VIEWPOINT

Functional Movement Disorder as a Prodromal Symptom of Parkinson's Disease—Clinical and Pathophysiological Insights

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ABSTRACT: Functional movement disorder (FMD) is a common manifestation of functional neurological disorder. FMD can occur alongside other neurological conditions, but especially in patients with established Parkinson's disease (PD). An interesting observation emerging across cohort studies and case series is that FMD can precede the diagnosis of PD, suggesting that FMD may itself be a prodromal symptom of neurodegeneration. Such a notion would have significant clinical implications for the assessment and management of people with FMD, particularly with respect to decisions around the use of auxiliary investigations, counselling, and follow-up. In this Viewpoint we review the evidence concerning the temporal relationship between FMD and PD. We discuss the potential explanations and mechanisms for FMD as a prodromal symptom of PD, and highlight clinical considerations and important outstanding questions in the field. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: functional neurological disorder; movement disorder; networks; neurodegeneration; pathophysiology; Parkinson's disease

Functional movement disorder (FMD) is a common manifestation of functional neurological disorder (FND) and accounts for up to 20% movement disorders outpatient clinic attendances.[1] FMD is defined by the existence of abnormal and involuntary hypo- or hyperkinetic movements with some characteristics of

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inconsistency (eg, disappearance of tremor with distraction, leg weakness with a positive Hoover's sign, tremor entrainment). FMD is recognized to occur alongside other neurological conditions, but is especially common in patients with co-existing Parkinson's disease (PD).[2] Among the most interesting findings emerging over the last decade is that FMD can precede the diagnosis of PD, raising the intriguing possibility that FMD may itself be a prodromal symptom of neurodegeneration. This idea would have significant clinical implications for the assessment and management of FMD patients, particularly with respect to decisions around the use of auxiliary investigations, counselling, and follow-up. In this work, we draw attention to this possible relationship between FMD and PD, discuss potential mechanisms, and highlight important outstanding questions in the field.

Functional Neurological Disorder in PD

Several studies have emphasized the co-occurrence of FND and neurodegenerative disorders, and PD especially (for recent reviews see Kurtis and Pareés,[2] Carrozzino et al,[3] and Ambar et al[4]). Seminal studies of a large cohort of patients with neurodegenerative conditions have shown that "somatoform disorders" occur in the highest frequency in patients with dementia with Lewy bodies (DLB) (12%–18%) and PD (7%–7.5%) with a lower proportion in other neurodegenerative disorders including Alzheimer's disease and progressive supranuclear palsy (0%–3%).[5,6] Although functional motor symptoms were very commonly reported in these studies, diagnosis of somatic symptoms as "functional" is inherently more difficult as some may relate to early autonomic and neuropsychiatric symptoms which are now established non-motor features of Lewy body disorders and occur at a similar rate.[7–9] Likewise, large multicenter prospective cohort studies of patients with FMDs found that comorbid neurological conditions occurred in 21%, with parkinsonism being among the most common.[10] Tremor seems to be the most common functional motor manifestation within these cohorts, although a broader range of functional motor symptoms have been reported.[4] Rates of PD among series of patients with functional parkinsonism vary between 7% and 67%.[11] FMD symptoms seem more likely to appear on the side affected by the PD.[12] These symptoms have been recognized to pose diagnostic and management challenges and often required the use of auxiliary investigations such as dopamine transporter imaging to confirm the diagnosis.[11] Although FMD has been described in association with in other neurodegenerative conditions including Alzheimer's disease, progressive supranuclear palsy, and even as a presentation of prion disease,[13,14] this appears to be much rarer indeed suggesting a more

TABLE 1 *Summary of studies reporting cases of functional neurological disorder and comorbid parkinsonism highlighting the proportion of cases with FND presenting before PD.*

