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Published in:
Parkinsonism & Related Disorders

DOI:
[10.1016/j.parkreldis.2019.11.018](https://doi.org/10.1016/j.parkreldis.2019.11.018)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gelauff, J. M., Rosmalen, J. G. M., Gardien, J., Stone, J., & Tijssen, M. A. J. (2020). Shared demographics and comorbidities in different functional motor disorders. *Parkinsonism & Related Disorders*, 70, 1-6.
<https://doi.org/10.1016/j.parkreldis.2019.11.018>

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Shared demographics and comorbidities in different functional motor disorders

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ARTICLE INFO

Keywords:

Functional motor disorders
Functional movement disorders
Non-motor features
Conversion disorder
Psychogenic movement disorders

ABSTRACT

Introduction: Functional motor disorders are often delineated according to the dominant motor symptom. In a large cohort, we aimed to find if there were differences in demographics, mode of onset, pain, fatigue, depression and anxiety and levels of physical functioning, quality of life and social adjustment between patients with different dominant motor symptoms.

Methods: Baseline data from the Self-Help and Education on the Internet for Functional Motor Disorders Trial was used. Patients were divided into dominant motor symptom groups based on the diagnosis of the referring neurologist. Data on the above topics were collected by means of an online questionnaire and compared between groups using parametric and nonparametric statistics.

Results: In 160 patients a dominant motor symptom could be determined, 31 had tremor, 45 myoclonus, 23 dystonia, 30 paresis, 31 gait disorder. No statistical differences between groups were detected for demographics, mode of onset and severity of pain, fatigue, depression and anxiety. Physical functioning was worse in the gait disorder group (median 20, IQR 25) compared to tremor (50 (55), $p = 0.002$) and myoclonus (50 (52), $p = 0.001$). Work and social adjustment was less impaired in the myoclonus group (median 20, IQR 18) compared to gait disorder (median 30, IQR18, $p < 0.001$) and paresis (28, IQR 10, $p = 0.001$). Self-report showed large overlap in motor symptoms.

Conclusion: No differences were detected between groups of functional motor symptoms, regarding demographics, mode of onset, depression, anxiety, pain and fatigue. The large overlap in symptoms contributes to the hypothesis of shared underlying mechanisms of functional motor disorders.

1. Introduction

Functional motor disorders (FMD) consist of involuntary movements, posturing, gait disorder and paresis, that are internally inconsistent or incongruent with patterns of pathophysiological disease [1]. In organic movement disorders, detailed phenotyping of the motor symptoms is important to determine a phenomenological classification and to make an etiological diagnosis. This is increasingly expanded with motor phenotype specific associated non-motor features, like anxiety, depression, pain and fatigue and demographic differences [2–4]. It is unclear if these same associations exist in FMD.

FMDs are often delineated according to the dominant movement disorder such as tremor, dystonia or paresis. All FMD are assumed to share the same pathophysiological mechanism, but a shared mechanism cannot explain why one patient would suffer from paresis and another

from tremor. It has been suggested based on clinical experience that specific FMDs are associated with for example gender, age at onset or pain. A small study in which functional paresis was compared to functional movement disorders has found relatively non-specific differences, like male predominance, lower psychiatric hospitalisation and higher incidence of head trauma in functional paresis [5]. When comparing patients with non-epileptic attacks to FMD, differences in risk factors, etiological background and psychological comorbidity were found [6,7]. A review paper comparing non-epileptic attacks and FMD however, concluded that similarities exceed the differences in terms of demographics and associated psychological and physical symptoms [8]. From individual studies focussing on single FMD non-motor symptoms like depression, anxiety, fatigue and pain seem to be comparably high [9–13]. However, a direct comparison between groups has not been performed.

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Here, we aimed to find if there were differences between different FMDs, by comparing demographics, mode of onset, non-motor symptoms pain, fatigue, depression and anxiety and levels of physical functioning, quality of life and social adjustment and self-rated additional motor symptoms between patients with different dominant motor symptoms, as categorised by the referring neurologist.

