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SHORT COMMUNICATION

Functional motor disorders associated with other neurological diseases: Beyond the boundaries of "organic" neurology

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Abbreviations: FMDs, functional motor disorders; PD, Parkinson's disease; PNES, paroxysmal non-epileptic seizures.

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Co-investigators of the IRFMDs are presented in the Appendix.

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Abstract

Background and purpose: The aims of this study were to describe the clinical manifestations of functional motor disorders (FMDs) coexisting with other neurological diseases ("comorbid FMDs"), and to compare comorbid FMDs with FMDs not overlapping with other neurological diseases ("pure FMDs").

Methods: For this multicenter observational study, we enrolled outpatients with a definite FMD diagnosis attending 25 tertiary movement disorder centers in Italy. Each patient with FMDs underwent a detailed clinical assessment including screening for other associated neurological conditions. Group comparisons (comorbid FMDs vs. pure FMDs) were performed in order to compare demographic and clinical variables. Logistic regression models were created to estimate the adjusted odds ratios (95% confidence intervals) of comorbid FMDs (dependent variable) in relation to sociodemographic and clinical characteristics (independent variables).

Results: Out of 410 FMDs, 21.7% of patients (n = 89) had comorbid FMDs. The most frequent coexisting neurological diseases were migraine, cerebrovascular disease and parkinsonism. In the majority of cases (86.5%), FMDs appeared after the diagnosis of a neurological disease. Patients with comorbid FMDs were older, and more frequently had tremor, non-neurological comorbidities, paroxysmal non-epileptic seizures, major depressive disorders, and benzodiazepine intake. Multivariate regression analysis showed that diagnosis of comorbid FMDs was more likely associated with longer time lag until the final diagnosis of FMD, presence of tremor and non-neurological comorbidities.

Conclusions: Our findings highlight the need for prompt diagnosis of FMDs, given the relatively high frequency of associated neurological and non-neurological diseases.

KEYWORDS
functional dystonia, functional neurological disorders, functional tremor, functional weakness, neurological diseases, organic

INTRODUCTION

Historically, functional motor disorders (FMDs) have been stigmatized as disorders of "mind" as opposed to the so-called "organic" disorders, which were considered the quintessential "brain" disorders. This dichotomy is misleading for two main reasons: several abnormalities in brain networks associated with motor control, sensory integration and emotional processing have been demonstrated in people with FMDs [1,2]; the boundaries between FMDs and other neurological disorders have become less defined, as FMDs may co-exist with other neurological disorders such as epilepsy, [3] Parkinson's disease (PD), [4–7] multiple sclerosis, [8] and stroke [9].

The association between specific FMDs and neurological disorders is increasingly reported. A prospective study found that 19.6% and 8.9% of patients assessed in the emergency department had comorbid functional symptoms in addition to stroke and migraine, respectively [9]. A recent systematic review showed that onset of functional symptoms often predated or occurred at the same time as PD diagnosis and was more likely to involve the side most affected by parkinsonism [4]. Another systematic review highlighted a 12% frequency of paroxysmal non-epileptic seizures (PNES) in subjects with a primary diagnosis of epilepsy [10], whereas the reported rate of epilepsy among a large sample of people with a primary diagnosis of PNES was 5.3% [11].

To date, there has been little information on the frequency of neurological comorbidities in a large sample of subjects with different FMDs phenotypes. Furthermore, the demographic and clinical features of FMDs associated with other neurological disorders are unknown. Finally, it is not clear at what point FMDs occur during the course of another neurological disease.

We aimed, therefore, to describe the latency of onset and the clinical manifestations of FMDs associated with other neurological conditions, and to compare comorbid FMDs with FMDs with no neurological comorbidities.

METHODS

For this cross-sectional study, data were extracted from the Italian Registry of Functional Motor Disorders (IRFMD), 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). Full methods of the IRFMD are explained elsewhere [12].

