



Functional or not functional; that's the question

Can we predict the diagnosis functional movement disorder based on associated features?

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Background and purpose: Functional movement disorders (FMDs) pose a diagnostic challenge for clinicians. Over the years several associated features have been shown to be suggestive for FMDs. Which features mentioned in the literature are discriminative between FMDs and non-FMDs were examined in a large cohort. In addition, a preliminary prediction model distinguishing these disorders was developed based on differentiating features.

Method: Medical records of all consecutive patients who visited our hyperkinetic outpatient clinic from 2012 to 2019 were retrospectively reviewed and 12 associated features in FMDs versus non-FMDs were compared. An independent *t* test for age of onset and Pearson chi-squared analyses for all categorical variables were performed. Multivariate logistic regression analysis was performed to develop a preliminary predictive model for FMDs.

Results: A total of 874 patients were eligible for inclusion, of whom 320 had an FMD and 554 a non-FMD. Differentiating features between these groups were age of onset, sex, psychiatric history, family history, more than one motor phenotype, pain, fatigue, abrupt onset, waxing and waning over long term, and fluctuations during the day. Based on these a preliminary predictive model was computed with a discriminative value of 91%.

Discussion: Ten associated features are shown to be not only suggestive but also discriminative between hyperkinetic FMDs and non-FMDs. Clinicians can use these features to identify patients suspected for FMDs and can subsequently alert them to test for positive symptoms at examination. Although a first preliminary model has good predictive accuracy, further validation should be performed prospectively in a multi-center study.

Introduction

Functional movement disorders (FMDs) pose a diagnostic challenge for clinicians. Although several studies have demonstrated the large share of FMDs in neurology outpatients, with frequencies ranging from 15% to 33% [1,2], they are still

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underrepresented in neurology training programs and one of the most common reasons for referral to movement disorder specialists [3]. A possible explanation for this high referral rate is the concern about missing an 'organic' disorder; however, studies show that the number of misdiagnoses is actually low [4,5]. This fear may also lead to unnecessary expensive laboratory and imaging tests, which cause even more delay, whilst early diagnosis seems to be one of the strongest prognostic factors for good outcome in FMD patients [6].

In the original criteria by Fahn and Williams, various clinical and historical characteristics were labeled with degrees of diagnostic certainty for FMDs, historically also called ‘psychogenic’, ‘conversion’ or ‘non-organic’ disorders [7,8]. These authors proposed to separate historical clues, such as psychiatric disturbance, abrupt onset, inconsistency over time and pain, from clinical clues, such as inconsistency, incongruence and distractibility. The historical clues were presumed to be suggestive for a diagnosis, whilst the clinical clues were used to establish a diagnosis of an FMD. Over the years, various studies provided strong evidence for the historical clues female gender, educational status, early age of onset, previous expansion to a disease model, paroxysmal disease course, dissociative symptoms, and fatigue as additional risk factors for FMD [9–12], whereas limited evidence was published for employment in a health profession, witnessing an organic movement disorder in a family member, relational status and possible secondary gain [13,14]. In addition to this expansion of historical clues, in patients with tremor and myoclonus electrophysiological testing turned out to be of value in cases where the clinical diagnosis remained uncertain [15,16]. In the current DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders, 2013), former historical clues are now called ‘associated features’ or ‘clinical characteristics’ [17]. Still, these factors are considered supportive, whereas a definite diagnosis should be based on positive clinical findings at examination showing clear evidence of incompatibility with recognized neurological disease.

The aim of the present study was to examine which of the clinical characteristics and associated features mentioned in the literature are discriminative between FMDs and non-FMDs. These factors might assist clinicians to identify patients suspected for FMDs before phenotyping and alert them to focus on positive symptoms during clinical examination. In addition, a preliminary model was developed to predict the likelihood of an FMD in a movement disorder patient.