2. Methods

2.1. Participants

All patients were included as part of a randomised Self-Help and Education on the Internet for Functional Motor Disorders Trial (SHIFT) (clinicaltrials.gov: [NCT02589886](https://clinicaltrials.gov/ct2/show/study?term=NCT02589886)). This was a two-group parallel superiority non-blinded randomised controlled trial in which patients were randomised to receive an education and self-help website or usual care. Patients were referred from 31 neurology centres across the Netherlands.

Between October 2015 and July 2017, patients considered eligible by the referring neurologist were contacted and informed by email or post. Inclusion in the SHIFT study required a functional motor disorder diagnosed by a neurologist, associated distress or impairment in social, occupational or other important areas of functioning, regular access to the internet, and Dutch language proficiency. Patients were excluded if they were unable to provide informed consent due to cognitive problems and if they were under 18 years of age. All included patients provided written informed consent. Patients with co-morbid neurological disease were not excluded from the study, but were told that this intervention was aimed at their functional motor symptoms.

Data for the current study came from the baseline questionnaires for this trial gathered before randomization took place. We previously published an article on the high prevalence of fatigue, from this same baseline data [14]. Data for the SHIFT study was collected in accordance with the ethical and legal guidelines of the University Medical Center Groningen (Medical Ethical Committee reference number: METC 2015/141, M14.150920).

2.2. Determination of the dominant motor symptom

Categorisation of patients into groups of the dominant motor symptom was based on the neurologist rating of the motor symptoms. The dominant motor symptom for each patient was determined based on the diagnosis of the referring neurologist, either provided directly on request, or via their clinic letter. When the neurologist was unable to identify one dominant motor symptom but rather thought two or more symptoms were equally severe (and/or impairing) or when referring information could not be obtained (neurologists could not be contacted/referring letters were not available/patients did not consent to obtain this information), the dominant motor symptom was labeled 'unknown' and these patients were left out of the group comparisons.

2.3. Demographics and onset of symptoms

Patients filled out questionnaires online including their age and sex. A multiple choice question was used asking in how much time the motor symptoms had arisen, with the following options: within seconds to minutes, minutes to 6 h, more than 6 h, symptoms were present at awakening or after an operation. Furthermore, patients were asked if migraine, a panic attack, general anesthesia, illness due to an infection, medication side effects, sleep paralysis, a pain, fatigue, or injury preceded onset of the first motor symptom(s), or if symptoms were first noticed by a health care professional.

2.4. Pain, fatigue, depression and anxiety

With regard to non-motor features, we assessed pain using the pain

subscale of the RAND36 (the health-related quality of life questionnaire which is almost identical to the Short-Form 36 questionnaire, (maximum score is 100 which stands for low pain) [15], fatigue using the subdomain fatigue severity of the Checklist Individual Strength (CIS, 8–56) [16], depressive symptoms using the Patient Health Questionnaire 9 (PHQ-9; 0–27) [17] and anxiety measured using the Generalized Anxiety Disorder Questionnaire (GAD-7; 0–14) [18].

2.5. Physical functioning, quality of life, Occupational and Social Functioning

Physical functioning was measured with the corresponding subscale of the RAND36 (0–100, with 100 reflecting optimal functioning). Quality of life was measured with a single question from the WHO-QoL questionnaire: "How would you rate your quality of life on a 5-point Likert scale" [19]. Work and social adjustment were assessed using the Work and Social Adjustment Scale (score range 0–40, with 0 reflecting best adjustment) [20]. Patients were also asked to report their working status and whether they received benefits for health-related reasons by means of several multiple-choice questions.

2.6. Patient-rated motor symptoms

We asked patients to indicate the presence and severity of the functional motor symptoms they experience using a variety of descriptors, specifically tremor (tremor/trembling/shivering), myoclonus (myoclonus/jerky movements), dystonia (dystonia/abnormal posturing), paresis (paresis/weakness/loss of strength) and gait disorder. All patients rated each of these five functional motor symptoms. They were asked to rate the severity of each symptom on a 7-point Likert scale (0 = not present – 7 = very severe), conform the change in presenting symptoms scale baseline measurement (CPS).

