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Functional dystonia: A case-control study and risk prediction algorithm

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Abstract

Objective: Functional dystonia (FD) is a disabling and diagnostically challenging functional movement disorder (FMD). We sought to identify historical predictors of FD vs. other primary dystonias (ODs) and develop a practical prediction algorithm to guide neurologists. **Methods**: 1475 consecutive new patient medical records were reviewed at an adult/pediatric tertiary-referral dystonia clinic from 2005 to 2017. Ninety-nine met criteria for clinically established FD (85 adults and 14 pediatric), paired with 99 age/dystonia distribution-matched OD. Univariate and multivariate regression analyses were performed to identify predictors of FD and disability. We formed a prediction algorithm, assessed using the area under the receiver operating curve (AUC). **Results**: Multivariate logistic regression analysis investigating independent predictors of FD ($P < 0.001$) followed by development of a prediction algorithm showed that the most robust predictors included abrupt onset, spontaneous resolution/recurrence, pain, cognitive complaints, being on or pursuing disability, lifetime mood/anxiety disorder, comorbid functional somatic disorders, and having ≥3 medication allergies. The prediction algorithm had utility for both adult and pediatric FD, with excellent sensitivity/specificity (89%/92%) and an area under the curve (AUC) 0.95 (0.92-0.98). Greater disability (modified Rankin Scale) independently correlated with a number of functional examination features, unemployment/not attending school, number of medication allergies, and younger age of presentation. FD patients were high health-care utilizers and were more frequently prescribed opiates/opioids and benzodiazepines ($P < 0.003$). **Interpretation**: This case-control study provides an algorithm to guide clinicians in gauging their index of suspicion for a FD, with diagnostic confirmation subsequently informed by neurological examination. While this algorithm requires prospective validation, health-care utilization data underscore the importance and need for more research in FD.

Introduction

Functional dystonia (FD) is an under-recognized and debilitating functional movement disorder (FMD) subtype that is difficult to diagnose and treat.[1] FMD represents up to 20% of patients in movement disorders clinics[2] and presents across the lifespan, from children[3] to elderly adults.[4] Despite the prevalence of FMD, neurologists often report feeling ill-equipped in diagnosis and treatment.[5] Insights into the pathophysiology of FMD reveal abnormal attentional focus, heightened affective reactivity, abnormal beliefs/expectations and impaired self-agency perceptions.[6] There has been a welcomed move to diagnose FMD using "rule in" examination features,[7] in place of nonspecific historical/psychiatric features.[8] However, diagnostic challenges remain, when assessing complex phenomenology, as seen in FD.[9] Early evidence-based diagnosis of FMD is important, particularly given associations between diagnostic delays, illness duration, and poor prognosis.[10]

FD is potentially the second most common FMD and among the most disabling and diagnostically challenging FMD subtype.[1] Typical historical features include sudden symptom onset, fixed dystonia at onset, inconsistent and variable phenomenology, spontaneous remission/recurrence, atypical precipitating/relieving factors (including placebo response to medications), and age of onset inconsistent with other primary dystonias (OD).[11] FD is frequently associated with pain,[12] especially in fixed dystonia, which can be associated with complex regional pain syndrome (CRPS) type I.[13,14] While useful, the predictive ability of these historical features has not been comprehensively investigated. Prognosis of FD is often poor,[1] particularly in fixed dystonia,[15] where some patients develop contractures and rarely even elect for limb amputation.[16]

Examination features of FD depend on the dystonic subtype (mobile, fixed, cranial, and paroxysmal) and are incongruent with OD, including absent (or atypical) sensory tricks and other functional neurological signs.[17,18] Diagnostic challenges include that the unusual postures generally do not comply with the typical hallmarks of other FMD clinical signs, including the absence of distractibility or entrainment.[17,18] The knowledge that FD and OD can coexist may make neurologists wary of making a diagnosis.[2] It has therefore been suggested that FD should only be diagnosed by a movement disorders specialist.[19] However, this can still be a daunting task, particularly for those with limited experience of evaluating complex dystonias, given poor inter-rater reliability[9] and poor specificity of a "laboratory-supported diagnosis" in FD using electrophysiology/kinematics.[20] Therefore, a "diagnostic odyssey" involving multiple neurological consultations and costly diagnostic testing frequently occurs.[21]

In this study, we sought to address knowledge gaps in the diagnosis and concomitant features comparing a large cohort of FD to age- and dystonia distribution-matched OD at the first visit to a specialist dystonia clinic. The aims were: 1) to identify historical predictors of FD vs. OD; 2) to develop a practical prediction algorithm to triage index of suspicion for FD; 3) identify factors associated with disability and symptom burden; and 4) record health-care utilization patterns in patients with FD.

Materials and Methods

This study was approved by the Partners Healthcare Institutional Review Board. We performed a retrospective case-control study comparing FD to OD, with case record review of all patients attending the mixed adult/pediatric Massachusetts General Hospital (MGH) Dystonia Center from January 2005 to May 2017. Inclusion criteria were a diagnosis of clinically-established FD[22] or primary OD based on neurological examination in adults/children (age $\geq$ 4). Exclusion criteria were the presence of concomitant "organic" dystonia in FD, or functional neurological signs in OD. All patients were assessed by movement disorders specialists with expertise in the diagnosis of dystonia. Clinical variables assessed were those documented at the initial clinic assessment; however, to ensure diagnostic accuracy, rigorous review of all available documentation/investigations was performed (including other hospital systems' electronic medical record [EMR], through shared access) to confirm the consistency of FD/OD diagnoses. Diagnosis was revised during longitudinal follow-up in five cases, which were excluded. Each FD/OD patient was classified by semiology and neurological examination at first visit, using current classification guidelines.[23] We utilized our hospital and shared EMR access up to August 2020 to assess levels of follow-up and patient outcome in all patients.

Of the 1474 new consultations, 143 consecutive cases (9.7%) met criteria for clinically-established functional neurological disorder (FND): 99 FD, with 33 other FMD and 11 weakness/nonmotor FND excluded. FD was second only to cervical dystonia (n = 212) as the most common diagnosis. Ninety-nine ODs were chosen to match the distribution of age, dystonia, and sex (when possible) in the FD cohort. Where the distribution of FD could not be exactly paired with an OD patient, a more widespread OD dystonia distribution was included, to avoid attenuating the comparator group severity. We also attempted to match for the presence of additional movement disorders (combined dystonia), which were common in FD but rare in OD. We therefore enriched the OD cohort with

combined dystonias as a secondary criterion, while prioritizing dystonia distribution matching. For the composition of the OD cohort, see Table 1.

Chart review measurements

We assessed historical features at first visit, including semiology/triggers, past medical/psychiatric history, psychosocial history, prescribed medications, drug allergies, and prior medical workup, including neuroimaging, neurophysiology (electroencephalography [EEG] and electromyography [EMG]), and lumbar puncture (LP). The estimated modified Rankin Scale (mRS), previously used in FND,[24] was chosen as a measure of functional status/disability. As secondary measures of symptom severity, we constructed patient-reported symptom burden (count) and examination-based severity measurements. Subjective sensorimotor symptom count involved summing patient report of 12 symptoms – dystonia, tremor, twitching/jerking, gait difficulties, speech disturbance, swallowing difficulty, eye/visual disturbance, pain, weakness, sensory complaints, fatigue, and shortness of breath – as previously described,[25] with cognitive symptoms recorded separately. In the FD group only, we assessed examination-based severity, summing 11 functional signs[26]: FD, entrainable/distractible tremor, distractible jerks/myoclonus, functional slowness/parkinsonism, functional dyskinesia, gait, eye movements, or speech disorder, functional (dissociative) seizures (if these occurred during examination), collapsing/give-way weakness, and nondermatomal/midline-splitting sensory deficits.

