features stem from small cohorts of single neurological services.[9] A few studies have provided insights on the frequency of different FMDs phenotypes and their association with non-motor symptoms and other FND.[13-16] However, these reports had a retrospective design[14] or were based on review of clinical notes or email contact with the treating neurologists[13] or included cohorts followed up in tertiary referral centres[16] or FND specialist clinics.[14] Finally, it is unclear if people having single (isolated FMDs) or multiple (combined FMDs) motor manifestations may differ for associated demographic and clinical variables.

Based on these premises, this cross-sectional multicentre study in a large Italian cohort of FMDs patients was designed: 1) to describe the clinical manifestations of FMDs, including non-motor symptoms and occurrence of other FND; 2) to report the frequency of isolated and combined FMDs and their relationship with demographic and clinical variables.

METHODS

For this cross-sectional study, data were extracted from the Italian Registry of Functional Motor Disorders (IRFMDs) managed by the Department of Neurosciences, Biomedicine and

Movement Sciences, University of Verona, and by the Italian Academy for the Study of Parkinson's Disease and other Movement Disorders (Accademia LIMPE-DISMOV). The IRFMDs prospectively collects data on symptoms, natural history, risk factors, and comorbidity in FMDs.

Subjects

Consecutive outpatients with FMDs were recruited from 25 tertiary movement disorders centres (11 in northern, 5 in central, 6 in southern Italy, and 3 in Sardinia/Sicily) between 1 September 2018 and 31 August 2019. Patients identified with one (isolated FMDs) or multiple FMDs (combined; i.e. dystonia + tremor) underwent standardized clinical assessment.

In order to be recorded in the IRFMD, patient's medical and medication history had to be documented by medical records or statements from informed relatives. Patient information was recorded using a web-based, encrypted and anonymized system in the website of the Italian Academy for the Study of Parkinson's Disease and other Movement Disorders (https://www.accademialimpedismov.it), which complied with General Data Protection Regulation.

Patients were assessed at each centre in a single session by a neurologist specialized in movement disorders. Inclusion criteria were: age ≥ 10 years, a clinically definite diagnosis of FMDs based on Gupta and Lang diagnostic criteria[17] with the presence of distractibility manoeuvres and demonstration of positive signs[18]; presence of one or more clinical symptoms including tremor[19], weakness[20], jerks[21], dystonia[22], gait disorders[23], parkinsonism[24], and facial motor disorders[25]. Exclusion criteria were presence of cognitive or physical impairment that precluded signing the informed consent form for participation in the study.

IRFMDs was structured in three main sections: demographic data, clinical history and diagnosis, and clinical manifestations. Demographic data included age, gender

(male/female) and education level (years). We further classified education level as primary (including the first five grades of school), secondary (from grade sixth to high school diploma), and tertiary (University). The second section included clinical history and diagnosis. This part documented the number of physicians, investigations and the previous diagnoses ("organic" and "non organic") predating the final diagnosis of FMDs. The third section screened for the clinical manifestations of FMDs: 1) onset of FMDs (acute, defined as abrupt with deterioration within a few days or weeks; slowly progressing) and disease duration; 2) presence of spontaneous remissions; 3) phenotypes: tremor, weakness, dystonia, jerks, parkinsonism, gait disorders, facial movement disorders; 4) presence of other FND: sensory functional symptoms, non-epileptic seizures (PNES), visual and cognitive functional symptoms, fibromyalgia, functional bowel disorders; 5) patients' self-reported non-motor symptoms: anxiety, fatigue, pain, headache, insomnia, panic attacks, and depersonalization/derealization; 6) certified neurological comorbidities as per neurologist's diagnosis: migraine, neuropathy, hyperkinetic motor and seizures, Parkinson's disease and/or parkinsonism, multiple sclerosis, and chronic cerebrovascular diseases; 7) certified psychiatric comorbidities, as per psychiatrist's diagnosis: anxiety, major depression, somatoform disorder, eating disorders, fugue state, personality disorder, post-traumatic stress disorder, bipolar disorder, sexual dysfunction, schizophrenia, impulse-control disorder/obsessive compulsive disorder, gender dysphoria; 8) childhood predisposing factors (psychological trauma, physical trauma), precipitating factors (psychological trauma, surgery, physical trauma, general anesthesia, infections, adverse drug reactions) and positive family history for neurological diseases; 9) investigations and therapies: medication history and previous physiotherapy, cognitive behavioural therapy, transcranial magnetic stimulation, and hypnosis.

Information about education levels of the Italian population was obtained from the website of the Italian National Institute of Statistics (ISTAT, http://www.istat.it); the statistics regard

primary, secondary, and tertiary education levels of the population > 6 years old, year of reference 2011).

