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CLINICAL PRACTICE

BRIEF REPORT

Functional Movement Disorders and Deep Brain Stimulation: A Multi-Center Study

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ABSTRACT: Background: Functional movement disorders (FMD) are a commonly under-recognized diagnosis in patients with underlying neurodegenerative diseases. FMD have been observed in patients undergoing deep brain stimulation (DBS) for Parkinson's disease (PD) and other movement disorders. The prevalence of coexisting FMD among movement disorder-related DBS patients is unknown, and it may occur more often than previously recognized.

Methods: We retrospectively assessed the relative prevalence and clinical characteristics of FMD occurring post-DBS, in PD and dystonia patients (FMD+, n = 29). We compared this cohort with age at surgery-, sex-, and diagnosis-matched subjects without FMD post-DBS (FMD−, n = 29).

Results: Both the FMD prevalence (0.2%–2.1%) and the number of cases/DBS procedures/year varied across centers (0.15–3.65). A total of nine of 29 FMD+ cases reported worse outcomes following DBS. Although FMD+ and FMD− manifested similar features, FMD+ showed higher psychiatric comorbidity.

Conclusions: DBS may be complicated by the development of FMD in a subset of patients, particularly those with pre-morbid psychiatric conditions.

Functional movement disorders (FMD) may co-occur with Parkinson's disease (PD), dystonia, essential tremor (ET), and other movement disorders.[1,2] It is a commonly under-recognized diagnosis in those with underlying neurodegenerative diseases, although up to 7% of PD patients might develop FMD. The associated disability and quality of life impairment is similar to other non-functional ("organic") symptoms.[1,2] More recently, FMD have been observed in those undergoing deep brain stimulation (DBS) for PD and other movement disorders.[1,2] A similar phenomenon has been observed in patients undergoing epilepsy resection surgery.[3] The prevalence of coexisting FMD among movement disorder-related DBS patients is unknown, and it may occur more than previously recognized.[4] The co-occurrence of FMD can be an important predictor of outcome as improvements and worsening can impact the magnitude of postoperative complications and influence the perception(s) of dissatisfaction.[4]

It is unknown whether there are specific clinical or demographic features associated with the development of FMD post-DBS syndrome (FMD-pDBS). Clarifying the risk factors and the association between FMD and DBS outcomes will inform clinicians performing pre-operative screening and post-operative

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DBS management. This multi-center observational cohort aimed to begin to characterize features of FMD in patients treated with DBS across multiple movement disorder indications.

Methods

Population

Persons treated with DBS (considering all Food and Drug Administration-approved targets) between August 2006 through August 2019 at six expert North-American and European movement disorder centers were considered. The centers self-selected a cohort of patients and were required to treat 15 to 20 persons per year (and who positively responded to an email invitation). The center reported and patients who emerged with FMD-pDBS (FMD+) were included. A matched control group of DBS patients with same disease but without FMD (FMD−), was also included. The institutional review board of each participating center approved the study.

Inclusion/Exclusion Criteria

FMD+

Inclusion criteria consisted of clinically definite FMD, as per established criteria,[5] and the following for the respective diseases: idiopathic PD as per current criteria,[6] treated with DBS to attenuate motor fluctuations and/or levodopa-induced dyskinesias despite optimal pharmacological treatment; dystonia as per current criteria,[7] treated with DBS after insufficient benefits from pharmacological and botulinum toxin chemodenervation[8]; ET diagnosed according to the Movement Disorder Society criteria[9] treated with DBS after failing the highest tolerated doses of or combination of propranolol, primidone and topiramate.[10] Exclusion criteria included major post-surgical complications (stroke) and incomplete data.

Knowing that among the risk factors for developing FMD is the presence of an "organic disorder",[2] some patients with PD/dystonia/ET could have a coexistent FMD before DBS. Some of these cases could be discovered after DBS surgery when DBS improves the "organic" symptoms, but it is not effective on the FMD-related symptoms. Hence, we opted to include in our study also patients with a coexistent FMD before DBS, which in all cases came to the awareness of the treating physicians after surgery.

FMD−

The control group included persons without FMD with either idiopathic PD, dystonia, or ET who underwent DBS and were age-at-surgery-, sex-, and diagnosis-matched. Inclusion and exclusion criteria for idiopathic PD, dystonia, and ET diagnostic categories are identical.