To estimate the economic impact of the diagnostic odyssey of FD vs. OD, we assessed costs of nonlaboratory investigations. Given considerable cost variation in the US health care system, we used 2020 regional "fair" prices for those with insurance,[27] as follows: magnetic resonance imaging (MRI) brain without contrast ($726; with contrast, $1196), MRI spine ($727), MR head or neck angiography ($698), computed tomography (CT) head or spine ($602), CT head or neck angiography ($351), CT dopamine transporter scan/positron emission tomography ($794), and hospital-performed EEG ($829), EMG ($381), and LP ($405).

Table 1. Disease composition of the primary dystonia (OD) cohort.

Type of dystonia	Dystonia distribution	Diagnoses
Isolated (n = 71)	Focal (n = 23)	4 Blepharospasm
		7 Cervical dystonia
		2 Hemifacial spasm
		9 focal leg/foot dystonia
		1 Focal hand dystonia
	Segmental (n = 23)	5 Meige syndrome
		17 idiopathic segmental dystonia
		1 DYT1/DYT-TOR1A
	Multifocal (n = 12)	9 Idiopathic multifocal dystonia
		3 DYT1/DYT-TOR1A
	Generalized (n = 13)	9 Idiopathic generalized dystonia
		3 DYT1/DYT-TOR1A
		1 DYT6/DYT-THAP1
Combined (n = 10)	Dystonia parkinsonism	1 DYT3/DYT-TAF1
	Dystonia and myoclonus	4 DYT11/DYT-SGCE
		2 myoclonus dystonia phenotype with negative testing
	Dystonia parkinsonism/chorea	3 DYT12/DYT-ATP1A3
Paroxysmal (n = 18)	Paroxysmal dystonia ± dyskinesia	15 negative genetic testing
		3 DYT10/PxMD-PRRT2 PKD

Statistical analyses

We compared FD vs. OD characteristics using Chi-squared and Fisher's exact tests for categorical variables and student's t-test and Wilcoxon rank sum test for continuous variables. Univariate screens were performed, and significant findings (conservative threshold for inclusion $P < 0.001$, given multiple testing) entered a second-level multivariate logistic regression analyses to assess prediction utility for FD vs. OD. Within-group analyses in FD were performed using multiple linear regression to assess clinical predictors of greater disability (mRS) and patient-reported symptom burden. Collinearity of categorical variables was assessed with Pearson correlation coefficient. Data were complete for all primary variables. For the model including number of allergies, one patient was removed owing to a missing value.

We developed a prediction algorithm to classify FD, prioritizing limiting false positive classification. After first identifying two highly disproportionate predictors for FD (see results), we subsequently used a second-level risk score to categorize the remaining FD/OD patients. Weights for risk score factors were based on beta estimates from multivariate logistic regression, rounded to nearest 0.5 unit for ease of calculation. Sensitivity/specificity for each cut-off score was calculated and we created receiver operating characteristic (ROC) curves predicting FD, calculated the area under the curve (AUC), and selected a score cutoff based on our predetermined specificity threshold (>90%). As a sensitivity analysis, we performed twofold cross-validation of the risk score. Statistical analysis was performed with SAS 9.4 (SAS Institute, Cary, NC) and R3.6.0 (r-project.org).

Data availability

Upon reasonable request from any qualified investigator, de-identified data are available to be shared by contacting the corresponding author.

Results

Cohort characteristics

Characteristics including demographics and dystonia distribution for the FD (n = 99, 85 adult/14 pediatric) and OD (n = 99, 80 adult/19 pediatric) cohorts are summarized in Table 2. There were more children in OD, owing to multifocal/generalized OD being more common in children but despite this, there was no significant difference in dystonia distribution. FD dystonia distribution included focal (23.2%), segmental (25.3%), multifocal (22.2%), and generalized dystonia (8.1%). There were high rates of combined dystonia (25.3%) and paroxysmal dystonia (21.2%) in FD, which were uncommon in OD and therefore less well matched.

Despite attempts at sex matching, FD was more common in females and OD had a younger age of onset, with particularly disparate onset age in FD vs. OD paroxysmal dystonia (30.5 ± 16.0 vs. 10.3 ± 4.6 years, $P < 0.0001$), given the early onset of genetic paroxysmal dystonia/dyskinesias. No paroxysmal OD patient had an onset age ≥ 20 years. There were significantly lower levels of follow-up in FD vs. OD, although skewed (owing to frequent single visits). FD patients were more likely to be unemployed/not attending school ($P < 0.0001$), and adults with FD (n = 85) were more likely on/pursuing medical disability compared to adults with OD (n = 80) at 50.6% vs. 10.0% ($P < 0.0001$). Marital status and educational level were similar between groups.

Table 2. Demographic details and dystonia distribution in functional dystonia and other neurological primary dystonia cohorts.

	Entire cohort (n = 198)			Adult cohort (age 18+) (n = 165)			Pediatric cohort (age < 18) (n = 33)		
Variable	Functional dystonia (n = 99)	Other primary dystonia (n = 99)	*P*	Functional dystonia (n = 85)	Other primary dystonia (n = 80)	*P*	Functional dystonia (n = 14)	Other primary dystonia (n = 19)	*P*
Demographic details									
Female, n (%)	86 (86.9)	58 (58.6)	**<0.0001**	74 (87.1)	49 (61.3)	**0.0001**	12 (85.7)	9 (47.4)	**0.024**
White, n (%)	88 (88.9)	79 (79.8)	0.078	75 (88.2)	64 (80.0)	0.15	13 (92.9)	15 (79.0)	0.27
Age at presentation, yr mean (SD)	38.0 (15.8)	38.1 (17.3)	0.97	41.8 (13.6)	44.2 (13.0)	0.25	14.8 (1.4)	12.2 (3.8)	**0.012**
Age of onset, yr mean (SD)	33.2 (15.5)	27.3 (17.5)	**0.012**	36.4 (14.3)	31.3 (17.0)	**0.040**	13.9 (1.5)	10.1 (3.6)	**0.0004**
Follow-up, months; median (IQR)	2 (9 0,9)	23 (57 0,57)	**<0.0001**	2 (132 0,8)	16.5 (56.5 0, 56.5)	**0.0005**	3.5 (15 0,15)	38 (48 4,52)	**0.036**
Married, n (%)	44 (44.4)	38 (38.4)	0.42	44 (51.8)	38 (47.5)	0.58	N/A	N/A	
College graduate, n (%)	47 (47.5)	48 (48.5)	0.89	47 (55.3)	48 (60.0)	0.54	0 (0)	0 (0)	
Unemployed or not attending school, n (%)	59 (59.6)	27 (27.3)	**<0.0001**	58 (68.2)	26 (32.5)	**<0.0001**	1 (7.1)	1 (5.3)	1
On or pursuing disability, n (%)	43 (43.4)	8 (8.1)	**<0.0001**	43 (50.6)	8 (10.0)	**<0.0001**	0 (0)	0 (0)	
Distribution of dystonia									
Isolated dystonia, n (%)	74 (74.7)	84 (84.8)	0.077	63 (74.1)	72 (90.0)	**0.0082**	11 (78.6)	12 (63.1)	0.46
Combined dystonia, n (%)	25 (25.3)	15 (15.2)	0.077	22 (25.9)	8 (10.0)	**0.0082**	3 (21.4)	7 (36.8)	0.46
Fixed dystonia, n (%)	15 (15.2)	1 (1.0)	**0.0003**	10 (11.8)	1 (1.3)	**0.0096**	5 (35.7)	0 (0)	**0.0084**
Focal, n (%)	23 (23.2)	23 (23.2)	1	18 (21.2)	20 (25.0)	0.56	5 (35.7)	3 (15.8)	0.24
Focal cervical, n (%)	7 (7.1)	8 (8.1)	0.79	7 (8.2)	8 (10.0)	0.79	0 (0)	0 (0)	
Focal limb, n (%)	10 (10.1)	10 (10.1)	1	6 (7.1)	7 (8.8)	0.78	4 (28.6)	3 (15.8)	0.42
Focal cranial, n (%)	6 (6.1)	6 (6.1)	1	5 (5.9)	6 (7.5)	0.76	1 (3.0)	0 (0)	0.42
Segmental, n (%)	25 (25.3)	29 (29.3)	0.53	24 (28.4)	27 (33.8)	0.44	1 (7.1)	2 (10.5)	1
Meige syndrome, n (%)	5 (5.1)	6 (6.1)	0.76	5 (5.9)	6 (7.5)	0.76	0 (0)	0 (0)	0.19
Other segmental, n (%)	23 (23.2)	22 (22.2)	0.87	21 (24.7)	20 (25.0)	0.97	2 (14.3)	2 (10.5)	1
Multifocal, n (%)	22 (22.2)	13 (13.1)	0.095	17 (20.0)	10 (12.5)	0.19	5 (35.7)	3 (15.8)	0.24
Generalized, n (%)	8 (8.1)	16 (16.2)	0.082	7 (8.2)	13 (16.3)	0.12	1 (7.1)	3 (15.8)	0.62
Paroxysmal, n (%)	21 (21.2)	18 (18.2)	0.24	19 (22.4)	10 (12.5)	0.097	2 (14.3)	8 (42.1)	0.13

P values in bold type indicate significance ($P < 0.05$). Abbreviations: yr, year; SD, Standard deviation; IQR, interquartile range.