Study	No. of FND subjects with PD (M/F)	Average age (y)	FND before PD n (%)	Duration of FMD before PD (years)
Lang et al, 1995[17]	1 (1 M, 0 F)	48	1 (7)	6
Benaderette et al, 2006[18]	6 (3 M, 3 F)	47.2	0 (0)	–
Gaig et al, 2006[19]	1 (1 M, 0 F)	50	0 (0)	–
Felicio et al, 2010[20]	2 (1 M, 1 F)	38.5	0 (0)	–
Onofrj et al, 2011[6]	37 (19 M, 18 F)	71.2	33 (89.2)	NR
Baik, 2012[21]	1 (0 M, 1 F)	65	0 (0)	–
Pareés et al, 2013[22]	11 (4 M, 7 F)	55.4	4 (36.4)	2.5
Umeh et al, 2013[23]	2 (1 M, 1 F)	37.5	–	–
Colosimo, 2015[24]	1 (1 M, 0 F)	62	0 (0)	–
Erro et al, 2016[25]	1 (1 M, 0 F)	60	0 (0)	–
Wissel et al, 2018[12]	53 (17 M, 36 F)	61.9	14 (26)	2.2
Frasca Polara et al, 2018[11]	6 (3 M, 3 F)	39	4 (66.7)	3.1
Tinazzi et al, 2021[10]	13 (4 M, 9 F)	66	4 (30.8)	14.5
Total	130 (56 M, 74 F)	62.3	61 (49.6)	4.3

Note: Average duration of FMD before PD calculated only from those studies, which reported duration of FMD before PD (n = 27 patients).
Abbreviations: F, female; FMD, functional movement disorder; FND, functional neurological disorder; M, male; NR, not reported; PD, Parkinson's disease.

specific association between FMD and the pathophysiology of Lewy body disorders.[15]

Functional Motor Disorder Can Precede the Diagnosis of Parkinson's Disease

Typically, when functional symptoms co-occur with another neurological illness, FND follows the onset of the comorbid neurological disease. For instance, epilepsy often precedes the onset of functional seizures with a delay of up to a decade.[16] However, in PD, a previous systematic review of published cases suggested FMD as preceding or being present at the time of diagnosis of PD in 62% of cases.[4] Drawing on recent data from 410 FMD patients, FMD appeared concurrently with or after the diagnosis of neurological disease in ~87.5% with a mean latency of 9 years.[10] However, among the 13.5% patients where FMD appeared before diagnosis of another condition, PD was the most frequent associated disorder (30% of patients) with a mean latency of 14 years between diagnosis and onset of PD/parkinsonism. Across all published series of FND, strictly excluding those with symptoms at the time of diagnosis or where a comparison to onset was not reported, the figure is closer to 36% (38/104) of cases of FND occurring before the onset of PD (Table 1). Although this includes somatic symptoms, the majority were reported to have functional motor symptoms.[6] Within these studies, paresis, gait disturbance, tremor, and functional parkinsonism are commonly reported. Together, these data lend credence to the notion that FMD may be a prodromal symptom of PD and warrants further exploration of the mechanisms underlying this relationship.