Data Extraction

The following data were extracted from the electronic health records: demographics, past medical history, and clinical characteristics such as disease duration at DBS, age at DBS, unilateral/bilateral targeting of subthalamic nucleus (STN), globus pallidus internal (GPi), or ventral intermediate (VIM) nucleus of the thalamus, overall DBS outcome at 12 months (worsening defined as an increase or improvement defined as a stable or a decrease, in the clinical scales' total score), medications including levodopa equivalent daily dose (LEDD) (mg/day) in PD,[11] and psychiatric symptoms. In FMD+ patients, age at FMD onset, FMD duration, phenotype, and psychogenic movement disorders rating scale (PMDRS)[12] were also collected.

Aims

As primary aim, we assessed the relative prevalence of FMD-pDBS (FMD+) in the population of patients treated with DBS at participating centers. As secondary aims, we studied the differences in phenomenology between FMD+ and FMD−. We compared demographic data to characterize the FMD+ patient population.

Statistical Analysis

Outcomes (time frame, number of years, total DBS cases, FMD cases, relative prevalence, and cases/year) were reported per each movement disorder center. χ^2 analysis was used to compare sex, diagnosis, and psychiatric comorbidity between FMD+ and FMD−. Mann–Whitney *U*-test was used to compare continuous variables (age, disease duration at DBS, and LEDD) between FMD+ and FMD−. The results at P value <0.05 were considered statistically significant. Analyses were performed in STATA (Macintosh release 12.0; StataCorp, LP College Station, Texas).

Results

Twenty-nine FMD+ and 29 FMD− patients were included. The prevalence in this cohort, the number of cases/year, and the number of cases/numbers of DBS procedures/year in FMD+ patients is summarized in Table 1. The center prevalence of FMD ranged from 0.2%–2.1%, and the number of cases/numbers of DBS procedures/year also varied significantly across centers, ranging between 0.1 to 3.65.

Twenty –two of 29 were diagnosed with PD, 4/29 with cervical dystonia, and 3/29 with other dystonia types (two generalized dystonias and one dystonia within the context of cerebral palsy). No ET case was identified. Thirteen of 29 FMD+ patients were female (44.8%) (PD: 9; dystonia: 4). Disease duration (mean ± standard deviation) at DBS was 11.7 ± 6 years; age at DBS was 54.6 ± 12.9 years, and age at FMD onset was 55.1 ± 12.8 years. FMD occurred post DBS surgery in all PD patients and in 4/7 dystonia patients. In PD patients, FMD-pDBS occurred within 1 year of DBS surgery in 17/20 patients

TABLE 1 *Epidemiological data of patients with functional movement disorders and deep brain stimulation at the six movement disorder centers*

	Period	No. of years	Total DBS cases	Procedures/y	FMD cases	Prevalence (%)	Cases/ years
Cincinnati (Ohio[a])	2006–2019	13	533	41	1	0.2	0.08
Denver (Colorado[a])	2011–2019	8	311	38.9	4	1.3	0.50
Gainesville (Florida[a])	2003–2019	16	1122	70.1	4	0.4	0.25
The Hague/Leiden (Netherlands)	2013–2019	7	274	39.1	6	2.1	0.85
Seville (Spain)	2007–2019	12	217	18.1	2	0.9	0.17
Toronto (Canada)	2004–2019	15	743	49.5	11	1.5	0.73

Abbreviations: N, number; DBS, deep brain stimulation; FMD, functional movement disorders; y, year.[a]United States of America. Cases/y, number of cases of FMD+ divided by the number of years.