Regarding dystonia semiology, fixed dystonia was notably more frequent in FD. Paroxysmal FD had atypical triggers not present in OD (e.g., a slight touch and loud noises) and type of movements and duration of episodes (seconds to hours) were often highly variable. However, in OD, events were generally stereotyped and had a consistent duration. Five adults had unequivocal FD and a comorbid neurological condition (mild Parkinson's disease, multiple sclerosis, high-functioning Fragile X, Joubert spectrum disorder with slight intellectual impairment, and prior traumatic brain injury).

Symptoms and dystonia onset

Historical features comparing FD to OD are shown in Table 3. Historical features significantly more frequent in FD ($P < 0.0001$) included an abrupt onset of maximal symptom severity (70.7% vs. 2.0%; strikingly common in pediatric FD), a physical precipitant (injury, trauma, or surgery) (25.3% vs. 2.0%), and spontaneous resolution/recurrence of dystonic symptoms (26.3% vs. 0%). Concurrent symptoms associated with FD included the presence of pain (75.8% vs. 27.3%, $P < 0.0001$), and in adults only, cognitive complaints (24.2% vs. 5.1%, $P = 0.0002$). FD patients were less likely to describe effective sensory tricks (5.1% vs. 16.2%, $P = 0.019$) and while these were typical in OD, in FD, the nature of the sensory tricks was highly atypical, including stroking and flexing an arm, leading to rapid resolution and sometimes resulting in the abnormal posture transferring to the opposite limb, touching a side of the face causing facial spasm to move to the other side, head shaking suddenly halting blepharospasm, and facial spasms and lip pulling completely resolving with speech but also resolving when closing the mouth. FD patients also had other unusual features, with 7.1% displaying placebo responses to medication/therapeutic trials.

Medical/psychiatric comorbidities

FD had higher rates of functional somatic disorders (FSDs) (fibromyalgia, CRPS type 1, irritable bowel syndrome [IBS], chronic fatigue syndrome etc.) 28.3% vs. 3.0% ($P < 0.0001$) and in children, FSDs were solely present in FD (21.4%) and absent in OD. IBS and fibromyalgia were most highly associated with FD. Autonomic symptoms were prevalent in FD, including gastroparesis (10.1%), sometimes requiring gastrostomy tube placement, and postural orthostatic tachycardia syndrome (POTS) (7.1%), which were present only in FD and frequently occurred together.

Psychiatric conditions were more prevalent in FD vs. OD, including a lifetime history of mood or anxiety disorder (58.6% vs. 26.3%), with anxiety disorders particularly prevalent. This difference was most pronounced in children. A lifetime history of eating disorder was only present in FD (8.1%). Twelve FD patients (12.1%) had prior psychiatric hospitalizations.

Family history

Family history (FH) was assessed, although the OD comparator cohort was enriched with genetic causes of dystonia. A FH of movement disorders was roughly half as common in FD than OD (24.2% vs. 47.5%), and a FH of dystonia was even less common (7.1% vs. 24.2%). One FD patient had a sister with confirmed FD. In contrast, FD were more likely to have a FH of psychiatric disorders than OD (29.3% vs. 4.0%).

Medications and allergies

Regarding current medication prescriptions at first visit, there were similar prescribing rates of typical medications used to treat dystonia, including trihexyphenidyl (10%) and carbidopa/levodopa (9%) (for potential dopa-responsive dystonia), while fewer FD patients had received botulinum toxin injections (29.3% vs. 50.5%, $P = 0.0023$) (See Figure 1). Prescription of controlled drugs (opiates/opioids or benzodiazepines) was substantially more common in FD (56.6% vs. 27.3%, $P < 0.0001$). The prescription of benzodiazepines was almost twice as frequent in FD (45.5% vs. 25.3%, $P = 0.0029$), with opiates/opioids three times as frequent and only prescribed in adults (25.3% vs. 8.1%, $P = 0.002$). In adults, 14/85 (16.5%) FD and 6/80 (7.5%) OD patients had a concurrent prescription of opiates/opioids and benzodiazepines, although nonsignificant ($P = 0.097$). When further analyzing the prescription of controlled drugs in adults, this was more common in females with FD 46/74 (62.2%) vs. males 5/11 (45.4%), whereas this was similar across sex in OD with females 15/49 (30.6%) vs. males 10/31 (32.3%), despite attempted sex matching between cohorts. In adults prescribed controlled drugs (FD n = 51/85, OD n = 25/80), this occurred mainly in the 36-55 years age group (FD n = 26/51, OD n = 13/25), accounting for more than half of the prescriptions.

Additionally, self-reported mean number of medication allergies was higher in FD (1.9 ± 2.8 vs. 0.6 ± 1.5, $P < 0.0001$). Having ≥ 3 allergies (meeting criteria for multiple drug intolerance syndrome[28]) was similarly more common in FD than OD (23.2% vs. 5.1%, $P = 0.0004$).

Predictors of FD vs. OD

Based on variables from Tables 2 and 3, we first performed a univariate screen followed by regression analysis

Table 3. Neuropsychiatric characteristics comparing functional dystonia and other neurological primary dystonia cohorts.