Standard protocol approval, registration, and patient consents

Approval was obtained by the Institutional Ethics Committee of the Coordinator Centre (University of Verona, Azienda Ospedaliera Universitaria Integrata Verona, Prog. 1757CESC) and confirmed by the Committees of each participating centres. All patients (or their guardians) were informed about the nature of the study and gave their written consent to participate (consent for research). Participants were free to withdraw from the Registry at any time.

Statistical analysis

Data are expressed as mean ±standard deviation (SD and range for continuous variables, counts and percentages for categorical variables. The distribution of the patients' education levels was compared to that of the general population using a chi-square test. For groups comparisons, we employed unpaired t-test for continuous variables and chi-square test or Fisher's test (in case of expected frequencies $\leq$5) for categorical variables. Logistic regression models were created to estimate unadjusted and adjusted odds ratio (OR; 95% confidence interval [CI]) of combined FMDs (dependent variable) in relation to sociodemographic and clinical characteristics (independent variables). All tests were significant at $P < 0.05$. Statistical analyses were performed using SPSS statistical software (version 20; IBM-SPSS, Armonk, NY, USA).

RESULTS

Demographic data

We enrolled 410 patients with FMDs, 119 men (29%) (mean age 45.6±15.1 years, range 10-84) and 291 women (71%) (mean age: 47±16.1, range 10-85). Gender distribution was comparable among northern, central and southern Italy (p=0.81) (Supplementary Table S1). FMDs reported 11.7±3.8 years of schooling. Compared to the general population, the percentage of FMDs patients that attained only primary education was lower, while the percentage of those with secondary and tertiary education level was significantly greater (Figure 1).

Diagnosis of FMDs

The majority (N=257/410, 62.7%) had the diagnosis of FMDs in a hospital setting, most of them (N=322/410, 78.5%) from a neurologist specialized in movement disorders, far fewer from a general neurologist (N=71/410, 17.3%), a general physician (N=2/410, 0.5%), a psychiatrist (N=14/410, 3.4%), and a physiotherapist (N=1/410, 0.2%). 78% (N=320/410) of FMDs had been seen by one or more physicians (total sample: mean 2.7±2.5, range 1-25; isolated FMDs: mean 2.2±1.6, range 1-12; combined FMDs: mean 3.3±3.1, range 1-25) prior to receiving a definite diagnosis. Previously, patients received at least an “organic” (74.4%, N=238/320) and/or a “non-organic” diagnosis (24.7%, N=79/320). “Organic” diagnoses included: idiopathic/primary dystonia, Parkinson’s disease/parkinsonism, acute/chronic cerebrovascular disease, essential tremor, inflammatory nervous system diseases, disk herniation, epilepsy, ataxia, migraine. “Non-organic” diagnoses included: non-specific anxiety syndrome, conversion disorder, somatization, depression, “non-organic” disease, psychogenic disorder, hysteria, stress. Out of 320, sixty-two patients (19.4%) did not receive any diagnosis.

Clinical Manifestations

Acute onset occurred in the majority of cases (N=290/410, 70.7%). Approximately half experienced spontaneous remissions over the course of the disease (N=214/410, 52.2%).

Figure 2 reports the overall frequency of different FMDs phenotypes, their body distribution and associated non-motor symptoms as well as other FND. Table 1 reports neurological and psychiatric comorbidities, predisposing and precipitating factors, investigations and treatments.

The majority of the subjects had functional weakness (43.9%), tremor (40.7%), dystonia (29%) and gait disorders (26.6%), with most of them having one or more body districts affected. Lower limbs were more frequently affected in functional weakness (32.9%) whereas upper limbs were more frequently involved in functional tremor (34.1%). Hemiparesis was found in a smaller proportion of patients (N= 14 on the right side; N= 22 on the left side). Facial motor disorders occurred in 11.4%. For other motor phenotypes, abnormal movements affected with similar frequency all body parts.

FMDs patients often reported non-motor symptoms (83.9%) with anxiety (52.1%), fatigue (45.1%) and pain (41.9%) being the most frequent. Among other FND (occurring in 47.8% of subjects), sensory symptoms were the most frequent (25.3%). Interestingly 17.1% of FMDs patients had other comorbid neurological conditions, such as migraine and parkinsonism. Family history for neurological disorders was positive in 22.9%. A diagnosis of psychiatric disease was reached in 40.2% and childhood life stressors occurred only in 9.3%. Yet, a psychological trauma over lifetime occurred in 27.8% of patients and a physical trauma in 12.2%. Remarkably, 94.1% had undergone instrumental investigations before reaching the final diagnosis.