Mechanisms Underlying the Temporal Relationship between FMD and PD

Misdiagnosis

A proportion of FMD preceding a diagnosis of PD may represent misdiagnosis of PD as FMD in the first instance. Previous work has shown that FMD is associated with a delayed diagnosis of PD, compared to patients without functional symptoms.[11,12] In a study and review of patients presenting with functional parkinsonism, patients eventually confirmed to have comorbid functional parkinsonism and PD were less likely to be initially diagnosed with PD (33%), as opposed to those with "pure" functional parkinsonism (66%). The authors suggest that pure functional parkinsonism may present more typically with the classic triad of PD,[11] whereas PD in the presence of FMD may have less typical motor manifestations. Contributing to this diagnostic challenge is that inconsistency, a hallmark of FMD, can be a feature of PD such as is in the case of symptom variability in different emotional and social contexts, as well as paradoxical kinesia and motor/non-motor fluctuations (although these tend to be evident later in the course of PD).[26] FND tends to co-segregate with a higher burden of non-motor and neuropsychiatric symptoms, pain, and other somatic symptoms,[6,12] which may inappropriately skew the physician's diagnostic certainty. Furthermore, in patients where functional symptoms predominate, there may be cognitive bias among physicians and general neurologists toward making a singular diagnosis ("Occam's Razor") rather than entertaining a dual diagnosis. In cases of functional parkinsonism, dopaminergic imaging can be a useful tool to help detect the presence of PD. However, although the sensitivity of dopaminergic imaging for differentiating PD can be as high as 98%,[27] the sensitivity in early PD can be as low as 38%.[28] Its utility in prodromal stages is even less certain, with only 40% of patients with isolated rapid eye movement sleep behavior disorder (RBD) having abnormal dopaminergic imaging.[29] False-positive rates are uncommon (~1.4% in one study),[30] but can occur, particularly in the context of cerebral small-vessel disease and classes of drugs known to interfere with the interpretation of dopaminergic imaging.[31] Therefore, using an outmoded exclusionary investigative approach with dopaminergic imaging to make a diagnosis of FMD in patients with early or mild signs (where the risk is highest of false-negative scans) may lead to misdiagnosis, and reinforces the importance of relying on "positive" clinical signs for FMD. However, the accuracy of current diagnostic criteria for FMD and these "positive signs" of FMD in the setting of PD are unknown.[32]

Common Predisposing Factors

It is now well established that non-motor features including anxiety, depression, fatigue, and pain are common manifestations of PD and can predate the development of motor symptoms by up to a decade or longer.[33] Alexithymia, denoting an inability to self-identify emotions and associated physical symptoms is also seen in PD and prodromal PD.[34] These same neuropsychiatric co-morbidities commonly occur at a higher rate in people with FND than the general population[35,36] and have been proposed as risk factors and even "triggers" of FND. In this manner, neuropsychiatric and non-specific somatic symptoms arising in the context of prodromal PD could act similarly to trigger the development of FND.[10] In line with this, PD patients with FND were more likely to experience severe depression and anxiety compared to PD patients

without FND[12] or to have a psychiatric diagnosis such as bipolar disorder predating the diagnosis of PD.[37] Whether these non-motor symptoms simply act as predisposing factors or triggers for a separable pathophysiological process giving rise to FMD, as opposed to common mechanisms shared by both is far from established.

Early Neurodegeneration as a Shared Pathological Mechanism

Neurobiological models of FMD invoke a variety of mechanisms that interfere with motor control.[35,38] Studies using functional and structural neuroimaging have been able to map these mechanisms to brain networks associated with reduced sense of agency, altered emotional processing with typically increased limbic activation, changes in response inhibition, and shifts in attention from automatic to conscious motor processing, which is vulnerable to distraction.[39,40] These networks implicate a wide set of regions including the amygdala, supplementary motor area, insula, basal ganglia, thalamus, and dorsolateral prefrontal cortex (DLPFC) and cerebellum.

Alterations within the above regions and their corresponding networks are highly convergent with the neural correlates of PD symptoms across several domains. Affective symptoms and neuropsychiatric symptoms have been linked to changes in functional and structural connectivity within the limbic system, including amygdala hyper-connectivity.[41] Attentional network dysfunction, subserved by regions such as the DLPFC and insula, have been associated with cognitive symptoms and hallucinations in Lewy body disorders.[42,43] Indeed, hallucinations have been proposed to exist on a mechanistic continuum with FND with a recent model implicating central dysfunction of the thalamus.[43,44] Basal ganglia dysfunction arising from nigrostriatal cell loss accounts for many of the motor impairments of PD. Notable among these is a loss of automaticity, which has been proposed to intersect with many motor features of PD. Loss of motor automaticity is perhaps best exemplified by its most extreme form as gait initiation failure and freezing where conscious directed attention is required to execute normal movement (initiating and maintaining gait) and is affected by dual-tasking and emotional threat. This switch from automatic to "top-down" conscious modes of control in PD has been associated with hypoactivation in supplementary