Methods

Subjects

The medical records of all consecutive patients who visited the hyperkinetic Movement Disorders Outpatient Clinic of the University Medical Center Groningen, a tertiary referral center, between January 2012 and July 2019 were retrospectively reviewed. Clinical characteristics and associated features were manually extracted from the electronic medical record system

into a movement disorder database. All data were scored using the first visit consultation reports. The subjects extracted from the database were 18 years or older at the time of consultation and were diagnosed with a hyperkinetic FMD or non-FMD. The most recent clinical diagnosis was used as the gold standard: the final diagnosis after neurological examination, and in some cases additional imaging, laboratory or neurophysiological testing. Patients were excluded when there was lack of a final clinical diagnosis, a diagnosis which was not a movement disorder (e.g. primary psychiatric disorder or neuromuscular disorder), or more than one diagnosis (i.e. combination of an FMD and a non-FMD). This study was reviewed by the ethics committee of the University Medical Centre Groningen and according to local regulations no approval was needed. Obtaining informed consent was exempt because of the retrospective design and the extensive number of included patients.

Clinical characteristics and associated features

The following items from the database were used for this study: sex, age of onset, more than one motor phenotype, medical history, psychiatric history, cognitive symptoms, family history, pain, fatigue, abrupt onset, waxing and waning over long term, and fluctuations during the day. Apart from gender and age of onset, the features were dichotomized as present or absent. Medical history was scored present in the case of at least one previous, non-psychiatric medical condition. This also included previous functional medical disorders, such as fibromyalgia or irritable bowel syndrome. Thresholds for the features psychiatric history and cognitive symptoms had to be set high because of the retrospective study design. Only in patients with an established psychiatric diagnosis (e.g. depression, post-traumatic stress disorder) was psychiatric history scored as present and only in cases of intellectual disability (general learning disabilities and mental retardation), or when a patient was diagnosed with a dementia syndrome, were cognitive symptoms scored as present. The item family history was scored present if a patient had a first-degree relative with a movement disorder. The database did not contain sufficient information about education, employment, medical disability, relationship status, life events or any dissociative symptoms and it was not possible to define and extract possible secondary gain from the charts. Therefore, these factors could not be analyzed in the current study. Note that all other factors from former literature and current criteria were included. During the extraction of the data from the medical records, it was assumed that if features such as pain, fatigue,

abrupt onset, waxing and waning, and fluctuations during the day were not mentioned in the medical records, these were of such little impact that they could be replaced by absent.

Statistical analysis

Clinical characteristics and associated features were compared for patients with hyperkinetic FMDs versus non-FMDs. An independent *t* test for age of onset, the only continuous variable, and Pearson chi-squared analyses for all categorical variables were performed. Due to the number of tests, the significance level was set at $\alpha = 0.01$.

The significant variables were submitted to a multivariate logistic regression model for the prediction of FMD. The ability of our model to identify patients with FMDs was quantified as the area under the receiver operating characteristic curve (AUC). The adequacy of the fitted model was tested using the Hosmer and Lemeshow goodness-of-fit statistic. All statistical analyses were performed in SPSS 23 (SPSS, Chicago, IL, USA).

Results

In all, 1009 patients above 18 years were detected in the database. Of these, 99 were excluded due to a lack of a final or a non-movement disorder clinical diagnosis, and 36 due to more than one diagnosis (an FMD plus non-FMD). A total of 874 patients were eligible for inclusion in the study, of whom 554 (63%) had a non-FMD, including tremor 131 (24%), myoclonus 51 (10%), dystonia 257 (46%) and others 115 (20%). The remaining 320 (37%) were diagnosed with an FMD. In this group, the key symptom was tremor in 66 patients (21%), myoclonus in 102 patients (32%),