2.7. Statistical analyses

For group comparisons, ANOVA was used for normally distributed data and Kruskal Wallis tests for non-normally distributed and ordinal data. Chi squared tests were used to compare categorical variables. When statistical differences between groups were found with a p -value < 0.05, Mann-Whitney U tests were used for pairwise comparisons between groups. SPSS by IBM version 23 was used to perform statistical analyses. Correction for multiple comparisons according to Bonferroni was performed and resulted in a threshold p -value of 0.003.

To assess differences in prevalence of additional motor symptoms between dominant motor symptom groups, Chi squared tests were used. Correlations were made using Spearman's rho non-parametric analyses.

The patient-rated severity of the main motor symptom was compared to patient-rated severity of the other motor symptoms by a Friedman test.

3. Results

Of the 186 patients that were included in the SHIFT study, 31 had tremor, 45 myoclonus, 23 dystonia, 30 paresis, 31 gait disorder, 3 facial dystonia as the dominant motor symptom recorded by the neurologist and for 23 cases, classification according to their dominant motor symptom was not possible because the referring neurologists could not be contacted ($n = 19$) or he/she considered two or more motor symptoms to be comparably prominent ($n = 4$). Cases with facial dystonia ($n = 3$) were not included in the between group analyses, given their low prevalence.

3.1. Demographics and motor symptom characteristics

Mean age of the overall cohort ($n = 186$) was 48 years (SD 15); females formed a large majority (71%). The median duration of

Table 1

Comparison of dominant motor symptom groups. Median and IQR are given unless otherwise specified. Statistical testing: ANOVA (^A) Chi square (^C) and Kruskal Wallis (^K) judged significant at the Bonferroni threshold of 0.003. Nonclassified cases (n = 23) and facial dystonia cases (n = 3) were not included in the group comparison. [#]Missing: data on fatigue in 3 patients, data on depression in 2 patients.