Demographic and clinical features in isolated and combined FMDs

Isolated (54.1%) FMDs were slightly more frequent than combined (45.8%). Table 2 shows the demographic and clinical features of these two groups. Age, gender, and education level were comparable between the two groups. Disease duration was longer in combined FMDs. Patients with combined FMDs had higher number of consultations prior to the diagnosis. All non-motor symptoms and other FND were more frequent in combined FMDs. Diagnosis of

combined FMDs was more frequently done by a neurologist specialized in movement disorders. Precipitating factors (surgery, anesthesia, adverse drug reactions), instrumental investigations, use of physiotherapy and of medications were more often reported by patients with combined FMDs (Table 2).

The univariate logistic regression model yielded a significant association between combined FMDs and many clinical and demographic variables (Table 2). After mutually adjusting for the variables reported in Table 3, the multivariate logistic regression model confirmed the association with the following variables: FMDs duration (adjusted OR 1.04; 95% CI 1-1.08), diagnosis made by a neurologist specialized in movement disorders (adjusted OR 7.09; 95% CI 1.57-31.9), pain (adjusted OR 2.05; 95% CI 1.21–3.48), insomnia (adjusted OR 2.09; 95% CI 1.19-3.68), somatoform disorder (adjusted OR 3.58; 95% CI 1.02-12.64) and use of antipsychotics (adjusted OR 2.85; 95% CI 1.09-7.38).

DISCUSSION

The results of this large multicentre cross-sectional study provide novel insights on patients with FMDs. Weakness and tremor were the most frequent FMDs phenotypes, more often affecting respectively the lower and upper limbs. People with FMDs had higher educational level, and frequent non-motor symptoms, especially anxiety, fatigue and pain. Almost half of FMDs patients had associated other FND, such as sensory symptoms, PNES and visual symptoms. When stratifying based on the presence of one or more FMDs, subjects with combined FMDs showed a higher burden of non-motor symptoms and more frequent occurrence of other FND. Multivariate regression analysis showed that FMDs duration, pain, insomnia, a diagnosis of somatoform disease were significantly associated to combined FMDs. Moreover, the diagnosis of combined FMDs was more likely to be delivered by a movement disorders neurologist. Finally, treatment with antipsychotic was significantly associated to having combined FMDs.

Demographic and Clinical features of Functional Motor Disorders

While confirming the higher prevalence of female gender[26] in the whole sample, the proportion of FMDs patients with a higher education level was greater than in the general population. There are no previous published data on educational level in FMDs, except two studies performed in small cohorts (N=42[27] and N=30[28]) which reported primary education level in most of the subjects. However, in a recent study of 132 subjects, 57% of FMDs had a college or higher degree.[29] This is an opposite trend compared to neurodegenerative and cardiovascular diseases which are associated with poor education.[30] Interestingly, it was demonstrated that higher educational level is associated with lower severity of motor impairment in Parkinson's disease.[31] Higher education level might be correlated to higher socio-economic status, but it is uncertain if these could be considered risk factors for FMDs and how it could modify their phenotype. Moreover, our data should be carefully interpreted as representative of the Italian population, as Italy has the lowest percentage of subjects aged 15-64 years who attained a higher educational level (2018 data, https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=edat_lfs_9903&lang=en).

Cross-cultural comparisons of educational level are needed.

Phenomenological description of FMDs has been extensively reported in the literature[2, 13, 14, 16, 25, 32-36], but most of these studies have a retrospective design and/or were based on tertiary movement disorders referral centres or specialistic FND clinic. Indeed, data on prevalence of different phenotypes from large cohorts are missing. A small single-centre retrospective cases series (N=28) from a Movement Disorders Clinic, identified tremor and dystonia as the most frequent FMDs manifestations.[37] A large multicentre Scottish study reporting 209 patients diagnosed with conversion disorder, showed that among 56 FMDs subjects, functional weakness was the most frequent clinical manifestation (62.5%) followed by movement disorders (16.1%).[38] However, in the same study there was no mention about the frequency of each FMDs phenotype. Among 410 patients, we showed that weakness,

tremor and dystonia were the most represented phenotypes (respectively 43.9, 40.7 and 29%), with weakness affecting mainly the leg.[20] The predilection of different phenotypes for specific body parts has been never investigated but it might be related to the nature of trigger or risk factors associated to them.