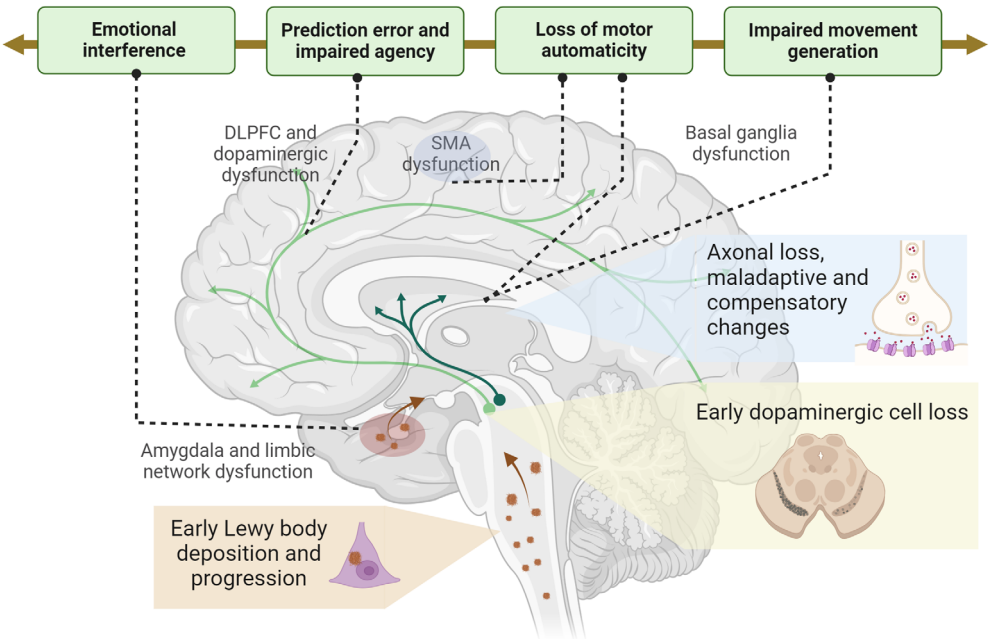

FIG. 1. FMD may arise as a direct result of early pathology in PD with shared pathophysiological mechanisms. FMD has been hypothesized to arise from dysfunction at all stages of the motor pathway, including but not limited to: altered motor generation; impaired emotional processing; loss of motor automaticity; and loss of agency understood in the framework of predictive coding as a mismatch between feedforward motor signals (generated in areas such as the DLPFC) and sensory signals of the final motor output. Similar dysfunction in shared networks has been described in PD and may precede the diagnosis. Cell loss may begin up to 14 years before the diagnosis of PD likely concurrent with or preceded by axonal loss and additional compensatory maladaptive molecular and cellular changes including aberrant arborization and dopamine transporter dysregulation. These may induce a state of relative nigrostriatal dopaminergic deficiency resulting in alterations in motor output through basal ganglia dysfunction. Through the involvement of dopamine in mechanisms of active inference, relative dopaminergic deficiency in mesocortical and mesolimbic pathways may induce errors in predictive coding resulting in a reduced sense of agency. Supplementary motor area dysfunction is commonly seen in PD, and early changes in this structure may contribute to loss of motor automaticity and an over-reliance on top-down attentional processing. Early Lewy pathology in other sites such as the amygdala may contribute to early impairments in limbic networks and emotional processing, which can interfere with motor planning. Although not exhaustive, these provide possible explanations of FMD as a prodromal feature of PD. DLPFC, dorsolateral prefrontal cortex; FMD, functional motor disorder; PD, Parkinson's disease. Image created using BioRender.com. [Color figure can be viewed at wileyonlinelibrary.com]

motor area and abnormal frontostriatal and limbic connectivity[45] and represents a crucial parallel to existing models of FMD.