Briefly, outpatients with FMDs were recruited from 25 tertiary movement disorder centers representative of the whole Italian territory between 1 September 2018 and 31 August 2019. Inclusion criteria were as follows: age ≥10 years; presence of one or more FMDs; and a clinically definite diagnosis of FMDs based on Gupta and Lang diagnostic criteria [13]. FMDs phenotypes were defined based on their specific phenomenological features, as previously reported [1], and included tremor [14], weakness [15], jerks [16], dystonia [17], gait disorders [18], parkinsonism [19], and facial motor disorders [20]. Exclusion criteria were presence of cognitive or physical impairment that precluded signing the informed consent form for participation in the study.

Patients were assessed at each centre in a single session by a neurologist specialized in movement disorders who confirmed the FMDs diagnosis and conducted a structured interview gathering several demographic, historical and clinical features. One section of the IRFMD also focused on the presence of any other neurological disorders besides FMDs, including migraine, cerebrovascular disease, PD or parkinsonism, neuropathy, hyperkinetic movement disorders (i.e., dystonia, tremor not due to FMDs), epilepsy, multiple sclerosis, and others (a free-text entry was allowed).

As per this section of the IRFMD, we defined patients with "comorbid FMDs" as those who had at least one other neurological disorder in addition to FMDs. Patients without any additional neurological comorbidity were defined as having "pure FMDs". To calculate the age at FMDs onset, we considered the first clinical manifestation of FMDs by patient interview. The onset of other neurological conditions was set based on the time of diagnosis given in the clinical records.

We also inquired about the presence of the following non-neurological comorbidities: heart disease; hypertension; arthritis and rheumatic diseases; tumors; thyroid disease; dyslipidemia; gastroenteric disease; and diabetes mellitus. Finally, patients were screened for the presence of other functional neurological disorders, including sensory functional symptoms, PNES, visual and cognitive functional symptoms, fibromyalgia, and functional bowel syndrome.

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 center. All patients (or their guardians) gave their written consent to participate.

Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and counts and percentages for categorical variables. For group comparisons, we used the unpaired *t*-test for continuous variables and the chi-squared test or Fisher's test (in case of expected frequencies ≤5) for categorical variables. Logistic regression models were created to estimate the adjusted odds ratios and 95% confidence intervals of comorbid 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).

RESULTS

Of 410 patients with FMDs, 21.7% ($n = 89$) had comorbid neurological diseases. Table S1 shows the distribution of FMDs phenotypes (occurring either in isolation or combination) [12] in the group with comorbid FMDs. Neurological comorbidities were more frequent in patients with functional tremor and weakness. Six out of eight patients diagnosed with functional parkinsonism had concomitant PD/parkinsonism. In the comorbid FMDs group, the most common neurological disorder was migraine, followed by cerebrovascular disease and PD/parkinsonism. Hyperkinetic movement disorders, neuropathy, epilepsy, and multiple sclerosis were less frequently associated to FMDs. Other neurological diseases occurred in 16.8% and included the following: lumbar back pain, carpal tunnel syndrome and cervical/dorsal/lumbar disc herniation (Figure 1a).

Functional motor disorders may appear before (13.5%, $n = 12$, mean latency 9 ± 14.1 years), but more frequently after the diagnosis of another neurological disease (86.5%, $n = 77$, mean latency = 8.7 years ± 12.7 years). FMDs predating a neurological disease were more frequently reported in those with PD/parkinsonism, whereas FMDs occurred always after the diagnosis of other hyperkinetic movement disorders or more frequently after the diagnosis of migraine (Figure 1b,c).

Patients with comorbid FMDs were older, presented more frequently with functional tremor, and had higher rates of non-neurological comorbidities (dyslipidemia, diabetes mellitus), PNES, major depressive disorders, and benzodiazepine use compared to those with pure FMDs (Table S2). The multivariate logistic regression model, after mutually adjusting for all variables, indicated that comorbid FMDs were associated with a longer time to reach FMDs diagnosis, presence of functional tremor and non-neurological comorbidities. Comorbid FMDs were also less likely to manifest with functional dystonia (Table 1).