In our sample, the clinical spectrum of FMDs was often enriched by a constellation of physical and psychiatric symptoms, such as anxiety, pain and fatigue. Pain and fatigue are very common symptoms in FMDs and should be recognised when planning treatment strategies.[13-15] In addition, patients often had functional sensory symptoms (25.3%) and PNES (13.6%), which represent the most frequent FND manifestations in outpatient clinics.[38]

A formal psychiatric diagnosis, more frequently anxiety and depression, was delivered in 40.2% of subjects and only a minority of them reported childhood predisposing trauma. More frequently, FMDs had precipitating factors, including psychological trauma or surgery and physical trauma. These findings reflect the complex interplay between life events, physical triggers and biological features which lead to development of FMDs. In addition, they further support to discard the dichotomy between mental and brain disorders which has been swept away by several evidences for a biological model of FMDs generation.[39]

Diagnostic challenges in FMDs patients

Most of the patients (78%) reported multiple consultations and numerous tests before receiving a diagnosis of FMDs. This data might be explained by the so-called “doctor shopping”, a patients’ practice which we believe might reflect several issues associated to the FMDs diagnosis, including miscommunication between physicians and patients, reluctance/failure to accept the diagnosis, absence of a clear therapeutic plan and treatment goals.[40] Likewise, misdiagnosis might be a significant determinant for multiple consultations and investigations. In our sample, this hypothesis is supported by the evidence that two third of patients had a previous diagnosis of an “organic” disease and people with combined

FMDs received more frequently the diagnosis from a movement disorders neurologist. Indeed, misdiagnosis may arise from lack of expertise for these disorders or poor diagnostic agreement especially when dealing with jerks and functional gait disorders.[41]

On a different perspective, our data demonstrates that FMDs may also occur over the course of other neurological diseases, as it has already reported with Parkinson's disease[42] and epilepsy.[43]

High burden of associated symptoms in combined FMDs

This is the first study to estimate the overall frequency of isolated and combined FMDs and to analyse the association with clinical variables. Some symptoms (weakness, tremor, dystonia and gait disorders) occurred by far more frequently in combination than in isolation, a pattern known so far only for functional gait disorders.[23] Patients with facial motor disorders are also known to develop often dystonia in the upper limbs, albeit most of the time they have a facial onset.[25]

Many factors were associated to combined FMDs, but only a few survived multivariate logistic regression analysis. All these factors may reflect the challenges in diagnosis and treatment of patients with FMDs. Specifically, the fact that combined FMDs had long duration of symptoms and needed more frequently a movement disorders neurologist to reach a diagnosis is in keeping with the tortuous diagnostic pathway and the difficulty in evaluating complex phenotypes (for example dystonia combined with tremor and/or gait disorders). The high frequency of pain and insomnia in this group of patients might be related to each other as chronic pain and sleep disorders are often comorbid.[44] Many factors may contribute to pain generation in combined FMDs, such as long duration of symptoms; yet, pain in combined FMDs seems to be an independent variable from co-occurrence of headache and fibromyalgia. Still, our data do not clarify how pain and insomnia impact on level of disability and quality of life in FMDs and which strategies might be successful in their treatment.

Novel and interesting associations with combined FMDs are a more frequent diagnosis of somatoform disorder and use of antipsychotics. Clinical trials on antipsychotics in FMDs are lacking, although there are anecdotical reports of antipsychotics use in a few patients with PNES.[45] This data might be also explained by the results of a recent Cochrane review, which disclosed a low-quality evidence in favour of combination treatment of SSRIs and antipsychotics in patients with somatoform disorders.[46] This is a data to verify in prospective cohorts assessed with detailed psychiatric assessment, given the potential for antipsychotic medications to cause drug induced movement disorders.[47]

Limitations, strengths and final remarks

The main limitation of our study is the lack of a control group as well the use of many variables based on clinical records or patient's interview. Yet, the cross-sectional design allowed us to have a standardized collection of clinical data in all centres. Moreover, we could not determine the severity of recorded symptoms as we did not employ any rating instrument for them. Finally, frequency of psychological stressor might be underestimated as we did not include a formal psychiatric interview.

The main strength of our work is represented by the large multicentre sample of FMDs patients that is representative of the whole Italian national territory. This allowed us to provide novel knowledge on a wide range of motor disturbances and their associated symptoms. Moreover, the diagnosis of definite FMDs[17] was here confirmed by a movement disorder neurologist.

That is, our findings highlight the need for multidimensional assessment in patients with FMDs, given the high frequency of non-motor symptoms and other FND, especially in patients with combined FMDs. Future prospective studies are needed to clarify how these factors affect quality of life and prognosis in different FMDs phenotypes in order to develop specific management strategies.

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ETHICAL COMPLIANCE STATEMENT

Approval was obtained by the Institutional Ethics Committee of the Coordinator Centre (University of Verona, Azienda Ospedaliera Universitaria Integrata Verona, Prog. 1757CESC) and confirmed by the Committees of each participating centres. All patients (or their guardians) were informed about the nature of the study and gave their written consent to participate (consent for research). Participants were free to withdraw from the Registry at any time. 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.

LEGEND TO FIGURES

Figure 1. Education levels in the Italian population aged > 6 years (reference year, 2011) and the Italian Registry of FMDs population (age range 10-85) (total sample is 364, 46 missing values).