	Entire cohort (n = 198)			Adult cohort (age 18+) (n = 165)			Pediatric cohort (age < 18) (n = 33)		
Variable	Functional dystonia (n = 99)	Other primary dystonia (n = 99)	*P*	Functional dystonia (n = 85)	Other primary dystonia (n = 80)	*P*	Functional dystonia (n = 14)	Other primary dystonia (n = 19)	*P*
Onset and course									
Abrupt onset, n (%)	70 (70.7)	2 (2.0)	**<0.0001**	58 (68.2)	1 (1.3)	**<0.0001**	12 (85.7)	1 (5.3)	<0.0001
Physical precipitating event, n (%)	25 (25.3)	2 (2.0)	**<0.0001**	22 (25.9)	2 (2.5)	**<0.0001**	3 (21.43)	0 (0)	0.067
Spontaneous resolution/ recurrences, n (%)	26 (26.3)	0 (0)	**<0.0001**	22 (25.9)	0 (0)	**<0.0001**	4 (28.6)	0 (0)	0.025
Psychiatric and somatic symptoms									
Any psychiatric history, n (%)	64 (64.6)	27 (27.3)	**<0.0001**	55 (64.7)	25 (31.3)	**<0.0001**	9 (64.3)	2 (10.5)	0.0023
Lifetime mood disorder, n (%)	44 (44.4)	21 (21.2)	**0.0005**	40 (47.1)	20 (25.0)	0.0032	4 (28.6)	1 (5.3)	0.14
Lifetime anxiety disorder, n (%)	43 (43.4)	15 (15.2)	**<0.0001**	36 (42.4)	13 (16.3)	**0.0002**	7 (50.0)	2 (10.5)	0.019
Functional somatic syndromes, n (%)	37 (37.4)	4 (4.0)	**<0.0001**	33 (38.82)	4 (5.0)	**<0.0001**	4 (28.6)	0 (0)	0.025
CRPS-1, n (%)	7 (7.1)	1 (1.0)	0.065	5 (5.9)	1 (1.3)	0.21	2 (14.3)	0 (0)	0.17
Chronic fatigue syndrome, n (%)	4 (4.0)	2 (2.0)	0.68	3 (3.5)	2 (2.5)	1	1 (7.1)	0 (0)	0.42
Fibromyalgia, n (%)	11 (11.1)	1 (1.0)	0.005	11 (12.9)	1 (1.3)	0.0049	0 (0)	0 (0)	
Irritable bowel syndrome, n (%)	13 (13.1)	0 (0)	**0.0002**	12 (14.1)	0 (0)	**0.0003**	1 (7.1)	0 (0)	0.42
Presence of cognitive symptoms, n (%)	24 (24.2)	5 (5.1)	**0.0002**	24 (28.2)	5 (6.3)	**0.0002**	0 (0)	0 (0)	
Pain on presentation, n, (%)	75 (75.8)	27 (27.3)	**<0.0001**	65 (76.5)	24 (30.0)	**<0.0001**	10 (71.4)	3 (15.8)	0.0031
Family history									
FH neurological disorders, n (%)	52 (52.5)	56 (56.6)	0.57	47 (55.3)	44 (55.0)	0.97	5 (35.7)	12 (63.2)	0.17
FH movement disorders, n (%)	24 (24.2)	47 (47.5)	**0.0007**	22 (25.9)	37 (46.3)	0.0064	2 (14.3)	10 (52.6)	**0.033**
FH dystonia, n (%)	7 (7.1)	24 (24.2)	0.0014	6 (7.1)	19 (23.8)	0.0041	1 (7.1)	5 (26.3)	0.21
FH psychiatric symptoms, n (%)	29 (29.3)	4 (4.0)	<0.0001	26 (30.6)	3 (3.8)	<0.0001	3 (21.4)	1 (5.3)	0.29
Current medication and allergies									
Benzodiazepines, n (%)	45 (45.5)	25 (25.3)	**0.0029**	40 (47.1)	23 (28.8)	0.016	5 (35.7)	2 (10.5)	0.11
Opiates/opioids, n (%)	25 (25.3)	8 (8.1)	**0.002**	25 (29.4)	8 (10.0)	0.0032	0 (0)	0 (0)	
Trihexyphenidyl, n (%)	12 (12.1)	11 (11.1)	0.83	9 (10.6)	9 (11.3)	0.89	3 (21.4)	2 (10.5)	0.63
Carbidopa/levodopa, n (%)	9 (9.1)	9 (9.1)	1	9 (10.6)	5 (6.3)	0.32	0 (0)	4 (21.1)	0.12
Trial of botulinum toxin injections, n (%)	29 (29.3)	50 (50.5)	0.0023	25 (29.4)	46 (57.5)	**0.0003**	4 (28.6)	4 (21.1)	0.70
No. of allergies, mean (SD)	1.9 (2.8)	0.6 (1.5)	<0.0001	2.1 (2.9)	0.7 (1.7)	**<0.0001**	0.8 (1.3)	0.3 (0.7)	0.0072
≥ 3 allergies	23 (23.2)	5 (5.1)	**0.0004**	21 (24.7)	5 (6.3)	**0.0012**	2 (14.3)	0 (0)	0.17
Functional status									
Requires walking aid or wheelchair, n (%)	28 (28.3)	6 (6.1)	**<0.0001**	23 (27.1)	6 (7.5)	**0.001**	5 (35.7)	0 (0)	0.0084
Wheelchair bound, n (%)	8 (8.1)	1 (1.0)	0.0349	6 (7.1)	1 (1.3)	0.12	2 (14.3)	0 (0)	0.17

P values (Fisher's exact or χ^2) in bold are those meeting the threshold for inclusion ($P < 0.001$) into second-level analysis. Family history of psychiatric disorders denotes the presence of mood/anxiety, personality, or psychotic disorders. Abbreviations: yr, year; SD, Standard deviation; IQR, interquartile range; CRPS-1, Chronic regional pain syndrome type 1; FH, Family history; No., Number.

in the entire cohort (n = 198) and separately assessed the adult (n = 165) and pediatric (n = 33) cohorts for factors associated with FD, using our conservative inclusion threshold for inclusion in successive multivariate models ($P < 0.001$) (Table 4). We excluded sex, age, and dystonia distribution, as the OD cohort was selectively sampled on

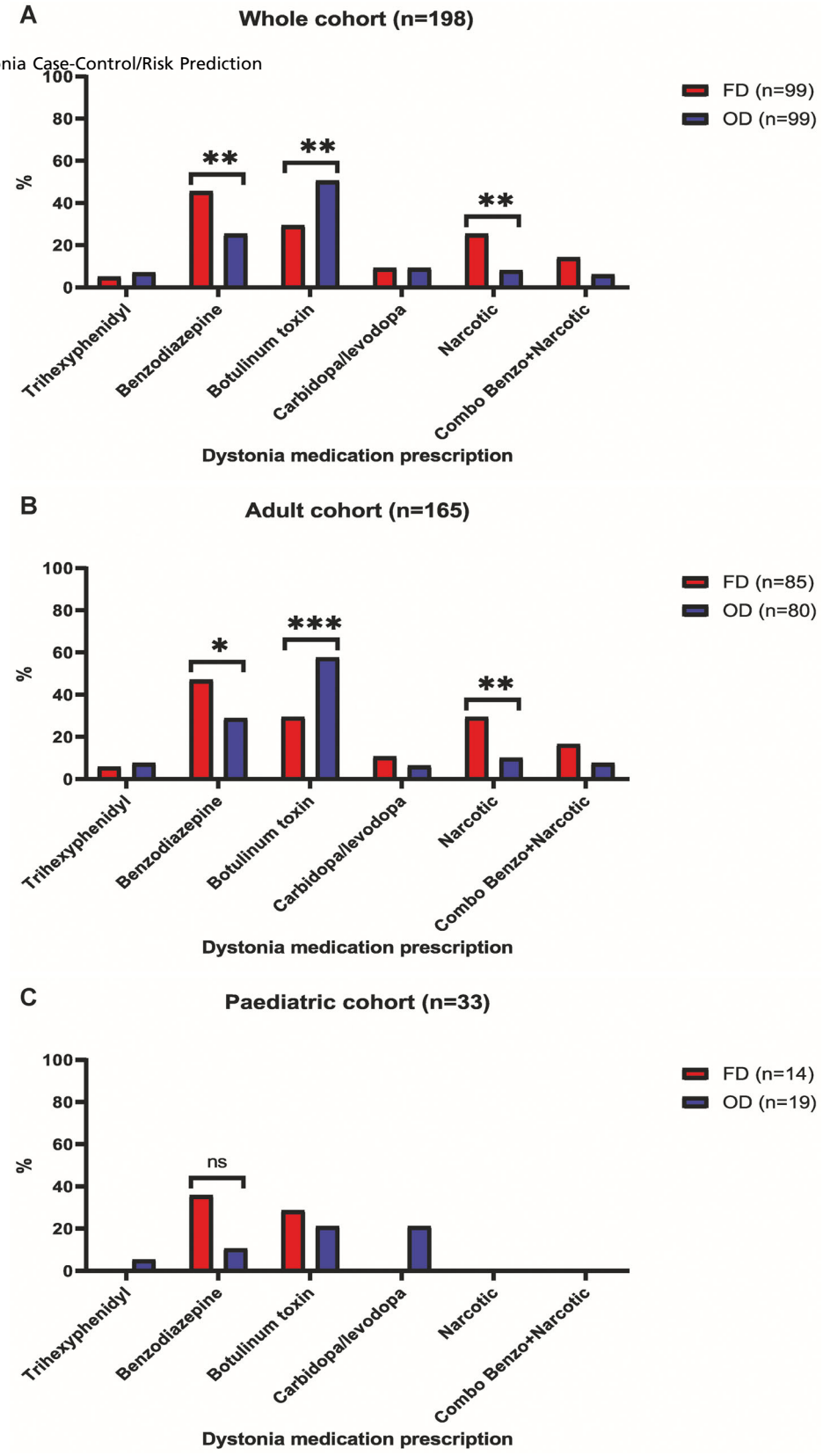

Figure 1. Current prescription of common medications to treat dystonia and movement disorders as taken by those with functional dystonia (FD) and those with other neurological causes of primary dystonia (OD). The bar charts depict the relative frequency of prescriptions of common medications to treat dystonia, as well as those of controlled drugs in the whole cohort (A), adult cohort (B), and pediatric cohort (C). Significance indicators: * ($P < 0.05$); ** ($P < 0.01$); *** ($P < 0.001$), NS (nonsignificant, $p \geq 0.05$). Abbreviations: Benzo: benzodiazepine; narcotic: opiate/opioid medication; combo: combination.