dystonia in 82 patients (26%) and others (21%). In the non-FMD group, 224 patients (40%) had more than one motor phenotype including dystonic tremor in 36%, myoclonus-dystonia in 10%, medication-induced movement disorders in 9%, and in the remaining 45% several other combinations were detected. In our FMD group 70 (24%) of the patients had more than one hyperkinetic movement disorder. All patients were diagnosed by an experienced movement disorder specialist. In more than 50% of the patients with functional tremor or myoclonus the diagnosis was supported by electrophysiological testing. Table 1 shows the mean and standard deviation of age at onset and the frequency of the associated categorical features for patients with FMDs versus non-FMDs. It was assumed that clinical characteristics, such as medical history or family history, were reported properly by the attending physician and therefore these items were scored as absent when they were not reported. In the case of unreported associated features, such as pain or fatigue, these missing values were replaced by absent. The percentage of missing values that were replaced is reported in the last column of the table. In FMD patients, symptoms had a significantly higher age of onset than in non-FMD patients. The features sex, psychiatric history, pain, fatigue, abrupt onset, waxing and waning over long term, and fluctuations during the day were more common ($P < 0.01$) in patients with FMDs, whilst more than one motor phenotype and positive family history were more prevalent in patients with non-FMDs ($P < 0.01$). The frequency of cognitive symptoms and medical history did not significantly differ between our two groups.

The 10 significant potential predictor variables (age of onset, sex, psychiatric history, family history, more than one motor phenotype, pain, fatigue, abrupt onset, waxing and waning over long term and

Table 1 Clinical characteristics and associated features in patients with hyperkinetic FMDs versus non-FMDs

Feature	FMDs (<i>n</i> = 320)	Non-FMDs (<i>n</i> = 554)	<i>P</i> value	Missing replaced by absent
Age of onset	40.8 ± 17.5	36.9 ± 23.3	<0.001	–
Sex, female	209 (65.3%)	309 (55.8%)	0.007	–
Medical history	267 (83.4%)	455 (82.1%)	0.644	–
Psychiatric history	103 (32.2%)	129 (23.3%)	0.005	–
Cognitive symptoms	12 (3.8%)	43 (7.8%)	0.020	–
Family history	31 (9.7%)	164 (29.6%)	<0.001	–
More than one motor phenotype	70 (21.8%)	224 (40.4%)	<0.001	–
Pain	197 (61.6%)	150 (27.1%)	<0.001	0.3%
Fatigue	175 (54.7%)	64 (11.6%)	<0.001	0.9%
Abrupt onset	158 (49.4%)	36 (6.5%)	<0.001	15.3%
Waxing and waning over long term	156 (48.8%)	35 (6.3%)	<0.001	9.4%
Fluctuations during the day	218 (68.1%)	184 (33.2%)	<0.001	22.5%

FMD, functional movement disorder. Bold numbers indicate significant associations.

fluctuations during the day) were submitted to the model. Sex did not contribute significantly and was therefore excluded, leading to a model with nine significant predictor variables. Table 2 depicts the prediction model that estimates the chance of being diagnosed with an FMD. The discriminative performance of the model was evaluated using the receiver operating characteristic curve with the AUC depicted by the blue line in Fig. 1. The AUC was 91% (95% confidence interval 88.8%–92.9%), which indicates a good discriminative ability between FMDs and non-FMDs. In addition, the non-significant Hosmer and Lemeshow statistic ($P = 0.169$) indicated a good model fit.

To estimate the individual probability of an FMD, the following predictive equation can be used:

$$P_{\text{FMD}} = e^{\{-3.155 + (0.014 * \text{age of onset}) + (0.604 * \text{psychiatric history}) - (1.300 * \text{family history}) - (0.607 * \text{more than one motor phenotype}) + (1.097 * \text{pain}) + (1.664 * \text{fatigue}) + (1.988 * \text{abrupt onset}) + (1.891 * \text{waxing and waning over long term}) + (0.911 * \text{fluctuations during the day})\}} / (1 + e^{\{-3.155 + (0.014 * \text{age of onset}) + (0.604 * \text{psychiatric history}) - (1.300 * \text{family history}) - (0.607 * \text{more than one motor phenotype}) + (1.097 * \text{pain}) + (1.662 * \text{fatigue}) + (1.988 * \text{abrupt onset}) + (1.891 * \text{waxing and waning over long term}) + (0.911 * \text{fluctuations during the day})\}}) * 100\%.$$