Figure 2. Clinical symptoms reported in patients with FMDs; patients can have one FMDs (isolated, e.g., only tremor or weakness) or more FMDs (e.g., weakness + tremor + gait disorders). A= represents the different FMDs phenomenologies and their body distribution. B= represents patient self-reported non-motor symptoms and other FND. The bar represents the percentage while the number above shows the absolute value. PNES, nonepileptic seizures; FS, functional symptoms; FMDs, Functional Motor Disorders; FND, Functional Neurological Disorders.

Supplementary Table S1. Gender distribution of FMDs among Italian regions.

Supplemental Appendix S1. Co-investigators. Italian Registry of Functional Motor Disorders (IRFMDs) Study Group.

Figure 1

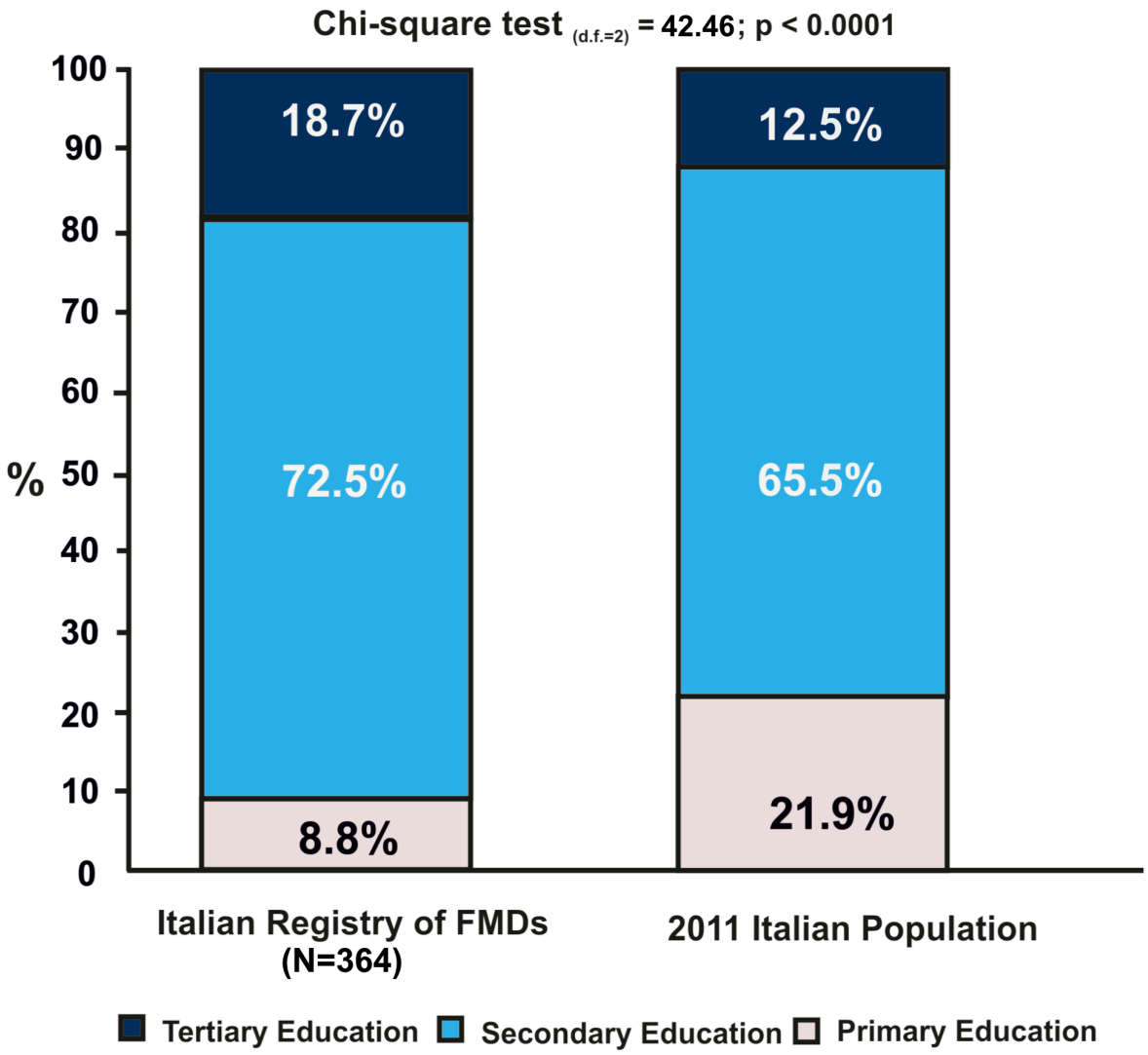
Chi-square test (d.f.=2) = 42.46; p < 0.0001
100
90
80
70
60
%
50
40
30
20
10
0
18.7%
72.5%
8.8%
12.5%
65.5%
21.9%
Italian Registry of FMDs
(N=364)
2011 Italian Population
Tertiary Education
Secondary Education
Primary Education

