# FUNCTIONAL MOTOR DISORDERS ASSOCIATED WITH OTHER NEUROLOGICAL DISEASES: BEYOND THE BOUNDARIES OF “ORGANIC” NEUROLOGY

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# ABSTRACT

**Objective**: 1) to describe the clinical manifestations of functional motor disorders (FMDs) coexisting with other neurological diseases (“comorbid-FMDs”); 2) to compare comorbid-FMDs to FMDs not overlapping with other neurological diseases (“pure FMDs”).

**Methods:** For this multicenter observational study, we enrolled outpatients with a definite diagnosis of FMDs attending 25 tertiary movement disorders centers in Italy. Each subject with FMDs underwent a detailed clinical assessment including screening for other associated neurological conditions. Groups comparisons (comorbid-FMDs versus pure-FMDs) were performed in order to compare demographical and clinical variables. Logistic regression models were created to estimate adjusted odds ratio (OR; 95% confidence interval) of comorbid-FMDs (dependent variable) in relation to sociodemographic and clinical characteristics (independent variables).

**Results:** Out of 410 FMDs, 21.7% (n=89) of patients 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 neurological disease. Patients with comorbid-FMDs were older, had more frequent 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 to reach the final diagnosis of FMDs, presence of tremor and non-neurological comorbidities.

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

# 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 FMDs1, 2; the boundaries between FMDs and other neurological disorders have become less defined, as FMDs may co-exist with other neurological disorders such as epilepsy3, Parkinson’s disease (PD)4-7, multiple sclerosis8, and stroke9.

The association between specific FMDs and neurological disorders is growingly reported. A prospective study found that 19.6% and 8.9% of patients assessed in an emergency department had comorbid functional symptoms in addition to respectively stroke and migraine9. A recent systematic review showed that onset of functional symptoms often predated or occurred at the same time of PD diagnosis and were more likely to involve the most affected side by parkinsonism4. Another systematic review highlighted a 12% frequency of paroxysmal non-epileptic seizures (PNES) in subjects with a primary diagnosis of epilepsy10, whereas the reported rate of epilepsy among a large sample of people with a primary diagnosis of PNES was 5.3%11.

So far, there is little information on the frequency of neurological comorbidities in a large sample of subjects with different FMDs phenotypes. Furthermore, demographical and clinical features of FMDs associated with other neurological disorders are unknown. Finally, it is unknown when FMDs occur over the course of another neurological disease.

Based on these premises, we aimed 1) to describe the latency of onset and the clinical manifestations of FMDs associated with other neurological conditions; 2) to compare comorbid-FMDs to FMDs without any neurological comorbidities.

# 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). Full methods for IRFMDs are explained elsewhere12.

Briefly, outpatients with FMDs were recruited from 25 tertiary movement disorders centers representative of all Italian territory between 1 September 2018 and 31 August 2019. Inclusion criteria were: age ≥ 10 years; presence ofone or more FMDs; and a clinically definite diagnosis of FMDs based on Gupta and Lang diagnostic criteria13. Phenotypes of FMDs were defined based on their specific phenomenological features as previously reported1 and included tremor14, weakness15, jerks16, dystonia17, gait disorders18, parkinsonism19, and facial motor disorders20; 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 FMD diagnosis and conducted a structured interview gathering several demographical, historical and clinical features. One section of the IRFMDs also focused on the presence of any other neurological disorders besides FMDs, including migraine, cerebrovascular disease, Parkinson’s disease (PD) or parkinsonism, neuropathy, hyperkinetic movement disorders (i.e. dystonia, tremor not due to FMDs), epilepsy, multiple sclerosis, and others (a free text enter was allowed).

As per this section of IRFMDs, we defined “comorbid-FMDs” those patients who had at least one other neurological disorder besides FMDs. Subjects without any additional neurological comorbidity were defined as “pure-FMDs”. To calculate the age at onset of FMDs onset, we considered the first clinical manifestation of FMDs by patient’s interview. The onset of other neurological conditions was set based on the time of diagnosis in clinical records.

We also inquired about the presence of the following non-neurological comorbidities: heart diseases, hypertension, arthritis and rheumatic diseases, tumors, thyroid diseases, dyslipidemia, gastroenteric diseases, diabetes mellitus. Finally, patients were screened for the presence of other functional neurological disorders (FNDs), 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 (SD) for continuous variables and counts and percentages for categorical variables. For groups comparisons, we employed unpaired t-test for continuous variables and chi-square test or Fisher’s test (in case of expected frequencies <5) for categorical variables. Logistic regression models were created to estimate adjusted odds ratio (OR; 95% confidence interval [CI]) 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, Armonk, NY, USA).