(two patients' data missing), 0.76 ± 1.13 years after surgery. In comparison, FMD-pDBS occurred earlier than DBS in 3/7 dystonic patients (mean 7 years) as "functional overlay" (namely, symptoms unexplained by the patients' disease diagnosis)[13] of preexisting dystonia (Table 2, cases: 24, 28, 29). In five cases (PD: 2; dystonia: 3) the timing of FMD was not clear, although they only emerged after DBS. The most common FMD type was tremor (11), followed by dystonia (9), ballism (3), bradykinesia (2), myoclonus (2), chorea (1), and tremor with dystonia (1). DBS targets were STN in 22/29 (PD:21; dystonia:1) and GPi in 7/29 (PD: 1; dystonia: 6) cases. At 12 months, the underlying movement disorder was markedly improved by DBS in 12, improved in 8, and worsened in 9 cases (Table 2; Table S1). LEDD for FMD+ PD patients were 1463.45 ± 503.4 mg pre-DBS and 946.7 ± 763.1 mg post-DBS. χ^2 analysis and Mann–Whitney *U*-test showed no differences in demographic (including social factors, as employment and marital status) or clinical features between FMD+ and FMD− groups (all *P* values >0.05), except for psychiatric comorbidity, which was significantly greater in FMD+ (72.4% vs. 37.9% in FMD−, $P = 0.008$). Among PD-FMD+ patients, 15/22 exhibited a tremor-dominant (TD) phenotype, and 7/22 the postural instability and gait disorder (PIGD) phenotype; among PD-FMD− patients 14/22 were TD and 8/22 were PIGD. Among dystonic FMD+ patients, 4/7 were cervical dystonia (CD), 2/7 had generalized dystonia, and 1/7 had dystonia within the context of cerebral palsy. Among dystonic FMD− patients, 4/7 had generalized dystonia, 2/7 had CD, and 1/7 had dystonia within the context of cerebral palsy (Tables S1, S2, and S3).

Discussion

The emergence of FMD syndrome in patients treated with DBS is relatively rare however, because 9/29 (31%) patients in this multi-country cohort worsened following surgery, it will be important to identify and understand this phenomenon. Interestingly, as patients with "organic disorders" have also comorbid FMD,[2,14] a small minority (10% of total; 43% of dystonias) had comorbid FMD before DBS, which manifested and/or tended to persist after surgery. Although this finding contrasted with previous reports of overall good outcome in dystonia patients with "functional overlay" before surgery,[15] it is fully in line with the psychogenic nonepileptic seizures presenting in patients undergoing epilepsy resection surgery.[3] The major finding was the higher prevalence of psychiatric comorbidity among FMD+ cases. However, all participants were considered psychiatrically stable after a thorough neuropsychological evaluation and had stable mental health for 6 months before DBS surgery. Finally, 68% of PD-FMD+ (vs. 64% of PD-FMD−) patients displayed the TD, whereas 32% (vs. 36% of PD-FMD–) the PIGD phenotype, respectively; regarding dystonic patients, the FMD+ group was mainly composed of patients with CD, and the FMD− group was mainly composed of patients with generalized dystonia (Tables S1 and S3). Unfortunately, no further data are available to discuss if there were any aspects of the PD/dystonic phenomenology, which may increase the likelihood of developing FMD.

FMD complicating the outcome of DBS has been previously shown in small single-center studies conducted in patients with ET, Tourette syndrome, and PD.[4,16,17] The authors of these reports suggested that surgery could serve as physical precipitating factor for the onset of functional symptoms within vulnerable populations.[18] In our cohort, when FMD occurred after DBS (26/29 cases), it appeared on average <1 year after surgery, therefore, suggesting indeed a possible "trigger" of the actual surgery for precipitating development of FMD. It is unknown how the actual surgical procedure, awake versus asleep may impact this issue. Differently, all three patients with FMD pre-DBS showed marked improvement of their "organic" symptoms post-DBS, although a functional overlay of their (dystonic) symptoms persisted.

Psychological (eg, expectations) and psychiatric (eg, comorbid depression) features, more than social (eg, employment, marital status) factors, may more heavily contribute to the development of FMD-pDBS, although data from this type of study cannot be conclusive. Although psychiatric comorbidities are more commonly observed in FMD,[19] this in itself is not a clinical

TABLE 2 *Main demographic and clinical features of participants with functional movement disorders (FMD+)*