Using this equation, it is possible in our cohort to predict whether a patient has an FMD. For example, a patient with depression in his medical history and a negative family history, who is tired because of progressive, non-painful dystonic posturing of his right foot since the age of 30, with an abrupt onset of his symptoms and fluctuations during the day has a

Table 2 Multivariate regression analysis of features independently related to FMDs

Feature	Regression coefficient	OR (95% CI)
Intercept (<i>a</i>)	-3.155	
Age of onset	0.014	1.01 (1.01–1.01)
Psychiatric history	0.604	1.83 (1.82–1.83)
Family history	-1.300	0.27 (0.27–0.27)
More than one movement disorder	-0.607	0.55 (0.54–0.55)
Pain	1.097	3.00 (2.99–3.00)
Fatigue	1.664	5.28 (5.27–5.30)
Abrupt onset	1.988	7.30 (7.28–7.32)
Waxing and waning over long term	1.891	6.62 (6.60–6.65)
Fluctuations during the day	0.911	2.49 (2.48–2.49)

CI, confidence interval; OR, odds ratio.

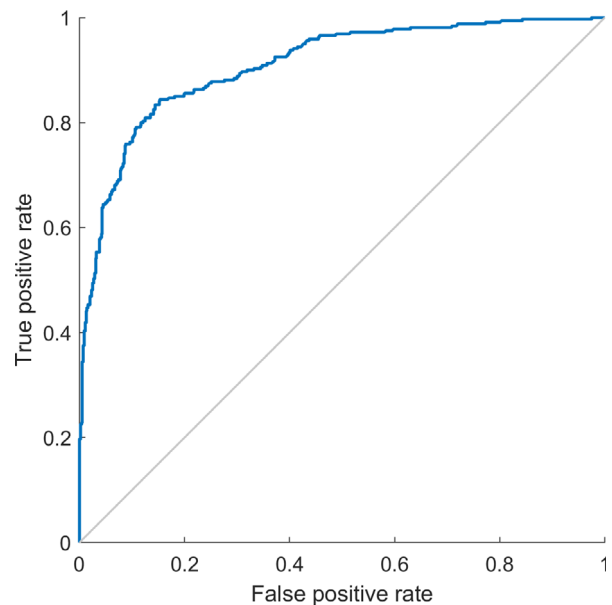


Figure 1 Area under the receiver operating characteristic curve. The blue line depicts the AUC of the multivariate logistic regression model and the grey line depicts the result of chance. [Colour figure can be viewed at wileyonlinelibrary.com]

predicted probability of being diagnosed with a FMD of 92%.

Discussion

The current study describes differences in clinical characteristics and associated features between FMD and non-FMD patients in a retrospective large cohort from a tertiary hyperkinetic movement disorder referral clinic. Ten associated features, mainly based on the current DSM-5, were significantly discriminative between the two groups. Age of onset was higher in FMD than in non-FMD patients. The categorical features sex, psychiatric history, pain, fatigue, abrupt onset, waxing and waning over long term and fluctuations over the day were more frequent in FMD patients, whilst more than one motor phenotype and a positive family history were more frequent in non-FMDs. The features medical history and cognitive symptoms were not discriminative between the two groups. Based on our retrospective results a preliminary predictive model was made with a discriminative ability of 91%.