Table 4. Logistic regression analysis of significant clinical history predictors of functional dystonia (FD) vs. other neurological causes of primary dystonia (OD) with models involved in the development of the risk algorithm.

	Model 1 (FD = 99, OD = 99)				Model 2A (FD = 99, OD = 99)				Model 2B* (FD = 25, OD = 97)				Model 3* (FD = 25, OD = 97) 6-factor risk model				Model 4* (FD = 25, OD = 97) 4-factor risk model			
Predictor	Beta (SE)	OR	95% CI	*P*	Beta (SE)	OR	95% CI	*P*	Beta (SE)	OR	95% CI	*P*	Beta (SE)	OR	95% CI	p	Beta (SE)	OR	95% CI	*P*
Unemployed or not attending school	0.23 (0.49)	1.23	0.48-3.27	0.65																
Unable to ambulate unaided	0.57 (0.61)	1.76	0.53-5.84	0.35																
Physical precipitating event	1.67 (0.82)	5.30	1.06-26.61	0.043	1.56 (0.81)	4.77	0.97-23.47	0.055	0.39 (1.24)	1.47	0.13-16.84	0.76								
No FH of movement disorders	1.94 (0.51)	6.98	2.56-19.06	0.0002	1.94 (0.51)	6.96	2.58-18.73	0.0001	1.45 (0.70)	4.27	1.09-16.75	0.037								
Pain on presentation	1.74 (0.47)	5.71	2.26-14.43	0.0002	1.87 (0.46)	6.48	2.64-15.91	<0.0001	1.78 (0.69)	5.95	1.53-23.19	0.010	1.55 (0.66)	4.71	1.30-17.13	0.019				
≥3 different medication class allergies	1.28 (0.66)	3.58	0.98-13.10	0.054	1.34 (0.65)	3.83	1.06-13.75	0.040	1.21 (0.98)	3.36	0.49-23.11	0.22	0.90 (0.98)	2.47	0.36-17.02	0.36				
Functional somatic disorder (FSD)	1.60 (0.75)	4.95	1.13-21.65	0.034	1.74 (0.75)	5.71	1.31-24.79	0.020	1.64 (1.06)	5.16	0.64-41.56	0.12	1.64 (1.00)	5.14	0.73-36.47	0.10	2.55 (0.86)	12.77	2.37-68.88	0.0031
On or pursuing disability	0.94 (0.61)	2.57	0.78-8.43	0.12	1.18 (0.54)	3.26	1.14-9.29	0.027	1.16 (0.75)	3.19	0.73-13.98	0.12	1.05 (0.72)	2.85	0.70-11.62	0.14	1.65 (0.45)	5.2	1.45-18.57	0.011
Presence of cognitive symptoms	1.33 (0.63)	3.79	1.10-13.06	0.035	1.43 (0.63)	4.19	1.22-14.42	0.023	1.60 (0.87)	4.96	0.90-27.50	0.067	1.61 (0.89)	4.98	0.87-28.40	0.071	1.29 (0.80)	3.64	0.76-17.46	0.11
Lifetime mood or anxiety disorder	0.97 (0.45)	2.65	1.10-6.35	0.029	0.89 (0.44)	2.42	1.03-5.72	0.043	0.78 (0.67)	2.18	0.58-8.12	0.25	0.80 (0.64)	2.23	0.64-7.77	0.21	1.30 (0.59)	3.66	1.16-11.52	0.027
AUC (SE)	0.90 (0.021)		0.86-0.95		0.91 (0.021)		0.86-0.95		0.88 (0.047)		0.78-0.97		0.86 (0.050)		0.77-0.96		0.85 (0.047)		0.76-0.94	

The table illustrates the logistic regression models of the specified predictor variables, working toward the final choice (Model 4), which forms the basis for the risk score used in Step 3 of our prediction algorithm. Model 4 differs from the 4-factor risk score used, which is derived from this model but expressed as a single score produced from specified weighting of each of the variables. P designates Wald χ^2 *P* value. Abbreviations: SE, standard error; OR: odds ratio; CI: confidence interval; FH, family history; AUC: Area under the receiver operating characteristic curve.
*Indicates models with patients describing resolution/recurrence of symptoms (Step 1 of prediction algorithm) or an abrupt onset of maximal symptoms (Step 2 of prediction algorithm) excluded from analysis, as these steps already correctly classified 74 FD and misclassified 2 OD patients, as per Figure 2.

those factors. Disproportionately strong associations with FD across the whole cohort included the presence of spontaneous resolution/recurrence, abrupt onset of maximal symptom severity, and a physical precipitating event. In children, other than resolution/recurrence, features only present in FD included a physical precipitant (21.4%), comorbid FSD (28.6%), ≥3 medication allergies (14.3%), and inability to ambulate unaided (35.7%).

Subsequently, successive multiple logistic regression models were performed (Table 4). Owing to the very strong association, both the presence of spontaneous symptom resolution and an abrupt onset of maximum symptom severity were removed from the regression analysis and considered separately in the prediction algorithm. There was collinearity across being on/applying for medical disability and employment/school enrollment status (phi= 0.58, $P < 0.0001$), while inability to walk unaided had less correlation (phi= 0.28, $P < 0.0001$). Therefore, employment/school enrollment status and inability to walk unaided were excluded from Model 2 onwards. The final regression model assessing the entire cohort (Model 2A) revealed that at first visit, a physical precipitating event ($P = 0.040$), cognitive symptoms ($P = 0.028$), pain ($P < 0.0001$), being on/pursuing disability ($P = 0.015$) (not relevant for pediatric dystonia), lifetime mood/anxiety disorder ($P = 0.033$), comorbid FSD ($P = 0.018$), no FH of movement disorders ($P = 0.0001$), and ≥ 3 medication allergies ($P = 0.039$) were significant, independent predictors for FD vs. OD for the whole FD/OD cohorts.

With a view to producing a second level risk prediction score, we further refined the model by removing patients who endorsed the strongest historical predictors of FD (presence of resolution/recurrence of symptoms and abrupt onset of maximal symptom severity), leaving 25 FD and 97 OD patients remaining (Model 2B). In this reduced dataset, the presence of a physical precipitating event had a high overlap with abrupt onset (phi= 0.403, $P < 0.0001$) and was excluded. Furthermore, as the OD cohort was enriched with genetic dystonias, although there was a significant, independent association with FD diagnosis and not having a family history of movement disorders, this was also excluded from the six factor Model 3 risk score. An alternative four factor model (Model 4) with pain and having ≥ 3 medication allergies removed performed nearly as well as Model 3, seemingly preferrable to avoid misclassification of OD with pain (e.g., cervical dystonia).