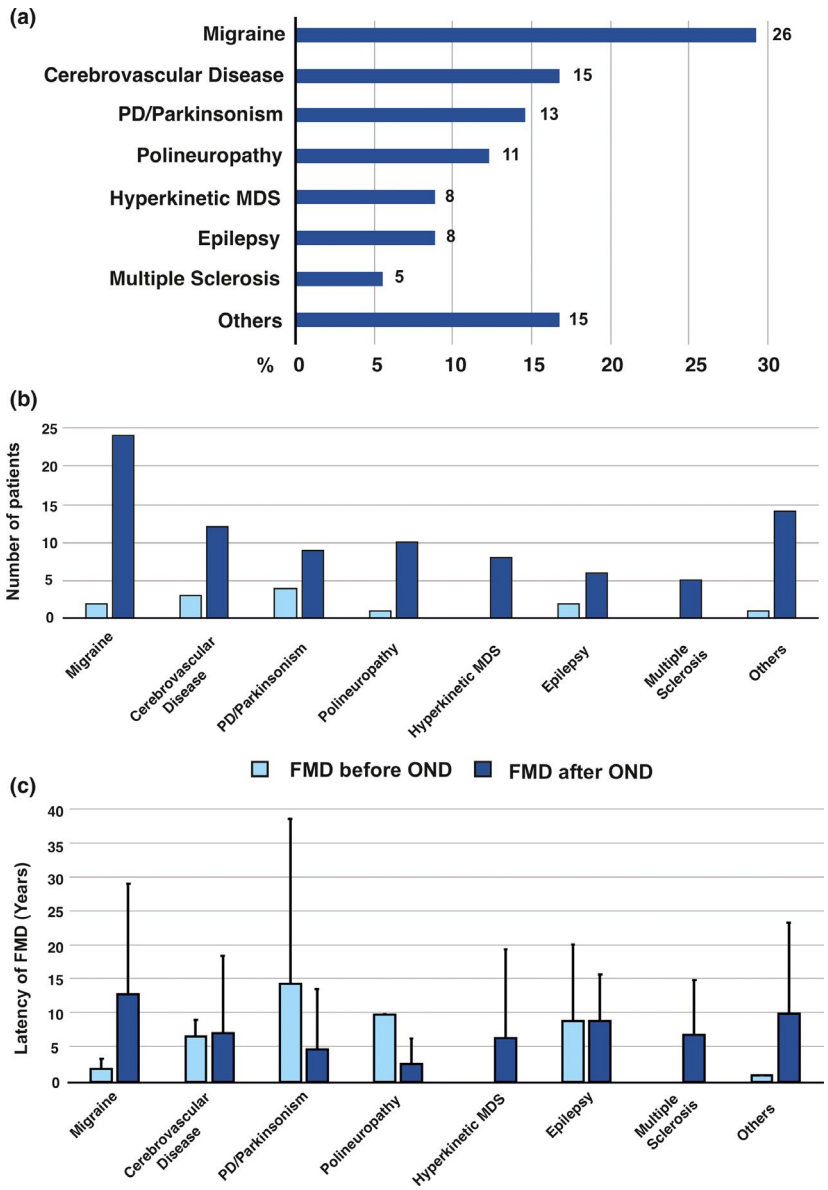

FIG. 1 (a) Absolute frequency (and percentage) of functional motor disorders (FMDs) patients with one or more neurological disease.(b) Absolute frequency of patients with a neurological disease started before and after the definitive diagnosis of FMDs. (c) Latency of FMDs onset (years) in patients with another neurological disease . MDS, movement disorders; OND, other neurological diseases; PD, Parkinson's disease. [Colour figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

In this large multicenter study, we demonstrated that FMDs may co-exist with other neurological disorders in 22% of patients. Migraine, cerebrovascular disease, and parkinsonism were the most frequent neurological diseases occurring in association with FMDs. In the majority of subjects, FMDs appeared after the diagnosis of a neurological disease but, in patients with PD/parkinsonism, functional manifestations often predated the parkinsonism diagnosis. On multivariate regression analysis, the comorbid FMDs group more frequently had functional tremor, non-neurological comorbidities, longer time lag until FMDs diagnosis and less frequent functional dystonia phenotype.