Dominant functional motor symptom	Total	Tremor	Myoclonus	Dystonia	Paresis	Gait disorder	Group comparison
N	186	31	45	23	30	31	–
Demographics and symptoms							
Age in years (mean, SD, min-max)	48 (15, 18–78)	55 (16, 21–78)	49 (17, 20–73)	44 (13, 18–65)	45 (14, 19–67)	51 (11, 20–69)	F = 2.5, p = 0.017 ^A
Sex (n,%female)	132 (71%)	19 (61%)	33 (73%)	15 (65%)	24 (80%)	23 (74%)	Chi ² = 4.0, p = 0.406 ^C
Duration of motor symptoms in months, median (IQR)	24 (6–69)	21 (5–69)	25 (9–104)	36 (18–154)	18 (3–50)	21 (11–73)	Chi ² = 5.5, p = 0.238 ^A
Mode of Onset							Chi ² = 4.5, p = 0.345 ^A
Within minutes	74 (40%)	14 (45%)	20 (44%)	7 (30%)	11 (37%)	9 (29%)	
Minutes-6 hours	16 (9%)	3 (10%)	4 (9%)	1 (4%)	7 (23%)	–	
> 6 h	60 (32%)	10 (32%)	13 (29%)	9 (39%)	3 (10%)	15 (49%)	
At waking up	27 (14%)	4 (13%)	5 (11%)	4 (17%)	6 (20%)	6 (19%)	
After general anesthesia	9 (5%)	–	3 (7%)	2 (9%)	3 (10%)	1 (3%)	
Any other functional motor symptom	161 (87%)	27 (87%)	35 (77%)	23 (100%)	27 (90%)	28 (90%)	Chi ² = 8.1, p = 0.088 ^A
Self-rated additional motor symptoms (% severity ≥ 2 on CPS)							Chi ² = 4.4, p = 0.357 ^A
Tremor	–	–	22 (49%)	11 (48%)	12 (40%)	12 (39%)	
Myoclonus	–	21 (68%)	–	8 (35%)	7 (23%)	10 (32%)	
Dystonia	–	6 (20%)	13 (29%)	–	11 (37%)	15 (48%)	
Paresis	–	10 (33%)	15 (33%)	14 (61%)	–	20 (65%)	
Gait disorder	–	7 (23%)	14 (31%)	11 (48%)	20 (67%)	–	
Pain (RAND36, range 0–100), median (IQR)	46 (22–80)	67 (22–100)	57 (40–95)	47 (22–78)	45 (22–60)	45 (22–78)	Chi ² = 7.8 p = 0.100 ^A
Fatigue (CIS range 8–56), median (IQR) [#]	44 (35–44)	42 (35–53)	40 (32–52)	37 (20–51)	48 (42–54)	49 (38–54)	Chi ² = 9.7 p = 0.045 ^A
Depression (PHQ-9, range 0–27), median (IQR) [#]	8 (4–13)	7 (4–14)	6 (3–14)	6 (1–9)	10 (6–15)	8 (5–13)	Chi ² = 8.7 p = 0.069 ^A
Anxiety (GAD-7, range 0–14), median (IQR)	5 (0–9)	4 (0–9)	6 (0–9)	3 (0–8)	4 (0–10)	6 (0–9)	Chi ² = 1.1 p = 0.899 ^A
Physical Functioning, Quality of Life, Occupational and Social Impairment							
Physical functioning (RAND36) median (IQR)	40 (20–65)	50 (25–80)	50 (25–78)	25 (10–70)	38 (15–50)	20 (15–40)	Chi ² = 16.0, p = 0.003 ^A
Quality of life (WHO-QoL, range 1–5), median (IQR)	3 (2–4)	3 (2–4)	3 (3–4)	3 (2–4)	3 (2–3)	3 (2–4)	Chi ² = 2.7 p = 0.615 ^A
In work/Studying	48 (26%)	7 (22,5%)	17 (38%)	6 (26%)	8 (27%)	2 (6%)	Chi ² = 12.7, p = 0.013 ^A
Not in work							
for non-medical reasons	34 (18%)	7 (22,5%)	11 (24%)	2 (9%)	3 (10%)	8 (26%)	
on benefits ≤ 2 years	35 (19%)	4 (13%)	8 (18%)	3 (13%)	7 (23%)	7 (23%)	
on benefits > 2 years	69 (37%)	13 (42%)	9 (20%)	12 (52%)	12 (40%)	14 (45%)	
Work and social adjustment (WSAS, range 0–40) median (IQR)	26 (16–32)	21 (13–32)	20 (9–27)	21 (16–30)	28 (24–34)	30 (26–34)	Chi ² = 21.8, p < 0.001 ^A

Table 2

Prevalence of clinical features at onset. More than one answer possible. *data missing: for 2 patients from the tremor group, 3 patients from the myoclonus group and 2 patients from the gait disorders group. Nonclassified cases (n = 23) and facial dystonia patients (n = 3) were not included in the group comparison.

Clinical features at onset	Total (n = 179)	Tremor (n = 29)	Myoclonus (n = 42)	Dystonia (n = 23)	Paresis (n = 30)	Gait disorder (n = 29)	Group comparison chi-squared P value
Pain	46 (26%)	6 (21%)	8 (19%)	10 (44%)	8 (27%)	9 (29%)	Chi ² 5.3, P = 0.255
Panic	8 (5%)	2 (7%)	1 (2%)	1 (4%)	3 (10%)	1 (3%)	Chi ² 4.4, P = 0.348
Injury	15 (8%)	1 (3%)	3 (7%)	4 (17%)	3 (10%)	3 (10%)	Chi ² 3.3, P = 0.514
General anaesthesia	14 (8%)	2 (7%)	5 (12%)	2 (9%)	4 (14%)	1 (3%)	Chi ² 2.3, P = 0.678
Medication	6 (3%)	1 (3%)	1 (2%)	1 (4%)	1 (3%)	1 (3%)	Chi ² 0.2, P = 0.996
Sleep paralysis	4 (2%)	–	–	–	2 (7%)	1 (3%)	Chi ² 5.6, P = 0.228
Infection	8 (5%)	1 (3%)	2 (5%)	1 (4%)	1 (3%)	2 (7%)	Chi ² 0.6, P = 0.968
Migraine	3 (2%)	2 (7%)	–	1 (4%)	1 (3%)	–	Chi ² 3.9, P = 0.419
First noticed by health care professional	18 (10%)	2 (7%)	4 (10%)	4 (17%)	4 (13%)	2 (7%)	Chi ² 2.3, P = 0.689