Figure 2

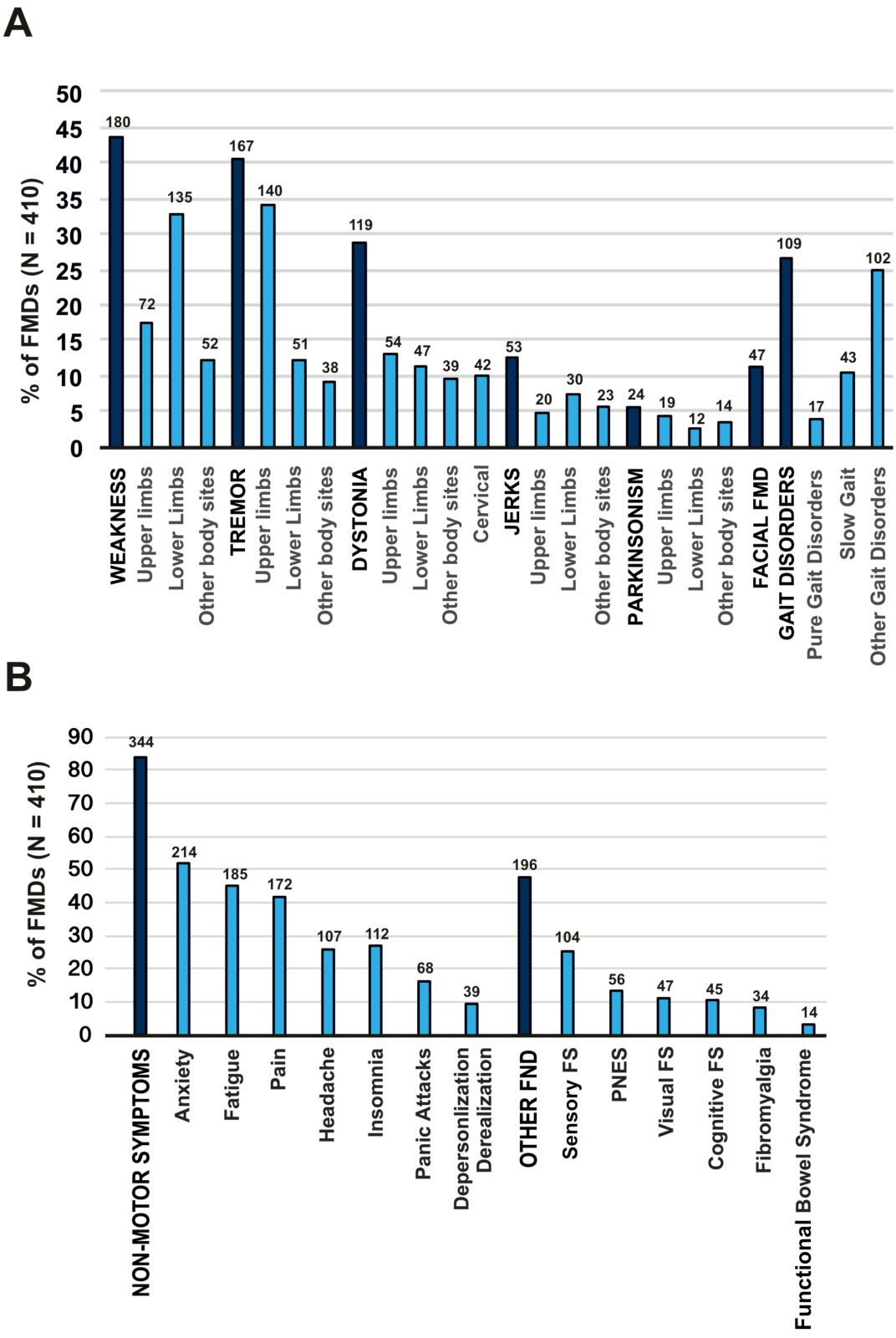
A
% of FMDs (N = 410)
50
45
40
35
30
25
20
15
10
5
0
180
72
135
52
167
140
51
38
119
54
47
39
42
53
20
30
23
24
19
12
14
47
109
17
43
102
WEAKNESS
Upper limbs
Lower Limbs
Other body sites
TREMOR
Upper limbs
Lower Limbs
Other body sites
DYSTONIA
Upper limbs
Lower Limbs
Other body sites
Cervical
JERKS
Upper limbs
Lower Limbs
Other body sites
PARKINSONISM
Upper limbs
Lower Limbs
Other body sites
FACIAL FMD
GAIT DISORDERS
Pure Gait Disorders
Slow Gait
Other Gait Disorders
B
% of FMDs (N = 410)
90
80
70
60
50
40
30
20
10
0
344
214
185
172
107
112
68
39
196
104
56
47
45
34
14
NON-MOTOR SYMPTOMS
Anxiety
Fatigue
Pain
Headache
Insomnia
Panic Attacks
Depersonlization
Derealization
OTHER FND
Sensory FS
PNES
Visual FS
Cognitive FS
Fibromyalgia
Functional Bowel Syndrome