Case	Sex	Organic diagnosis	DD at DBS	Age at DBS	Age at FMD onset	FMD at DBS (m)	FMD phenotype	PMDRS total	DBS target	DBS outcome	Psychiatric symptoms	LEDD pre-DBS	LEDD post-DBS
1	F	PD	9	64	64	<12	Trem	27	STN-B	W	D, A	1200	3292.5
2	M	PD	7	53	53	<12	Trem	63	STN-B	I+	A	1164	1265
3	F	PD	13	56	57	12	Chor	28	STN-B	W	A	1650	875
4	M	PD	11	66	66	<12	Trem	36	STN-L	W	SAD	1032	490
5	M	PD	33	60	60	<12	Ball	18	STN-B	W	D, A	2130	866
6	M	PD	13	70	70	<12	Myo	10	STN-B	W	A	2060	1915
7	M	PD	6	52	52	<12	Dys	8	STN-L	I+	D	950	600
8	M	PD	7	50	52	24	Myo	12	STN-B	I+	A, P	1150	525
9	F	PD	13	67	67	<12	Trem	28	STN-B	W	A	1675	1750
10	F	PD	18	61	–	After	Brady	46	STN-B	W	None	1650	1940
11	F	PD	16	53	–	After	Brady	58	STN-B	W	None	2780	630
12	F	PD	8	65	68	36	Ball	41	STN-B	W	None	1100	465
13	F	PD	20	65	66	12	Trem	10	STN-B	I+	A, D, OCD	1700	995
14	M	PD	7	45	45	<12	Dys	19	STN-B	I+	A	1150	200
15	M	PD	15	56	56	<12	Trem	9	STN-B	I	A	2300	112
16	M	PD	19	63	64	12	Ball	54	STN-B	I	D	1340	
17	F	PD	7	52	53	12	Trem	7	STN-B	I	D, A	1150	150
18	M	PD	11	55	55	<12	Gait dis	11	STN-B	I	D, A	1615	910
19	M	PD	12	71	72	12	Trem	–	STN-L	I	None	900	500
20	M	PD	13	63	63	<12	Trem	–	GPi-B	I	D	1350	1350
21	M	PD	10	40	44	48	Trem/Dys	–	STN-B	I+	D	750	450
22	F	PD	8	63	63	<12	Trem	–	STN-B	I	D, A	1400	600
23	F	DYT	16	20	22	24	Dys	30	GPi-B	I	A		
24	M	CD	7	47	43	−4	Func. Overl. Dys	21	GPi-B	I+	None		
25	F	CD	8	48	–	After	Trem	5	GPi-B	I+	None		
26	F	CD	6	73	–	After	Func. Overl. Dys	–	GPi-R	I+	D, A		
27	M	Dys	9	22	–	After	Dys	3	GPi-B	I+	None		

(Continues)

TABLE 2 *Continued*

Case	Sex	Organic diagnosis	DD at DBS	Age at DBS	Age at FMD onset	FMD at DBS (m)	FMD phenotype	PMDRS total	DBS target	DBS outcome	Psychiatric symptoms	LEDD pre-DBS	LEDD post-DBS
28	M	CD	15	45	30	−180	Func. Overl. Dys	–	STN-B	I+	A, D		
29	F	Dys	2	40	38	−24	Func. Overl. Dys	–	GPi-B	I+	None		
Total	16 M/13 F	22 PD/7 Dys	11.7 ± 6	54.6 ± 12.9	55.1 ± 12.8			24.8 ± 18	22 STN/7GPi			1463.45 ± 503.4	946.7 ± 763.1

Values are expressed as average ± SD. Some patients were also taking other drugs: patient 23 was on anticholinergics and botulinum toxin; patient 24 was on anticholinergics, clonazepam, and tetrabenazine; patient 28 was on clonazepam; patient 29 was on clonazepam and baclofen. All the reported psychiatric diagnoses were assessed before and after DBS surgery at follow-up evaluation; BoNT, botulinum neurotoxin. Cases 24, 28, and 29 represent patients with FMD occurring before DBS.