As being on or pursuing disability can be related to a variety of factors, we additionally sought to compare this across the FD and OD groups (adults only). Comparing adult FD patients (n = 85) who were on or pursuing disability (n = 43) vs. those who were not (n = 42), mean mRS was significantly different between groups (2.3 ± 0.8 vs. 1.9 ± 0.7, $P = 0.0041$), whereas mean disease duration was similar between groups (65.4 ± 62.5 vs. 64.6 ± 71.9 months, $P = 0.96$). In adult OD patients (n = 80) who were on or pursuing disability (n = 8) vs. those who were not (n = 72), mRS was also significantly different between groups (1.9 ± 0.4 vs. 1.3 ± 0.6, $P = 0.0080$) and while mean disease duration was higher in those on or pursuing disability (184.5 ± 185.5 vs. 130.5 ± 139.0), this difference was not statistically significant ($P = 0.32$).

FD prediction algorithm

Thereafter, we produced a simple decision tree to classify FD patients by historical features to guide the clinician in the whole cohort (Figure 2). Step one (spontaneous resolution/recurrence) classified 26/99 (26.3%) FD, without false positives. Step two (abrupt onset of maximal symptoms) classified 48/73 of the remaining FD (cumulative 74.7%), with 2/99 OD false positives (2.0%). Step three involves applying a risk score to the remaining cohort (FD n = 25, OD n = 97) based on the final regression model (model 4, Table 3). Given the enriched genetic OD group, we also excluded the absence of a movement disorders FH. We adopted the following formula, based on the point estimates of the logistic regression: E (Suspected FD) = 2.5*[Presence of a comorbid FSD] + 1.5*[On or pursuing disability] + 1.5*[Presence of cognitive symptoms] + 1.5*[Lifetime history of mood or anxiety disorder]. Applying a score cutoff of ≥3 (indicating the presence of two or more risk score factors), further classified 14 FD patients (cumulative total sensitivity of 88.9% for FD), while misclassifying a further six OD patients (9.1% sensitivity and 91.9% specificity). We chose cutoffs based on maintaining a specificity >90%. Our algorithm was even more accurate for pediatric FD, where 12/14 were correctly classified after steps 1-2 (with only one false positive) and overall, yielding a sensitivity of 85.7% and specificity of 94.7% (see Supplemental Figure S1). We plotted ROC curves for the risk score applied to the remaining cohort and the entire 3-step algorithm (Figure 3). AUC for the 4-factor risk score model (step three) was 0.85 (95% CI 0.76-0.94), suggesting an excellent discriminatory ability. We compared this model with models including pain and having ≥3 medication allergies (such as Model 3) but these contributed little to the discriminatory capacity (6-factor model AUC 0.86 [95% CI 0.77-0.96]). When the entire 3-step algorithm was assessed, this yielded an AUC of 0.95 (95% CI 0.92-0.98). As a sensitivity analysis to address potential for overfitting of the risk score, a twofold cross-validation was performed. The AUCs from the cross-validation were similar to what was seen in the full cohort (AUC: 0.95 [95% CI 0.91-0.99]

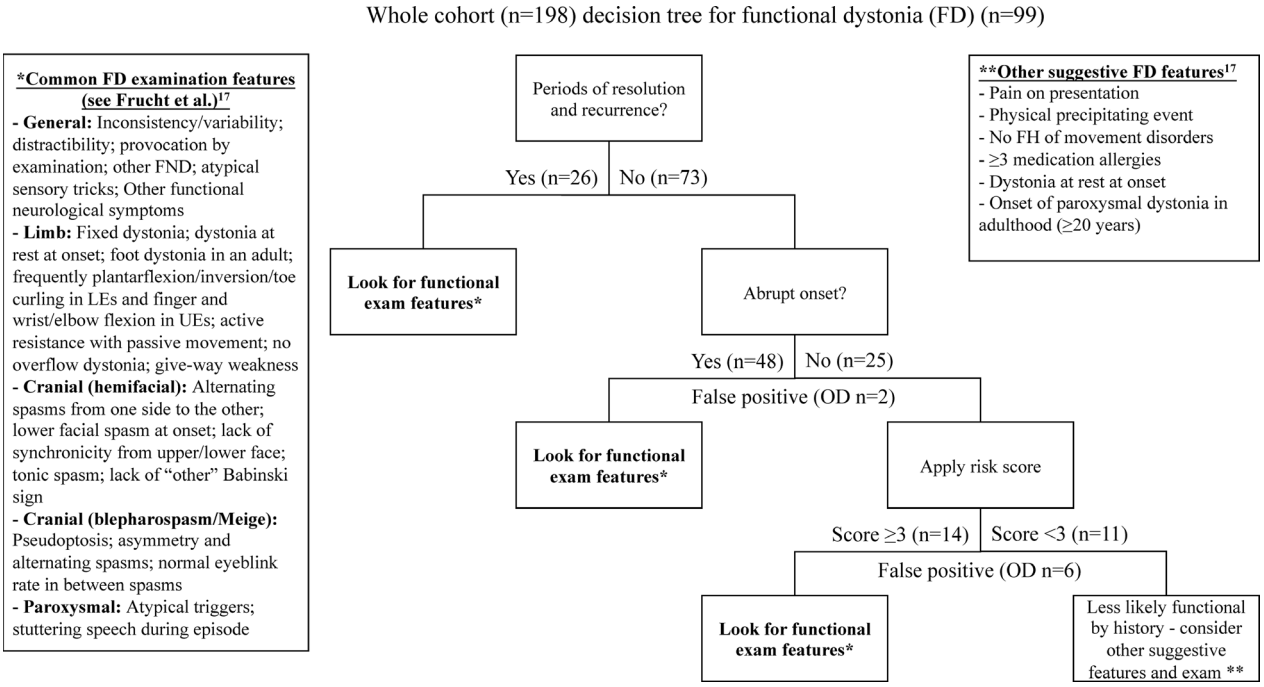

Figure 2. Decision tree with prediction algorithm for the whole cohort using historical features to aid in diagnosis of functional dystonia. Sensitivity of the algorithm for the whole cohort (n = 198) is 88.9% and specificity is 91.9%. Abbreviations: FND: functional neurological disorder; LEs: lower extremities; UEs: upper extremities.

and AUC: 0.93 [95% CI 0.88-0.98]) indicating less bias due to overfitting.

Measures and predictors of disability and patient-reported symptom count in FD

FD had higher levels of disability, with mean mRS 2.1 ± 0.8 vs. 1.4 ± 0.6 ($P < 0.0001$). A considerable majority of FD reported disability (mRS ≥ 2) related to their symptoms (83.8% vs. 31.3%, $P < 0.0001$). More FD patients were unable to ambulate unaided (28.3% vs. 6.1%, $P < 0.0001$) and 8.1% vs. 1.0% required a wheelchair ($P = 0.035$). FD also had a higher mean verbal symptom count than their OD counterparts (4.7 ± 2.3 vs. 1.8 ± 0.9 symptoms, $P < 0.0001$). In FD, mean functional examination signs were 2.4 ± 1.4 in adults and 2.2 ± 0.8 in children. There was moderate correlation between mRS and verbal symptom count (r = 0.45, $P < 0.0001$), and mRS and number of functional examination signs (r = 0.49, $P < 0.0001$).

In multivariate linear regression analyses, a worse mRS score independently correlated with a number of functional examination features ($P = 0.0067$), unemployment/not attending school ($P = 0.0056$), number of medication allergies ($P = 0.019$), and younger age of presentation ($P = 0.031$) (Table 5). Increased patient-reported symptom count independently correlated with increased functional examination features ($P < 0.0001$), presence of spontaneous resolution/recurrence ($P = 0.021$), and cognitive symptoms ($P < 0.0001$).