symptoms was 24 months (IQR 6–69). Symptom onset was acute (within minutes) in 40% (n = 74) of cases. There were no significant differences between groups in terms of age, sex, symptom duration, onset duration or mode of onset. Reported mode and clinical features at onset were equally distributed in all five dominant motor symptom groups with no statistical differences between groups. In the total group the commonest factors at onset were pain (n = 46, 26%), noticed by a health care professional (n = 18, 10%), injury (n = 15, 8%) and general anesthesia (n = 14, 8%) (Table 2).

3.2. Pain, fatigue, depression and anxiety

Scores were high for pain and fatigue in the entire cohort (Table 1);

pain median 46 (IQR 22–80) and fatigue median 44 (IQR 25–44). The median scores of depressive and anxiety symptoms were respectively 8 (IQR 4–13) out of a maximum score of 27 on the PHQ9 and 5 (IQR 0–9) of 14 on the GAD7. There were no statistically significant differences in the levels of pain, depression and anxiety between the dominant motor symptom groups. Differences in fatigue scores between groups did not remain significant after correction for multiple comparisons.

3.3. Physical functioning, quality of life, occupational and social functioning

Physical functioning (median 40 (IQR 20–65, score maximum 100)) and quality of life scores (median 3 out of 5 (IQR 2–4) were low in a

majority of patients. The work and social adjustment score represents high impairment (26, (IQR 16–32), score maximum 40) and 56% ($n = 104$) of patients were (temporarily or permanently) not in work and received benefits. Scores on physical functioning and work and social adjustment were different between groups. Pairwise comparisons showed that the gait disorder group had significantly worse physical functioning (median 20, IQR 15–40) than the tremor (50 (25–80), $p = 0.002$) and myoclonus (50 (25–78), $p = 0.001$) groups. The work and social adjustment scale was significantly more impaired in the gait disorder and paresis group compared to myoclonus (gait disorder: median 30 (IQR 26–34), versus myoclonus 20 (9–27), $p < 0.001$, paresis 28 (24–34) versus myoclonus, $p = 0.001$). There were no statistically significant differences between groups in quality of life scores, or in percentages of patients in work or receiving benefits for health-related reasons.

3.4. Patient-rated motor symptom severity

The severity of the dominant motor symptom on a scale from 0 to 7 (0 corresponding to total absence of the symptom, 7 corresponding to most severe) in each group was: Tremor median 4 (IQR 3–5) (61% of patients had marked (5), severe (6) or very severe (7) symptoms), Myoclonus median 3 (IQR 2–4) (44% marked-very severe), dystonia median 3 (IQR 2–6) (43% marked-very severe), paresis median 3 (IQR 1–4) (47% marked-very severe), Gait disorder median 4 (IQR 3–5) (61% marked-very severe). The dominant motor symptom (as indicated by the neurologist) was self-rated as the most severe motor symptom in all groups (Friedman test for every group $p < 0.001$) when compared to other motor symptoms that patients reported. Only in the dystonia group, paresis severity (median 3, IQR 0–5) was reported as high as dystonia severity (median 3, IQR 2–6) ($\chi^2 = 14$, Friedman test $p = 0.008$).