The 874 patients in our study cohort were selected from a highly specialized outpatient clinic with only hyperkinetic movement disorders. Despite the fact that most FMDs are hyperkinetic [18], our cohort did not represent the general movement disorder clinic with a large proportion of Parkinson patients. In our adult non-FMD group (554) the dominant motor

phenotype was dystonia 46%, followed by tremor 24% and myoclonus 10%. In the 320 FMD patients the dominant motor phenotype was more represented by myoclonus in 32%, followed by dystonia in 26% and tremor in 21% of patients. These top three were similar to a previous FMD study, but with different percentages: tremor 55%, dystonia 39% and myoclonus 13% [19]. This is probably due to the fact that our center has a great interest in jerky movements. As noted, the distribution of the dominant motor phenotype was not the same in the FMD and non-FMD groups, with an overrepresentation of dystonia in the non-FMD group. This might have influenced our results as functional dystonia is considered a more challenging clinical diagnosis than functional myoclonus or tremor that can be supported with electrophysiological testing (as was performed in 50% of cases). It is known from the literature that many clinical characteristics and features are not significantly different in the different FMD motor phenotypes [20]; our cohort was considered not fully representative for a general movement disorder clinic but compatible with the hyperkinetic FMD and non-FMD patients in a specialized center.

In our cohort, a relatively high age of onset was found in patients with FMDs compared to non-FMDs, where former studies in different patient populations suggest the opposite [7,21]. A possible explanation could be that the relatively old group of hypokinetic patients, i.e. parkinsonian patients, was excluded. Another explanation could be that our cohort comes from a tertiary movement disorder clinic, implying that younger patients might have already been diagnosed by their first attending physician. Interestingly, the mean age in our FMD cohort is in line with the literature that FMDs are not uncommon in the elderly [22].

The categorical features female sex, psychiatric history, pain, fatigue, abrupt onset and inconsistency over time were more frequent in FMDs. In general practice and the aforementioned literature female sex is supposed to be an important risk factor for FMDs [23]. In our cohort also, the female to male ratio was 2:1 in FMD patients [5]. Next, whilst the criterion of psychological stress or psychiatric disturbance was removed from the current DSM-5 manual, in our cohort a positive psychiatric history turned out to be more prevalent in FMDs. Although significant, still two-thirds of our FMD patients did not have a previous psychiatric condition. Recent studies suggest that psychiatric illnesses are not a direct cause but might be a risk factor for developing an FMD, as part of an underlying model that integrates psychological and neurobiological perspectives [24]. It was detected that

pain was more frequent in FMD patients compatible with the literature where pain has been shown to be an important clue for a functional origin of a movement disorder [7]. Interestingly, pain is also a frequent feature in patients with non-FMDs, especially in (cervical) dystonia [25]. Despite the fact that dystonia was the most frequent motor phenotype (46%) in the non-FMD group, pain still showed to be discriminative in our cohort. Fatigue was also significantly more frequent in the FMD group. Over the last few years, fatigue has become an important feature in the FMD literature. In a previous study, it has been shown to be significantly more frequent in patients with FMDs compared to patients with neuromuscular disorders [26]. Our results support this discriminative capacity of fatigue and it is emphasized that the role of fatigue in FMD should be recognized in clinical practice. Next, abrupt onset was more frequent in the FMD group. In the original criteria, this feature was described as suggestive for FMD based on a small case series [7]. In the current larger study, abrupt onset turned out to be a discriminative factor as well. Finally, inconsistency over time, a feature which in our study was separated into waxing and waning over the long term and fluctuations during the day, was more frequent in the FMD group and had a discriminative value. In sum, the features female sex, psychiatric history, pain, fatigue, abrupt onset and inconsistency over time not only are suggestive for FMDs but could also help to discriminate these disorders from non-FMDs.

In the non-FMD group, the features more than one motor phenotype and positive family history were significantly more frequent compared to the FMD group. Interestingly, in some cases, the combination of more than one motor phenotype was the reason for the referring specialist to consider an FMD. This was based on the fact that in FMD more than one and overlapping motor phenotypes have been described. In our cohort, combinations were more frequently in the non-FMD group with diagnoses like myoclonus-dystonia and dystonic tremor. The lower numbers in the FMD group could be due to the fact that only hyperkinetic phenotypes were coded. The presence of concurrent limb weakness was not scored, but can be common in FMDs. Not surprisingly, patients in the group of non-FMDs more often had a first-degree relative with a movement disorder. However, also in 16% of our FMD patients there was a positive family history. Although underlying mechanisms for familial FMDs are still the subject of study [27], in one study up to 55% of patients with FMDs reported a positive family history for a movement disorder or were frequently exposed to individuals with neurological

disease [14]. Therefore, one should be aware that a positive family history in a patient with a movement disorder does not necessarily imply a non-FMD.