FD diagnostic odyssey

FD had more independent neurological consultations (within our system or out-of-state) than OD prior to assessment at our specialist dystonia clinic (mean prior neurologists 3.3 ± 2.0 vs. 2.0 ± 1.5, $P < 0.0001$) and one patient had 14 prior neurological opinions (See Supplemental Figure S2). The frequency of common neurological investigations is shown in Figure 4. FD had substantially higher rates of neuroimaging, including MRI brain/spine (86.9% vs. 62.6%, $P < 0.0001$) and CT head/spine imaging (37.4% vs. 11.1%, $P < 0.0001$), and were more likely to have repeated MRIs (25.3% vs. 9.1%, $P = 0.0042$). FD had significantly higher rates of neurophysiological testing, including EMG (37.4% vs. 21.2%, $P = 0.013$), EEG (38.4% vs. 17.2%, $P = 0.0009$), and LPs (15.2% vs. 5.1%, $P = 0.032$) and similar rates of nonstandard, often extensive laboratory testing. In adults, rates of investigation were significantly higher in FD, while in children, rates were similar. Using "fair" 2020 costs for investigations in our region (see methods), an approximate comparison of total neuroimaging, neurophysiology, and LP expenditure prior to first visit yielded significantly

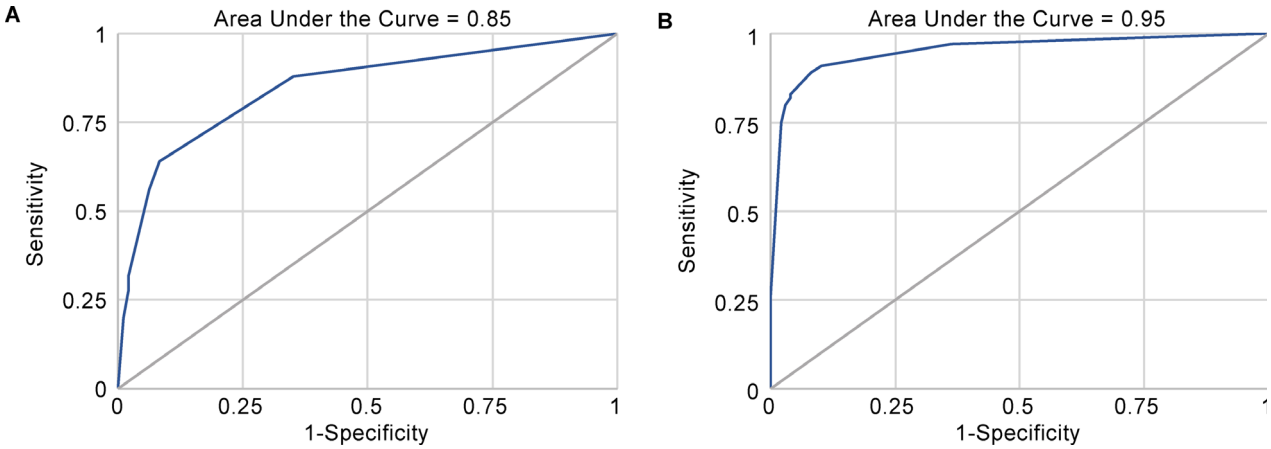

Figure 3. Receiver operating characteristic (ROC) curve for risk score predicting a diagnosis of functional dystonia (FD) vs. other neurological causes of primary dystonia (OD) for the remaining cohort (Step 3 only) and the entire algorithm (Steps 1-3). The figure illustrates the ROC curves for the risk score (step three) (A) and for the entire algorithm (B).

Table 5. Linear regression of significant clinical history predictors of disability and symptom burden in functional dystonia.

Functional Dystonia, n = 99	Beta	SE Beta	*P*
Worse modified Rankin Scale Score (mRS)			
Number of functional examination features	0.15	0.055	0.0067
Unemployed or not attending school	0.46	0.16	0.0056
Number of medication allergies	0.064	0.027	0.019
Age at presentation (years)	−0.011	0.005	0.031
Symptom Count (self-reported sensorimotor symptoms)			
Number of functional examination features	0.75	0.13	<0.0001
Spontaneous resolution/recurrences	0.91	0.39	0.021
Cognitive symptoms	2.26	0.40	<0.0001

Abbreviation: SE, standard error.

higher costs in FD ($2659 ± 1868 vs. $1340 ± 1367, $P < 0.0001$).

Exploring outcomes in FD vs. OD

Assessing outcomes was challenging in the FD cohort: 40 (40.4%) of FD and 30 (30.3%) of OD had a single visit. In patients with ≥12 months of follow-up (FD n = 24, OD n = 57), FD patients had low rates of self-rated symptom improvement at 1 year (20.8% vs. 76.4%), $P < 0.0001$. In FD patients, follow-up was offered to 74 patients (74.7%) and in the remainder, the plan was to follow with a local neurologist, generally related to patients living a long distance from our center. Of the FD patients offered follow-up, 59/74 (79.7%) returned for at least one follow-up appointment (including two that only followed up with allied MGH FND Clinic providers). A specialist FND Clinic at MGH was established in August 2014, and 11 of 42 (26.2%) eligible patients with FD were referred there. Regarding rehabilitative management, which includes physical therapy (PT), occupational therapy (OT), and speech and language therapy (SLP), 60 (60.6%) were referred for any rehabilitation (PT/OT/SLP), 55 (55.6%) were referred for PT, 15 (15.2%) were referred for OT, 7 (7.1%) were referred for SLP, and 14 (14.1%) were referred for multiple rehabilitative modalities. In addition, 56 (56.6%) were attending or recommended mental health care (psychiatry/psychology), including 11 patients referred to the MGH FND Clinic for their treatment program (only available after August 2014) and of those, 22/56 (39.3%) were referred to psychotherapy (generally cognitive behavioral therapy).

Over the course of their illness, FD patients had significantly higher rates of treatment interventions, including surgeries (not including deep brain stimulation [DBS]), injections/nerve blocks, and other procedures (20.2% vs. 2.0%, $P < 0.0001$). FD had potentially unnecessary procedures: two patients (one child and one adult) subsequently had DBS at another institution without improvement and one patient had a spinal cord stimulator placed, again without significant improvement. Fixed dystonia resulted in extensive orthopedic surgery or serial casting in two cases. Inexplicably, one adult FD patient had considerable improvement in functional symptoms following a cardiac arrest (iatrogenic from lorazepam for presumed functional [psychogenic nonepileptic/dissociative] seizures). FD patients were also more likely to have hospital visits in the 6 months before or after the first clinic visit than OD, with higher ED visits (43.4% vs.