Comorbid FMDs were reported in 20% to 67% of patients defined as having "hysteria", "psychogenic" or "conversion" disorders [21-23]. A prospective cohort study [24] found that 26% of patients with "organic neurological diseases" presented unexplained symptoms not linked to the underlying disease. Migraine has been described in 16.7% of patients with "medically unexplained symptoms" [24] and headache has been reported in 26.4% of patients with facial FMDs [20]. Discrepancies in prevalance rates of comorbid FMDs compared to our study are likely attributable to differences in case ascertainment (we considered only diagnoses certified by a neurologists) and cohort composition (we included different phenotypes of FMDs).

Functional tremor was the most frequent motor symptom in the comorbid FMDs group overall as well as in those patients

TABLE 1 Clinical and demographic characteristics associated to Comorbid FMDs (N = 410 FMDs) on multivariate logistic regression

	Adjusted		
Independent variables	**OR**	**95% CI**	***p****
Gender: male vs. female[a]	0.58	0.32–1.06	0.075
Age, years	1.01	0.99–1.03	0.106
Time lag from onset of symptoms to FMDs diagnosis, years	1.04	1.01–1.07	**0.023**
FMD phenotype			
Tremor: yes vs. no[a]	1.80	1.07–3.02	**0.025**
Dystonia: yes vs. no	0.45	0.23–0.86	**0.016**
Self-reported non-motor symptoms[a]			
Pain: yes vs. no[a]	0.58	0.33–1.01	0.053
Non-neurological comorbidities: yes vs. no[a]	1.87	1.08–3.26	**0.025**
Associated FNDs			
Non-epileptic seizures: yes vs. no[a]	1.78	0.87–3.63	0.113
Psychiatric comorbidities			
Major depressive disorder: yes vs. no[a]	1.22	0.61–2.45	0.576
Precipitating factors			
Psychological trauma: yes vs. no[a]	1.57	0.89–2.75	0.117
Oral medications			
Benzodiazepine: yes vs no[a]	1.44	0.81–2.54	0.210
Antiepileptics: yes vs. no[a]	1.65	0.85–3.20	0.138

Abbreviations: CI, confidence interval; FMD, functional motor disorder; FND, functional neurological disorder; OR, odds ratio.

[a]Reference category.

*Statistical significant values ($p < 0.05$) are presented in bold.

with a diagnosis of PD. This is in keeping both with tremor being a very frequent FMDs phenotype [12] and with the results of a systematic review demonstrating that tremor is the commonest functional symptom in PD, usually affecting the most affected side [4,5].

Comorbid FMDs patients were also more likely to have PNES as well as non-neurological comorbidities, a diagnosis of depression and use of benzodiazepines. This finding suggests that this group of patients might have a greater burden of disability determined both by physical and mental conditions.

One of the novelties of the present study relates to time of onset of different Comorbid FMDs. FMDs often occurred after the diagnosis of other neurological diseases, but sometimes they may be antecedent, especially in patients with PD as previously reported [5,7]. Yet, FMDs predating parkinsonism should be differentiated by unusual movement disorders such as paroxysmal exercise-induced dyskinesias that may occur before the onset of cardinal motor signs [25].