In view of the pathophysiological convergence described above, early FMD may relate, at least in part, to early pathological changes described in pre-clinical

TABLE 2 *Outstanding questions and avenues for future research*

Question	Potential study designs
Epidemiology • What is the true rate of development of PD in patients with FMD? • Is there a difference in the phenotype of FMD occurring before PD compared to FMD occurring with or after a diagnosis of PD? • Does prodromal FMD attenuate, change in phenotype, or worsen after a diagnosis of PD?	• Large, multicenter, prospective longitudinal cohort study of FMD with rich clinical phenotyping
Clinical phenotyping • What is the prevalence and utility of clinical prodromal markers of PD in patients with FMD? • Does age at onset of FMD predict development of PD? • What clinical markers predict development of PD in FMD?	• Large, multicenter, prospective longitudinal cohort study of FMD in the context of PD. • Cross-sectional and prospective longitudinal study of clinical markers in FMD including anosmia, color discrimination, RBD, autonomic symptoms etc.
Diagnosis • What is the reliability of FMD criteria (incongruence, inconsistency) in the context of PD? • What are the characteristics of motor abnormalities in early (pre-symptomatic) PD and do they overlap with features of FMD?	• Inter-rater reliability, accuracy, and predictive value of positive FMD signs in the context of known underlying PD pathology. • Manual (visual scoring) and automated (eg, video and AI assisted) characterization of evolution of motor symptoms in longitudinal prodromal cohort studies (eg, iRBD, anosmic patients who develop dopaminergic deficit). • Characterization of inconsistency and fluctuations of mild or early motor symptoms in longitudinal prodromal cohorts (eg, iRBD).
Laboratory based markers • What are the neurophysiological characteristics of FMD in the context of PD? • Does neurophysiological testing or instrumental gait assessment in FMD reduce rates of misdiagnosis? • What is the rate of positivity of objective markers of PD in FMD?	• Detailed cross-sectional and longitudinal tremor studies of a prospective cohort of functional tremor with reporting of associated changes in diagnosis / management • Detailed cross-sectional and longitudinal objective gait assessment (eg, gait mat with gait analysis software) in patients with functional gait disorder and other FMD. • Cross-sectional and prospective longitudinal study of PD biomarkers (eg, dopaminergic imaging, CSF α-synuclein seed amplification positivity etc) in patients with FMD.
Mechanism • Are there structural or functional network differences in patients with PD and FMD compared to patients with PD without FMD? • Do functional and structural alterations within discrete structures proposed to be involved in FMD (such as thalamus, amygdala, supplementary motor area) correlate with the presence of FMD in PD? • Does early or mild dopaminergic deficiency generate mismatch in top-down expectations and bottom-up information and is this associated with a loss of sense of agency?	• Cross sectional study looking at structural MRI (volumetric, cortical thickness, or diffusion measures) and resting state fMRI in patients with PD and FMD vs PD only involving whole brain and directed analytical approaches involving pre-specified regions of interest (eg, amygdala) or networks (eg, default mode network). • Task-based fMRI testing motor automaticity (eg, finger tapping, dual tasking), affective processing, agency, and "theory of event coding" paradigms in PD with and without FMD, as well as in patients with prodromal PD (eg, iRBD with abnormal dopamine imaging) • Assessing influence of dopaminergic medication on performance and functional measures derived from the above tasks.
Treatment • What proportion of FMD in the context of early PD responds to dopaminergic treatment? • Does treatment of psychiatric comorbidity in PD (anxiety, depression) improve symptoms of FMD?	• Cross-sectional and longitudinal study of subjective reporting, clinical evaluation, or neurophysiological measurement of motor change (eg, tremor, bradykinesia) following initiation of dopaminergic or anti-depressant therapy in patients with PD and FMD.