## Data sharing

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

# RESULTS

Out of 410 patients with FMDs, 21.7% (n=89) had comorbid neurological diseases. Supplementary table 1 shows the distribution of FMDs phenotypes (occurring either in isolation or combination)12 in comorbid-FMDs. Neurological comorbidities were more frequent in subjects with functional tremor and weakness. Six out of 8 patients diagnosed with functional parkinsonism had concomitant PD/parkinsonism. In comorbid-FMDs, the most common neurological disorder was migraine, followed by cerebrovascular disease and PD/parkinsonism. Hyperkinetic movement disorders, neuropathy, seizures and multiple sclerosis occurred less frequently in 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).

FMDs may appear before (13.5%, n=12, mean latency 9±14.1 years) but more frequently after the diagnosis of a neurological disease (86.5%, n=77, mean latency = 8.7 years ±12.7 years). FMDs predating a neurological disease were more frequently reported in 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 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 (Supplementary Table 2). 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).

# DISCUSSION

In this large multicenter study, we demonstrated that FMDs may coexist with other neurological disorders in 22% of patients. Migraine, cerebrovascular disease, and parkinsonism were the most frequent neurological diseases occurring in association to 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, comorbid-FMDs had more frequently functional tremor, non-neurological comorbidities, longer time-lag to reach FMDs diagnosis and less frequent functional dystonia phenotype.

Comorbid-FMDs were reported in 20-67% of patients defined as having “hysteria”, “psychogenic” or “conversion” disorders21-23. A prospective cohort study24 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 FMDs20. Prevalence discrepancies compared to our cohort are likely due 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 whole group of comorbid-FMDs patients as well as in those having a diagnosis of PD. This is in keeping with tremor being a very frequent FMDs phenotype12, and with the results of a systematic review demonstrating that tremor is the commonest functional symptom in PD, usually affecting the most affected side4, 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 our study relates to time of onset of different FMDs. In the majority of cases, they appeared after another neurological disorder, but sometimes FMDs may be early manifestations, especially in subjects with PD, as previously reported5, 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 signs25.

Neurologists should be both 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 subjects with neurological diseases was significantly longer. This data highlights 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 abnormalities26-28 or distinctive psychophysical29, 30 and neuroimaging attributes31 of FMDs. The demonstration of biological abnormalities represent 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 been also adopted for neurological diseases such as migraine or genetic epilepsy or dystonia, in which no structural change is found on brain MRI32, 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 perception33 and contribute to 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 network34 and neurochemical abnormalities4.

Among the limitations of our study, there is the lack of a control group for each neurological disease. Second, mis-diagnosis of FMDs at the time of assessment might have impact on 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 have included only clinical 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 subjects 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 FMDs time of onset is unlikely to have occurred at least for these diseases.

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

In conclusion, our findings highlight the need of 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.

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**Table. Clinical and demographic variables associated to FMDs associated to other neurological diseases (N= 410 FMDs)**

|  |  |
| --- | --- |
| **Independent Variables** | **Adjusted** |
|  | **OR**  | **95% CI** | **P Value\*** |
| Gender, males vs. females^ | 0.58 | 0.32-1.06 | 0.075 |
| Age, y | 1.01 | 0.99-1.03 | 0.106 |
| Time-lag from onset of symptoms to FMDs diagnosis, y | 1.04 | 1.01-1.07 | **0.023** |
| **FMDs phenotype** |  |  |  |
|  -Tremor, yes vs no^ | 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** |  |  |  |
|  - Pain, yes vs no^ | 0.58 | 0.33-1.01 | 0.053 |
| **Non-neurological comorbidities,** yes vs no^ | 1.87 | 1.08-3.26 | **0.025** |
| **Associated FNDs** |  |  |  |
|  - Non-epileptic seizures, yes vs no^ | 1.78 | 0.87-3.63 | 0.113 |
| **Psychiatric comorbidities** |  |  |  |
|  - Major depressive disorder, yes vs no^ | 1.22 | 0.61-2.45 | 0.576 |
| **Precipitating factors** |  |  |  |
|  - Psychological trauma, yes vs no^ | 1.57 | 0.89-2.75 | 0.117 |
| **Oral Medications** |  |  |  |
|  - Benzodiazepine, yes vs no^ | 1.44 | 0.81-2.54 | 0.210 |
|  - Antiepileptics, yes vs no^ | 1.65 | 0.85-3.20 | 0.138 |

**Abbreviations**: CI, confidence interval; FMDs, functional motor disorders; FNDs, functional neurological disorders; OR, odds ratio; y, years; ^reference category; \*in bold= statistical significant values p<0.05.