There was a high prevalence of self-rated additional functional motor symptoms in all dominant motor symptom groups (77% ($n = 35$) in the myoclonus group to 100% in the dystonia group, 87% ($n = 161$) overall, $\chi^2 7.0$, $p = 0.134$), when counting all symptoms with a severity of 2 ('mildly bothered') or higher. Table 1 shows these additional patient-rated motor symptoms per dominant motor group. Overall, the median number of motor symptoms, including the dominant motor symptom, was 2 (IQR 2–4), with no statistically significant differences between dominant motor symptom groups ($\chi^2 4.4$, $p = 0.357$).

4. Discussion

In this study, we did not find differences in demographics, mode of onset, non-motor features, levels of physical disability or quality of life between patients with different types of functional motor symptoms. We found equally high rates of fatigue, pain, depression and anxiety in all dominant motor groups. We had expected that some symptoms, particular functional dystonia, might be associated with more pain [21,22]. However, patients with functional paresis or gait disorder as a dominant motor symptom had more severe impairment of physical functioning. Self-reported overlap in motor symptoms was high in all groups.

Tremor and myoclonus were overrepresented in our data compared to general neurology clinics [23,24], probably due a large number of referrals from movement disorders clinics rather than general neurology clinics in our data. In line with studies in this field, patients were mainly female, had a long symptom duration and were on average middle-aged. In 8% of our cohort, patients suffered some form of injury before symptom onset. This is lower than previously reported (10–37%), and would contradict the theory that the type of trigger might determine the motor phenotype in FMD. However, it is not clear to what extent the questionnaire used in this study can accurately assess triggering events as compared to the previously used interviews [25–27]. The speed of symptom onset was within minutes in 40% and

within 6 h in 49%, in line with findings in the literature, in which 54% of patients with movement disorders [25] and 49% of patients with paresis [26] had an acute onset. Acute onset in organic tremor, myoclonus and dystonia is rare and therefore could be a supportive diagnostic sign.

We did not find correlations between non-motor features fatigue, pain, depression and anxiety and groups of dominant motor symptoms. The high pain and fatigue scores in all groups underline the growing realisation that non-motor symptoms are relevant in both functional and organic movement disorders and should be recognised when treatment strategies are chosen [14]. The lack of differences between groups stresses the importance of addressing non-motor features in all FMD patients. There are varying reports of psychopathology in functional motor symptoms. In the largest study into functional paresis ($n = 107$) scores on pain and fatigue (median 33 (IQR 22) and 30 (35) of the SF36 scale respectively) and psychopathology (any current affective 61%, generalised anxiety in 21% of cases) were high [13]. It is possible that the frequency of depression and anxiety is higher than it appears in the data. Patients with FMD have been found to report lower rates in questionnaires than when questioned directly, because of stigma of mental illness and/or because of alexithymia [13,28]. We did not confirm small studies in which psychopathology seems less frequent in functional tremor and myoclonus [12,29].

Physical functioning and work and social activities were highly impaired in most patients and worse in paresis and gait disorders who are more likely to have persistent symptoms and problems walking than for example patients with tremor or myoclonus which is intermittent and doesn't affect ambulation. For the entire cohort, data relating to physical functioning, not being in work due to ill health and scores on the work and social adjustment scale, were comparable to the data in the literature [13,30,31].

This large overlap between patient-reported symptoms is an important finding. The current literature shows variable overlap in motor symptoms ranging from only 8%–72% of patients with paresis reporting an additional motor symptom [9,13,32], and up to 79% of patients with a functional movement disorder that had another motor symptom [33]. The high rate in our study could be explained by the fact that we explicitly asked for severity of all motor symptoms within our questionnaire. Self-report could have led to an overestimation, compared to findings in neurological examination (at one timepoint), although for a disorder in which subjective report is arguably the key feature of the disorder [34], it is a valid method of assessment. Also, there was concordance between patients and neurologists when indicating the dominant motor symptom, which lends some weight to our exploratory analysis of motor symptom overlap.