Abbreviations: AI, artificial intelligence; CSF, cerebrospinal fluid; FMD, functional movement disorder; fMRI, functional MRI; iRBD, isolated rapid eye movement sleep behavior disorder; MRI, magnetic resonance imaging; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder.

stages of PD (Fig. 1). At the time of diagnosis with PD, patients would have been estimated to have lost 50% to 70% of cells in the substantia nigra pars compacta, and recent modeling work suggests this process begins up to 14 years before diagnosis.[46] Interestingly, this is similar to the latency described for the appearance of FMD[10] and other prodromal symptoms such as RBD. At this stage, loss of dopaminergic cell loss could lead to more covert changes in motor output with a mild loss of motor automaticity and a switch to the more top-down conscious control of movement thought to occur in FMD. Additionally, models of active inference have shown that dopamine is important in balancing the influence of bottom-up sensory information and top-down expectations.[47] Therefore, early loss of dopaminergic neurons may increase likelihood of a mismatch between predictions of the sensory consequences of planned movement and actual sensory feedback, something that is thought to be relevant to the disrupted sense of agency in patients with FMD.[35,38]

Current models of pathological spread posit that Lewy body pathology predates neuronal loss and that its "seeding" in brainstem, olfactory, and limbic regions accounts for the early emergence of non-motor symptoms.[48,49] The amygdala is one important component of the limbic system often affected early by Lewy body pathology, and its involvement has been associated with a variety of prodromal neuropsychiatric symptoms including depression and anxiety.[41] Such changes may have links to the aberrant activity in the amygdala and associated limbic networks reported in people with FMD without PD, and which have been proposed to interfere with normal motor programs, especially in strong emotional contexts.[50] Altogether, these mechanisms provide plausible and testable hypotheses supporting FMD as a prodromal feature of PD and providing a pathway for further research and understanding.

Clinical Implications

The observation that FMD may precede PD in a number of cases raises several considerations for clinicians managing patients with FMD. Firstly, it is reasonable to consider, in a patient with positive signs of FMD, if there could be another co-morbid diagnosis. In such patients, clinicians should be alert to the presence of other non-motor features of PD such as RBD, autonomic symptoms, or hyposmia, and have a greater index of suspicion of an underlying neurodegenerative condition with advancing age (50 years or above). Importantly, the presence of additional psychiatric comorbidity and non-motor somatic symptoms should not detract from this careful evaluation as these are common across a range of neurological disorders, including PD. To avoid misdiagnosis, physicians should actively apply positive signs to make a diagnosis of FMD and/or PD when assessing patients and to avoid relying on investigations of exclusion such as dopaminergic imaging, which may be normal at early stages in a small proportion of cases. More adjunctive use of neurophysiological testing (eg, tremor studies) could also mitigate misdiagnosis. There are also implications for follow-up. Depending on resource availability, clinicians should ensure follow up of patients with FMD, both as best practice for managing the functional disorder, but also to assess for the development of other conditions, especially PD. Alternatively, patients or local practitioners should be advised to assess for evolution of symptoms and to access re-referral if needed.

Conclusions and Future Directions

Accumulating evidence supports a unique relationship between FMD and PD with a consistent finding that FMD commonly precedes PD. Several outstanding questions remain, and further research is required to better understand the nature of this relationship and to guide clinical management. A set of proposals for future research avenues is provided in Table 2. In addition to hypothesis-driven experiments focused on pathophysiology, large, multicenter, prospective cohorts of FMD with long-term follow-up applying both clinical and laboratory-based markers[51] will be needed to minimize selection or recall bias and to determine the proportion of cases where FMD precedes PD. Such studies may inform the minimum set of heuristics (such as based on age, comorbidities, and phenomenology) and biomarkers that may guide clinicians on patient selection and duration of follow-up. In any case, the conceptualization of FMD as a prodromal symptom of PD also opens new lines of inquiry with exciting implications. Application of clinical phenotyping (eg, anosmia, color discrimination) and biological markers (eg, α-synuclein seeding assay, synuclein skin biopsy) may eventually be used in a subset of patients to recruit for disease modifying trials in early or prodromal PD. This reinforces the importance of approaching the diagnosis of FMD in a manner that preserves the trust in the physician and avoids estranging patients from the healthcare system, which could lead to future delays in diagnosis and treatment. ■

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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