Table 1: Neurological and psychiatric comorbidities, predisposing and precipitating factors, investigation and treatments in subjects with Functional Motor Disorders (N=410)

	N	%
Neurological comorbidities	70	17.1
Migraine	26	6.3
Parkinsonism	13	3.2
Neuropathy	11	2.7
Hyperkinetic motor disorders	8	2.0
Seizures	8	2.0
Multiple sclerosis	5	1.2
Stroke	5	1.2
Psychiatric comorbidities	165	40.2
Anxiety disorders	110	26.8
Major depressive disorders	55	13.4
Somatoform disorder	19	4.6
Eating disorder	10	2.4
Fugue state	9	2.2
Personality disorder	8	2.0
Post-traumatic stress disorder	6	1.5
Bipolar disorder	5	1.2
Impulse control disorder/OCD	5	1.2
Sexual dysfunction	4	1.0
Schizophrenia	3	0.7
Gender dysphoria	1	0.2
Familiarity for neurological diseases	94	22.9
Childhood Predisposing factors	38	9.3
Psychological trauma	25	6.1
Physical trauma	8	2.0
Both psychological and physical trauma	5	1.2
Precipitating factors	206	50.2
Psychological trauma	114	27.8
Surgery	63	15.4
Physical trauma	50	12.2
General anesthesia	33	8.0
Infections	18	4.4
Adverse drug reactions	16	3.9
Instrumental investigations	386	94.1
Magnetic resonance imaging	357	87.1
Computerized tomography	149	36.3
DAT SPECT	61	14.9
Electroencephalography	48	11.7
Neurophysiological tests	101	24.6
Other tests	51	12.4
Oral Medications	209	50.9
Antidepressants§	135	32.9
Benzodiazepines¥	111	27.1
Antiepileptics#	73	17.8
Antipsychotic drugs*	35	8.5
Other drugs	77	18.8
Other Treatments	180	43.9

Physiotherapy	116	28.3
Botulinum toxin injection	52	12.7
Cognitive behavioral therapy	42	10.2
Other therapies	40	9.8

DAT= dopamine transporter; OCD= obsessive compulsive disorder
§ Amitriptyline, duloxetine and paroxetine; ¥ Clonazepam; # Pregabalin, gabapentin and valproic acid; * Quetiapine and olanzapine

Table 2. Demographic and clinical features of patients with combined and isolated FMDs

Variable	Isolated FMDs (N=222)	Combined FMDs (N=188)	P-Value (Combined vs. Isolated)
Gender, n (%)			
Female	158 (71.2)	133 (70.7)	0.924
Age, y, mean (SD)	45.5 (16.8)	47.9 (14.4)	0.115
Education, y, mean (SD)	11.7 (3.7)	11.7 (3.9)	0.902
Previous consultations (%)	163 (73.4)	157 (83.5)	**0.014***
FMDs duration, y, mean (SD)	4.8 (5.8)	6.4 (7.7)	**0.020***
FMDs phenotype (%)			
Weakness	74 (33.3)	106 (56.4)	**<0.001***
Tremor	58 (26.1)	109 (58)	**<0.001***
Dystonia	41 (18.5)	78 (41.5)	**<0.001***
Gait disorders	17 (7.7)	92 (48.9)	**<0.001***
Jerks	18 (8.1)	35 (18.6)	**0.002***
Facial Motor Disorders	12 (5.4)	35 (18.6)	**<0.001***
Parkinsonism	2 (0.9)	22 (11.7)	**<0.001***
Diagnosis of FMDs^ (%)			
General Neurologist	47(21.2)	24 (12.8)	**0.025***
Movement disorders Neurologist	162 (73)	160 (85.1)	**0.003***
Non-motor symptoms (%)			
Anxiety	104 (46.8)	110 (58.5)	**0.018***
Fatigue	77(34.7)	108 (57.4)	**<0.001***
Pain	68 (30.6)	104 (55.3)	**<0.001***
Headache	47(21.2)	60 (31.9)	**0.014***
Insomnia	44 (19.8)	68 (36.2)	**<0.001***
Panic attacks	27 (12.2)	41 (21.8)	**0.009***
Other FND (%)			
Visual functional symptoms	16 (7.2)	31 (16.5)	**0.003***
Cognitive functional symptoms	17 (7.7)	28 (14.9)	**0.020***
Fibromyalgia	12 (5.4)	22 (11.7)	**0.021***
Psychiatric comorbidities, (%)			
Major depressive disorder	21 (9.5)	34 (18.1)	**0.011***
Somatoform disorder	5 (2.3)	14 (7.4)	**0.013***
Precipitating factors (%)			
Surgery	26 (11.7)	37 (19.7)	**0.026***
General anesthesia	11 (5)	22 (11.7)	**0.012***
Adverse drug reactions	4 (1.8)	12 (6.4)	**0.017***
DAT SPECT (%)	23 (10.4)	38 (20.2)	**0.005***
Physiotherapy (%)	51 (23)	65 (34.6)	**0.009***
Oral Medications (%)			
Antidepressants	60 (27)	75 (39.9)	**0.006***
Benzodiazepine	51 (23)	60 (31.9)	**0.042***
Antipsychotic drug	10 (4.5)	25 (13.3)	**0.001***