# FIGURE

Fig. 1. A: Absolute frequency (and percentage) of 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 a neurological disease started before and after the definitive diagnosis of FMDs



**Supplementary table 1: Frequency of different FMDs phenotypes in patients with comorbid-FMDs according to different neurological diseases**

|  |  |
| --- | --- |
|  | **FMDs phenotypes** |
|  | **Weakness**  | **Tremor**  | **Dystonia**  | **Jerks**  | **Gait disorders**  | **Facial Motor Disorders**  | **Parkinsonism**  |
| **All Neurological Diseases**  | 39 | 49 | 16 | 14 | 27 | 13 | 8 |
| **Migraine** | 15 | 11 | 5 | 4 | 7 | 5 | 1 |
| **Cerebrovascular diseases** | 8 | 8 | 1 | 1 | 4 | 0 | 1 |
| **Parkinsonism** | 2 | 9 | 4 | 0 | 2 | 2 | 6 |
| **Polyneuropathy** | 7 | 4 | 2 | 4 | 5 | 1 | 0 |
| **Hyperkinetic MDS** | 2 | 5 | 2 | 1 | 3 | 1 | 0 |
| **Epilepsy** | 4 | 3 | 2 | 2 | 2 | 1 | 1 |
| **Multiple Sclerosis** | 1 | 3 | 1 | 1 | 2 | 1 | 0 |
| **Other Neurological diseases** | 7 | 10 | 1 | 2 | 6 | 5 | 0 |

**Abbreviations**: FMDs, functional motor disorders; MDS = movement disorders. Other neurological diseases included: lumbar back pain, carpal tunnel syndrome and cervical/dorsal/lumbar disc herniation

Patients may have one or more neurological FMDs.