Finally, the features medical history and cognitive symptoms were not discriminative between our two patient groups. Due to the retrospective nature of our study, these two items were not optimally scored. The threshold for medical history was set low with 'only one medical condition including previous functional medical disorders', whereas the threshold for cognitive symptoms was set very high with 'only in cases of intellectual disabilities or dementia'. Prospective studies with structured questions are required to determine if there are differences between FMD and non-FMD patients.

Using the 10 significant associated features a preliminary prediction model was created for hyperkinetic FMD patients. Sex was dropped from the prediction model in multivariate logistic regression analysis, leaving nine features in our model: age of onset, psychiatric history, family history, more than one motor phenotype, pain, fatigue, abrupt onset, waxing and waning over long term and fluctuations during the day. The nine-feature model shows a good discriminative capacity to distinguish hyperkinetic FMD patients from non-FMD patients with an AUC of 91%, which indicates a good-to-excellent ability. To our knowledge, this is the first study to develop a preliminary prediction model based on associated features and not on positive signs. However, the current results of this retrospective study cannot yet answer the question whether FMDs can be predicted based on these factors. Future prospective studies are required.

This study included the whole spectrum of FMDs, where these movement disorders are often delineated according to the dominant motor phenotype, such as tremor, myoclonus or paresis. In clinical practice some of these functional phenotypes, e.g. functional tremor, can often be readily diagnosed using positive symptoms, whereas other phenotypes, e.g. functional dystonia, can be more challenging. The broad predictive model for FMDs lowered the sensitivity of our model, whilst in daily practice there might be a greater need for a model that could be used in specific FMD subtypes, where a positive diagnosis is hard to reach. However, previous studies on several characteristics and associated features have shown similar outcomes for all dominant motor phenotypes [20]. In addition, our study showed that there was a great variety of functional motor phenotypes referred to our movement disorder clinic, implying that for many physicians several kinds of FMD subtypes can be diagnostically challenging.

Our retrospective study had some limitations. In different associated features, missing values from the

medical records were replaced by absent. Clearly, this can result in an underestimation as well as an overestimation of each of these features. The number of replacements was low, however. As already mentioned, the threshold for medical history was set low, whereas the threshold for cognitive symptoms was set very high. Structured questions are required to study these features. Furthermore, it is possible that some of the clinical characteristics and associated features were used to make the diagnosis (diagnostic suspicion bias), although the diagnosis of FMD should preferably be made on positive symptoms. This is difficult to rule out. Prospective studies are required to further elucidate which features have additional discriminative value.

Despite the limitations, the discriminative capacity of several associated features and our preliminary model are promising. Prospective studies to validate our results in more representative and dominant motor phenotype matched cohorts in academic and non-academic hospitals are required. These prospective studies should involve systematic assessments with questionnaires and clearly defined variables, including educational status, dissociative symptoms, medical disability and relational status. Future predictive models could assist to identify FMDs earlier, lowering referral rates and resulting in a reduction of medical costs. Even more important, early recognition might lead to earlier treatment which is critical for long-term outcome in these patients.

Conclusion

It is concluded that 10 clinical characteristics and associated features described in the literature are discriminative between patients with hyperkinetic FMDs and non-FMDs in a large retrospective tertiary clinic cohort. The features sex, age of onset, psychiatric history, family history, more than one motor phenotype, pain, fatigue, abrupt onset, waxing and waning over long term, and fluctuations during the day were not only suggestive but also discriminative between our two patient groups. A preliminary predictive model combining these factors might help clinicians to identify patients suspected to have FMDs before phenotyping and create awareness to test for positive symptoms. However, this concept needs extensive further testing and validation in prospective studies in more representative cohorts.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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