FMDs, functional motor disorders; FND= functional neurological disorders; SD, standard deviation; ^ Before enrollment. * Bold indicates significant values.

Table 3. Clinical and demographic variables associated with combined FMDs.

Independent Variable	Total Sample	Unadjusted			Adjusted		
		OR	95% CI	P Value	OR	95% CI	P Value
Patients, n	410						
Gender, males vs. females^		1.02	0.66-1.56	0.92	1.33	0.78-2.26	0.29
Age, y		1.01	0.99-1.02	0.12	1.01	0.99-1.03	0.29
Education, y§		1	0.95-1.06	0.90	1.04	0.97-1.12	0.21
Previous consultations, yes vs no^		1.83	1.13-2.98	**0.01***	1.20	0.64-2.26	0.56
FMDs duration, y		1.04	1.01-1.07	**0.021***	1.04	1.01-1.08	**0.028***
Diagnosis of FMDs°							
General neurologist, yes vs no^		0.54	0.32-0.93	**0.03***	4.25	0.85-21.08	0.07
Neurologist specialized in movement disorders, yes vs no^		2.12	1.28-3.48	**0.003***	7.09	1.57-31.9	**0.011***
Non-motor symptoms							
Anxiety, yes vs no^		1.60	1.08-2.37	**0.019***	0.71	0.41-1.22	0.21
Fatigue, yes vs no^		2.54	1.70-3.79	**<0.001***	1.58	0.94-2.65	0.08
Pain, yes vs no^		2.80	1.87-4.20	**<0.001***	2.05	1.21-3.48	**0.008***
Headache, yes vs no^		1.74	1.12-2.72	**0.01***	1.05	0.59-1.84	0.87
Insomnia, yes vs no^		2.29	1.47-3.57	**<0.001***	2.09	1.19-3.68	**0.010***
Panic attacks, yes vs no^		2.01	1.18-3.42	**0.010***	1.81	0.89-3.66	0.09
Other FND							
Visual functional symptoms, yes vs no^		2.54	1.34-4.81	**0.004***	2	0.88-4.54	0.09
Cognitive functional symptoms, yes vs no^		2.11	1.12-3.99	**0.022***	1.43	0.64-3.19	0.38
Fibromyalgia, yes vs no^		2.32	1.11-4.82	**0.024***	0.71	0.27-1.88	0.49
Psychiatric comorbidities							
Major depressive disorder, yes vs no^		2.11	1.18-3.78	**0.012***	1.39	0.64-3.04	0.40
Somatoform disorder, yes vs no^		3.49	1.23-9.88	**0.018***	3.58	1.02-12.64	**0.047***
Precipitating factors							
Surgery, yes vs no^		1.85	1.07-3.18	**0.027***	1.23	0.49-3.09	0.66
General anesthesia, yes vs no^		2.54	1.19-5.39	**0.015***	1.59	0.47-5.36	0.45
Adverse drug reactions, yes vs no^		3.72	1.18-11.72	**0.025***	4.15	0.93-18.59	0.06
Oral Medications							
Antidepressants, yes vs no^		1.79	1.18-2.72	**0.006***	1.43	0.82-2.50	0.20
Benzodiazepine, yes vs no^		1.57	1.01-2.43	**0.043***	1.03	0.57-1.85	0.91
Antipsychotics drugs, yes vs no^		3.25	1.52-6.96	**0.002***	2.85	1.09-7.38	**0.031***

^reference category; n, number; y, years; °the diagnosis of FMDs before enrollment in this study; CI, confidence interval; FND, functional neurological disorders; OR, odds ratio; significant associations at $P < 0.05$; Bold indicates significant values; §, 46 missing value for the education variable.

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