|  |
| --- |
| **Supplementary Table 2. Demographic and clinical features of FMDs patients without and with neurological diseases.** |
| **Variable** | **Pure-FMDs****N=321 (78.3%)** | **Comorbid-FMDs****N=89 (21.7%)** |  **P Value\*** |
| Female, n (%) | 223 (69.5) | 68 (76.4) | .202 |
| Age, y, mean (SD) | 45.3 (15.7) | 51.5 (15.2) | **.001** |
| Education, y, mean (SD)^ | 11.8 (3.8) | 11.2 (3.7) | .234 |
| Previous consultations, n (%) | 251 (78.2) | 69 (77.5) | .893 |
| Time-lag from onset of symptoms to final diagnosis of FMDs, y, mean (SD) | 5.1 (5.7) | 7.1 (9.6) | .067 |
| **FMDs phenotype, n (% in each group)** |  |  |  |
|  Weakness  | 141 (43.9) | 39 (43.8) | .986 |
|  Tremor | 118 (36.8) | 49 (55.1) | **.002** |
|  Dystonia | 103 (32.1) | 16 (18) | **.009** |
|  Gait disorders | 82 (25.5) | 27 (30.3) | .365 |
|  Jerks | 39 (12.1) | 14 (15.7) | .373 |
|  Facial Motor Disorders | 34 (10.6) | 13 (14.6) | .293 |
|  Parkinsonism | 16 (5) | 8 (9) | .154 |
| **FMDs onset, n (%)** |  |  |  |
|  Acute progressing  | 232 (72.3) | 58 (65.2) | .192 |
|  Slowly progressing  | 89 (27.7) | 31 (34.8) |
| **FMDs spontaneous remissions, n (%)** | 166 (51.7) | 48 (53.9) | .711 |
| **Diagnosis of FMDs, n (%)** |  |  |  |
|  General Neurologist | 52 (16.2) | 19 (21.3) | .256 |
|  Neurologist specialized in movement disorders | 253 (78.8) | 69 (77.5) | .793 |
| **Non-motor symptoms, n (%)** |  |  |  |
|  Anxiety | 165 (51.4) | 49 (55.1) | .541 |
|  Fatigue | 143 (44.5) | 42 (47.2) | .658 |
|  Pain | 144 (44.9) | 28 (31.5) | **.023** |
|  Headache | 78 (24.3) | 29 (32.6) | .115 |
|  Insomnia | 89 (27.7) | 23 (25.8) | .724 |
|  Panic attacks | 57 (17.8) | 11 (12.4) | .226 |
|  Depersonalization/derealization | 31 (9.7) | 8 (9) | .849 |
| **Non-Neurological Comorbidities, n (%)** |  |  |  |
|  All non-neurological comorbidities | 129 (40.2) | 51 (57.3) | **.004** |
|  Heart diseases | 25 (7.8) | 3 (3.4) | .144 |
|  High blood pressure | 48 (15) | 20 (22.5) | .092 |
|  Arthrosis and rheumatic diseases | 23 (7.2) | 8 (9) | .565 |
|  Tumors | 7 (2.2) | 5 (5.6) | .145 |
|  Thyroid diseases | 27 (8.4) | 11 (12.4) | .256 |
|  Dyslipidemia | 23 (7.2) | 16 (18) | **.002** |
|  Gastroenteric diseases | 13 (4) | 8 (9) | .097 |
|  Diabetes Mellitus | 10 (3.1) | 9 (10.1) | **.010** |
| **Other FNDs, n (%)** |  |  |  |
|  Sensory functional symptoms | 84 (26.2) | 20 (22.5) | .478 |
|  PNES | 38 (11.8) | 18 (20.2) | **.041** |
|  Visual functional symptoms | 35 (10.9) | 12 (13.5) | .499 |
|  Cognitive functional symptoms | 33 (10.3) | 12 (13.5) | .392 |
|  Fibromyalgia | 24 (7.5) | 10 (11.2) | .255 |
|  Irritable bowel syndrome | 11 (3.4) | 3 (3.4) | 1.000 |
| **Psychiatric comorbidities, n (%)** |  |  |  |
|  Anxiety disorder | 89 (27.7) | 21 (23.6) | .436 |
|  Major depressive disorder | 37 (11.5) | 18 (20.2) | **.033** |
|  Somatoform disorder | 15 (4.7) | 4 (4.5) | 1.000 |
| **Predisposing factors, n (%)** |  |  |  |
|  Childhood psychological trauma | 19 (5.9) | 6 (6.7) | .774 |
|  Childhood physical trauma | 7 (2.2) | 1 (1.1) | 1.000 |
| **Precipitating factors, n (%)** |  |  |  |
|  Psychological trauma | 82 (25.5) | 32 (36) | .052 |
|  Surgery | 49 (15.3) | 14 (15.7) | .914 |
|  Physical trauma | 38 (11.8) | 12 (13.5) | .675 |
|  General anesthesia | 22 (6.9) | 11 (12.4) | .091 |
|  Infections | 14 (4.4) | 4 (4.5) | 1.000 |
|  Adverse drug reactions | 11 (3.4) | 5 (5.6) | .356 |
|  Physiotherapy | 93 (29) | 23 (25.8) | .562 |
|  Botulinum toxin injection | 44 (13.7) | 8 (9) | .237 |
|  Cognitive behavioral therapy | 36 (11.2) | 6 (6.7) | .218 |
| **Oral medications, n (%)** |  |  |  |
|  Antidepressants | 99 (30.8) | 36 (40.4) | .088 |
|  Benzodiazepine | 79 (24.6) | 32 (36) | **.033** |
|  Antiepileptics | 51 (15.9) | 22 (24.7) | .054 |
|  Antipsychotic drug | 30 (9.3) | 5 (5.6) | .265 |
| ^the education variable reported 46 missing; n=number; FMDs, functional motor disorders; FNDs= functional neurological disorders; SD, standard deviation; PNES, non-epileptic seizures; Antidepressants= amitriptyline, duloxetine, and paroxetine; benzodiazepine= clonazepam; antiepileptics= pregabalin, gabapentin and valproic acid; antipsychotic drug= quetiapine and olanzapine; \*in bold= statistical significant values p<0.05. |

# DISCLOSURES

# 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 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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2.       Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3.       Manuscript: A. Writing of the first draft, B. Review and Critique;

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