There are several possible explanations for the lack of differences between groups. Similar rates of non-motor features, comparable demographics and the fact that we did not find an association between typical patterns of mode of onset and motor phenotypes, might indicate a (at least partly) shared pathophysiological mechanism between the different motor symptoms. The large overlap between groups in terms of self-rated additional motor symptoms adds to that argument. Authors have highlighted the similarities between the broader group of functional syndromes, like sex ratios, comorbid emotional disorders and etiological factors and a comparable response to similar treatments across studies [35], which would be supported by the findings in our sample. Another explanation could be the potential difficulty physicians face when phenotyping functional motor disorders, because they are by definition clinically incongruent with recognized neurological disease. Myoclonus and tremor appear most linked, as we noticed that these terms were often used interchangeably in the history, examination and conclusion sections in the referral letters. However, the concordance between patients and neurologists when indicating the dominant motor symptom, affirms the existence of distinct dominant motor phenotypes.

Our data do not indicate specific treatment targets for the non-motor features in different motor symptom groups. Thus far, treatment

that has been found effective for FMD is either symptom focused, like in physiotherapy [32], or a combination of elements generic to shared disability and symptoms (e.g. rehabilitation advice), symptom specific elements and/or individual elements (e.g. in psychotherapy) [36–38]. It therefore seems optimal to combine specific symptom-tailored with a recognition of the likelihood of shared comorbidities. Measuring outcome in FMD is subject of debate. Our data show that motor symptoms are not distinctive for non-motor profiles or general outcome. Therefore they support the notion that with respect to FMD, it may not be necessary to focus excessively on motor symptom phenomenology to categorise and measure outcome in FMD. This approach has also been adopted by the ‘Simplified Functional Movement Disorders Scale’ for example [39].

Our study has several limitations. Differences between groups might have been missed due to the relatively small size of the groups or due to co-morbid neurological disease that might have been present in some cases. The results might be partly skewed by recall bias or due to the fact that we cannot be sure the online questionnaires were always filled out by the patients themselves. As discussed above, self-report has disadvantages. Especially the fact that motor symptom severity in this study was rated by patients themselves should be taken into account when interpreting the data.

5. Conclusion

In this study we did not find clinically relevant differences between groups of functional motor symptoms, regarding demographics, triggers and non-motor features such as depression, anxiety, pain and fatigue. Also, patients rated a large number of additional motor symptoms, apart from the dominant motor symptom as reported by the neurologist. This suggests a large overlap in phenotype and possibly underlying mechanisms of functional motor symptoms. High pain and fatigue scores in all groups underline the growing evidence that non-motor symptoms are relevant in both functional and organic movement disorders and should be recognised when planning treatment strategies.

Financial disclosures

JMG received an unrestricted grant from MIND (previously Fonds Psychische Gezondheid) in order to perform the Self-Help on the Internet for Functional Motor Disorders randomised trial, from which the data in this manuscript was derived. MT reports grants from the European Fund for Regional Development from the European Union (01492947) and the province of Friesland, Dystonia Medical Research Foundation, grants from Stichting Wetenschapsfonds Dystonie Vereniging, grants from Prinses Beatrix Foundation, grants from Fonds NutsOhra, from Jacques and Gloria Gossweiler Foundation, grants from Fonds Psychische Gezondheid, grants from Phelps Stichting, grants from Ipsen & Allergan Pharmaceuticals, Merz, Medtronic, and Actelion. JS carries out independent expert witness work in cases of personal injury that include patients with functional neurological disorders. He also reports royalties from UpToDate for articles on functional neurological disorder and runs a free self-help website, www.neurosymptoms.org.

Authors' roles

JG participated in conception, organization, execution of the research project, design and execution of statistical analysis and wrote the first draft.

JR participated in the conception and design of the study, the design of the statistical methods and reviewed the results and the manuscript.

JG participated in conception, organization and execution of the research project and helped writing the first draft.

JS reviewed and critiqued the statistical analysis and the manuscript.

MT participated in the conception and design of the study, the

organization and execution of the project and reviewed the results and the manuscript.

Declaration of competing interest

None.

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