Abbreviations: DD, disease duration; DBS, deep brain stimulation; FMD, functional movement disorder; PMDRS, psychogenic movement disorders rating scale; LEDD, levodopa equivalent daily doses (expressed in mg); F, female; M, male; PD, Parkinson's disease; CD, cervical dystonia; Trem, tremor; Chor, chorea; Ball, ballism; Myo, myoclonus; Dys, dystonia; Brady, bradykinesia; Gait dis, gait disorder; Func. Overl Dys, functional overlay of dystonia (the term "functional overlay" indicates symptoms unexplained by the patients' disease diagnosis); STN-B, subthalamic nucleus bilateral; STN-L, subthalamic nucleus left; GPi-B, globus pallidus internal bilateral; GPi-L, globus pallidus internal left; –, in the "Age at DBS onset" column, indicates that we do not know the exact timing, but all cases emerged after DBS (In that case, column FMD duration at DBS is marked with "After"). In all other columns, "–" indicates not available; m, months; W, worsened; I, improved; I +, markedly improved; D, depression; A, anxiety; SAD, seasonal affective disorder; P, panic attacks; OCD, obsessive compulsive disorder.

differentiator or predictor of its occurrence. The effect of DBS on limbic areas of basal ganglia, and spread of current to limbic STN or GPi may possibly contribute to this issue; however, there is little data supportive of these pathways playing a role in the underlying cause of FMD. Advanced imaging and connectomic analysis of larger numbers of cases could bring clarity to this possibility.

Our data did not demonstrate a difference when comparing the motor outcomes between FMD+ and FMD− patients. This may have been because of a "cancellation effect" because two-thirds of the subjects improved and one-third worsened. The results could have also been driven by the large heterogeneity of the study participants. Alternatively, we can speculate that we found no difference because the onset of FMD could be unrelated to the motor improvement of the underlying disease, and could be because of other factors, such as the extent of perceived improvement. Because of the retrospective design, we had no data on satisfaction. FMD was not recognized among ET patients as in the previously published study, suggesting that FMD complicating the successful treatment of a non-functional tremor with DBS surgery may be a less common occurrence, despite tremor being a common FMD presentation.[16] Interestingly, FMD was recently reported in a person undergoing magnetic resonance imaging (MRI)-guided focused ultrasound thalamotomy for ET.[20]

The small sample size of our multi-center study highlights that emergence of a FMD syndrome in DBS-treated patients is rare. Our small sample size and retrospective approach rendered it hard to determine the actual prevalence. Correct diagnosis and enrollment for such as study would be challenging and impossible in a single center. Data collected tend to be heterogeneous and lack standardized scales. Finally, the sample size may have contributed to the lack of groupwise differences. Finally, although all FMD diagnoses were made in a tertiary referral movement disorders center, some FMD+ patients had FMD before their surgery, further highlighting the difficulties in making the diagnosis pre-operatively.

FMD-pDBS is a complication that may emerge post-surgery, or rarely be present before DBS. Psychiatric comorbidities may be an important risk factor; however, this factor is common in the general population of patients undergoing DBS. Therefore, clinicians prescribing DBS need to be aware of this possible issue. Future studies will need to examine possible other factors contributing to FMD-pDBS.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

L.M.: 1A, 1B, 1C, 2A, 2B, 2C, 3A.
E.G.K.: 1C, 2C, 3A.
R.M.: 1C, 2C, 3B.
M.F.C.: 1C, 2C, 3B.
R.Z.: 1C, 2C, 3B.
M.S.O.: 2C, 3B.
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W.D.: 1C, 2C, 3B.
D.K.: 1C, 2C, 3B.
D.M.G.: 1C, 2C, 3B.
F.C.: 1C, 2C, 3B.
P.M.: 2C, 3B.
A.M.: 2C, 3B.
A.J.E.: 2C, 3B.
A.F.: 1C, 2C, 3A, 3B.

Disclosures

Ethical Compliance Statement: The Institutional Review Board of each participating center approved the study (Cincinnati 2018–7859; The Hague T19-091; Gainesville IRB201901807; Toronto IRB00001256; Denver COMIRB16-1060; Seville 0216-N-21). All study procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Informed patient consent was not necessary for this work. The authors confirm that they 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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Data Availability Statement

L.M. and A.F. had full access to all the data in the study and take responsibility for the integrity of the data, the accuracy of the data analysis, and the conduct of the research. They have the

right to publish any and all data, separate and apart from the guidance of any sponsor. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Detailed features of FMD+ patients' group.

Table S2. Statistical analysis comparing demographics and clinical features between FMD+ and FMD− patients' groups.

Table S3. Main demographic and clinical features of control participants without functional movement disorders (FMD−).