Neurologists should both be aware of the risk of developing FMDs in patients with chronic neurological disorders and monitor FMDs for the subsequent development of other neurological disorders. In clinical practice, the overlap between FMDs and other neurological disorders is underrecognized, as shown by the results of multivariate regression analysis demonstrating that time to reach a diagnosis of FMDs in patients with neurological diseases was significantly longer. These data highlight not only the diagnostic challenge when dissecting functional symptoms from other neurological diseases, but also how in modern neurology there is still a dichotomy between "organic" and "functional" disorders, despite strong evidence of shared neurophysiological abnormalities [26–28] or distinctive psychophysical [29,30] and neuroimaging attributes [31] of FMDs. The demonstration of biological abnormalities represents a strong argument against the term "organic", which historically has been used to label conditions characterized by structural or other pathological changes, but it has also been adopted for neurological diseases such as migraine or genetic epilepsy or dystonia, in which no structural change is found on brain magnetic resonance imaging [32], despite being determined by network abnormalities within the central nervous system. The same network abnormalities, together with abnormal overweighting of prior expectancies about symptoms might distort sensory perception [33] and contribute to the development of comorbid FMDs. We do not have enough evidence to explain the occurrence of FMDs before PD, but it is likely that functional symptoms arise through the same network [34] and neurochemical abnormalities [4].

Limitations of the present study include the lack of a control group for each neurological disease. In addition, misdiagnosis of FMDs at the time of assessment might have affected the results, especially in those with other neurological diseases, considering that there are no diagnostic biomarkers for FMDs. However, despite not being validated, we relied on Gupta and Lang criteria which are currently used to support FMDs diagnosis and we included only clinically definite cases. We also recognize that it might be challenging to define the time of onset of FMDs in people with other neurological disorders, especially in patients whose historical clinical manifestations might be difficult to distinguish from neurological disorders with a similar phenomenology. However, in our sample of comorbid FMDs, migraine and cerebrovascular diseases represented the commonest "other neurological disorders" and incorrect identification of time of onset of FMDs is unlikely to have occurred at least for these diseases.

The main strength of the present study is the large multicenter sample of FMDs patients and the inclusion of different motor phenotypes. In addition, the cross-sectional design allowed standardized collection of clinical data in all centers on a wide range of FMDs.

In conclusion, our findings highlight the need for a prompt diagnosis of FMDs, given their possible occurrence with other neurological diseases. Correct recognition of the nature of the neurological symptoms in these patients has crucial implications both in terms of offering adequate therapeutic options and avoiding inappropriate interventions, such as treatment escalations or second-line therapies

in patients experiencing a worsening of their status because of the development of a functional overlay.

ETHICS 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 center. 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.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Michele Tinazzi: research project (conception, organization, execution); statistics (design, review and critique); manuscript (writing of the first draft, review and critique). Christian Geroin: research project (conception, organization, execution); statistics (design, execution); manuscript (writing of the first draft, review and critique). Roberto Erro: research project (execution); manuscript (writing of the first draft, review and critique). Enrico Marcuzzo, Sofia Cuoco, Roberto Ceravolo, Sonia Mazzucchi, Andrea Pilotto, Alessandro Padovani, Luigi Michele Romito, Roberto Eleopra, Mario Zappia, Alessandra Nicoletti, Carlo Dallocchio, Carla Arbasino, Francesco Bono, Angelo Pascarella, Benedetta Demartini, Orsola Gambini, Nicola Modugno, Enrica Olivola, Laura Bonanni, Elena Antelmi, Alberto Albanese, Gina Ferrazzano, Rosa de Micco, Leonardo Lopiano, Giovanna Calandra-Buonaura, Martina Petracca, Marcello Esposito, Antonio Pisani, Paolo Manganotti, Fabrizio Stocchi, Mario Coletti Moja, Angelo Antonini: research project (execution); manuscript (review and critique). Elisabetta Zanolin: research project (execution); statistics (design, execution, review and critique); manuscript (review and critique). Francesca Morgante: research project (execution); statistics (design, review and critique); manuscript (writing of the first draft, review and critique).

DATA AVAILABILITY STATEMENT

Data for this study are available from the corresponding authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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