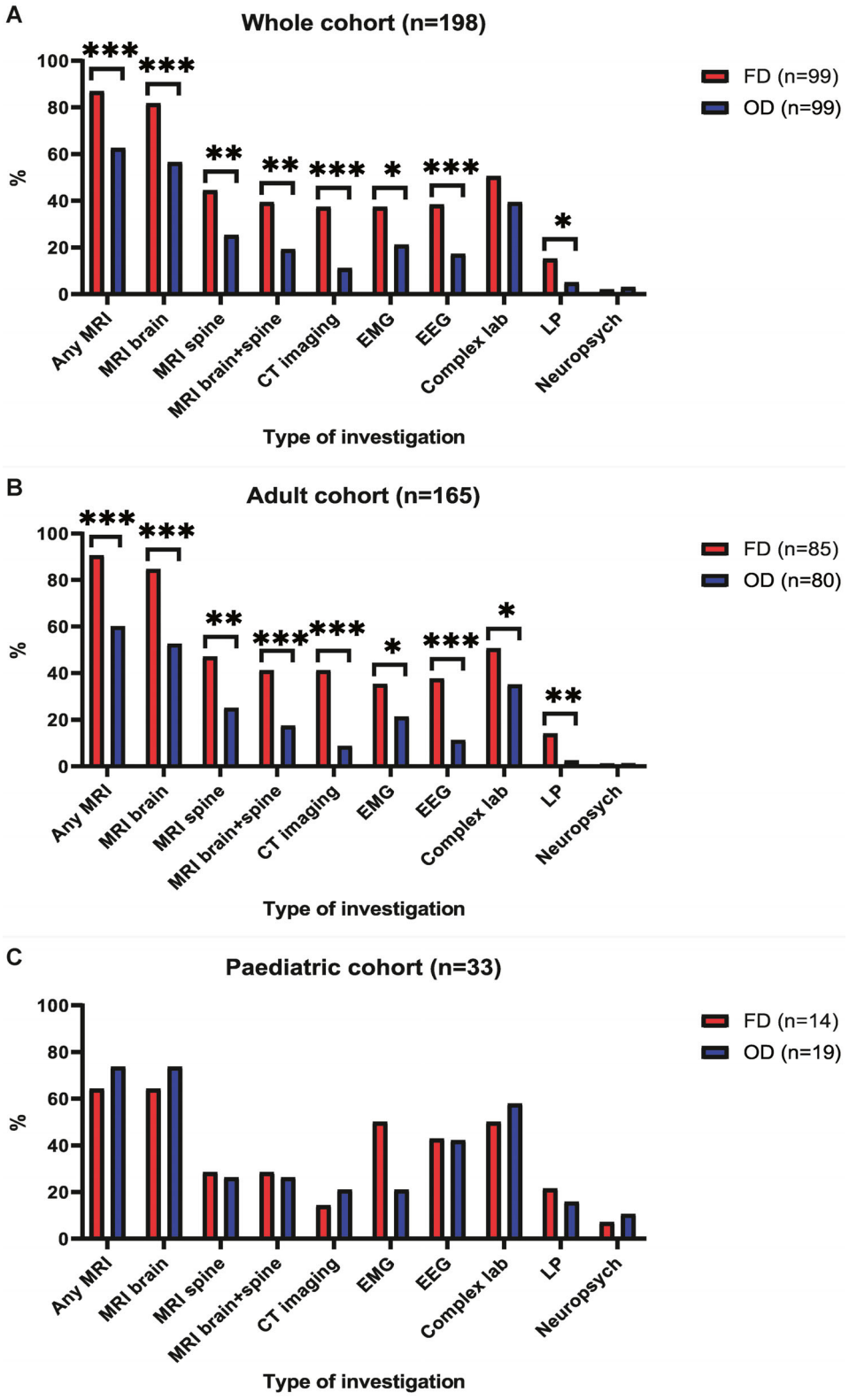

Figure 4. Relative frequency of common neurological investigations in functional dystonia (FD) vs. other neurological causes of primary dystonia (OD). The bar charts depict the relative frequency of investigations in the whole cohort (A), adult cohort (B), and pediatric cohort (C). Significance indicators: * ($P < 0.05$); ** ($P < 0.01$); *** ($P < 0.001$). Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; EMG, electromyogram; EEG, electroencephalogram; LP, lumbar puncture; Neuropsych, neuropsychological testing.

14.1%) and nonelective hospitalizations (29.3% vs. 5.1%), both $P < 0.0001$. As a reflection of the diagnostic odyssey and high health-care utilization, 37/99 FD patients (37.4%) sought additional neurological consultations following their Dystonia Center assessment, sometimes seeking multiple opinions across several states.

Discussion

This study compared a large cohort of 99 adult and pediatric FD patients with age-/distribution-matched OD controls, identifying several historical features that robustly differentiated FD from OD at first visit. We subsequently developed a practical risk prediction algorithm (verified with twofold cross-validation) based on our findings to prompt clinicians to raise their index of suspicion for a functional neurological etiology and subsequently probe for "rule in" functional examination features to confirm the diagnosis.[17] We also highlight a major public health concern: an increased tendency for FD patients to be prescribed controlled drugs. FD had a considerable diagnostic odyssey and higher health-care utilization than their OD counterparts.

Patients with FD exhibited phenotypic, historical, medical/psychiatric, and psychosocial characteristics that distinguished this population from OD. Paroxysmal FD was common (rare in OD), and had an older age of onset.[29] Combined dystonia[30] and fixed dystonia were also rare in OD but common in FD. FD rarely had a comorbid major neurological condition.[31] Abrupt symptom onset (particularly in children[3]), a physical precipitating event, and spontaneous symptom resolution/recurrence were strongly associated with FD.[11,17] Although spontaneous remissions can occur in OD, they are highly uncommon, mainly described in cervical dystonia and blepharospasm/Meige syndrome.[32,33] Although in the present OD cohort no patients had complete resolution/recurrences of symptoms, in our clinical experience (assessing the full records of all OD patients presenting to the Dystonia Center), we have seen exceptionally rare cases of this occurring, primarily in cervical dystonia, as has been reported in the literature. In such cases, however, the abnormal neck posture in question tended to occur in the setting of acute pain or injury, sometimes involving a fixed posture and frequently afterwards, there was the development of a more typical dynamic dystonia phenomenology. For this and other reasons, differentiating FD from OD is especially fraught with difficulty in cases of suspected functional cervical dystonia,[17] particularly posttraumatic dystonia, where those with quick onset after the inciting event may have functional neurological features.[34] This difficulty is mitigated by the small proportion (<10%) of focal cervical forms in both cohorts.

Nonmotor symptoms also differentiated FD from OD. FD more frequently endorsed pain on presentation and cognitive symptoms.[12] The strong association between pain and FD is noteworthy, as concurrent pain is correlated with poor clinical outcomes.[17,35] However, pain is not infrequent in OD, and is a common symptom in cervical dystonia[36,37] and a powerful determinant of disability.[38] In comparison, cognitive symptoms are generally not associated with OD but are increasingly recognized in FMD.[39]

Representing a notable public health concern, FD patients were more likely to be prescribed habit-forming medications, namely opiates/opioids and benzodiazepines, particularly in females aged 36-55. Increased opiate use in FD may be related to painful functional muscle spasms and associations with fibromyalgia/other FSDs (higher in FD) that are poorly responsive to typical analgesics.[40] In OD, Mahajan et al. noted substance abuse in 11% of a large cohort of cervical dystonia.[41] Co-prescription of opioids and benzodiazepines (higher in FD) is associated with higher risks of overdose.[42] FD were also more likely to report ≥3 medication class allergies, meeting criteria for multiple drug intolerance syndrome.[28] A higher number of medication allergies have distinguished dissociative seizures from epilepsy[43] and predicted longer illness duration.[44]

We created a practical decision tree to allow historical classification of suspected FD in adults and children. We began with the strongest predictors of FD: step one (symptom resolution/recurrence) and step two (an abrupt onset of maximal symptom severity), followed by step three, applying a risk score involving strong predictors of the remaining cohort (presence of FSD, being on/pursuing disability, cognitive symptoms, or a lifetime history of mood/anxiety disorder), using the presence of ≥2 predictors as a cutoff. Being on/pursuing disability is not relevant to pediatric FD but was included given its utility across the age range. These three steps yielded a cumulative sensitivity and specificity of approximately 90% across the entire cohort, with an excellent discriminatory ability and was even more accurate in predicting pediatric FD, although limited by sample size.

This algorithm can be complemented by other strong historical indicators of FD from this study: 1) paroxysmal patients with an age of onset ≥20 years (not present in OD); or 2) the presence of fixed dystonia, which was very rare in OD.[14,17] Although having a FH of movement disorders (and particularly dystonia) was significantly less frequent in FD than OD, we did not include this in our algorithm given the large number of genetic forms in our OD cohort (unavoidable owing to the widespread distributions and combined phenotypes, which, in OD, are invariably genetic in origin). It is notable, however, that

this observation has also been demonstrated in other reports and should be considered by clinicians.[45,46] Another useful clue for the clinician, which is reinforced in the present study, is the absence of, or the presence of atypical sensory tricks in FD, in comparison to more frequent (found in more than half of patients with facial/cervical dystonia) and typical sensory tricks in OD, consistent with previous findings.[11,17,47]

The importance of this adjunctive clinical tool is manifold. Since a general neurologist initially sees most patients with FD and local movement disorders expertise may not be readily available, this algorithm is meant to guide clinicians to raise their suspicion for FD. This would then prompt the clinician to carefully look for inconsistent and incongruent "rule in" functional signs for FD,[17] as well as including FD in their differential diagnosis for unusual dystonia presentations if an alternative diagnosis is not readily apparent.[17] This prediction algorithm requires further prospective validation to assess its utility.

We do not recommend that clinicians solely use these historical factors in making a diagnosis of FD, as the presence of highly discriminatory clinical examination features is essential for diagnosis.[8] Misdiagnosis may risk inappropriate treatment of OD as functional, particularly by those early in neurological training.[48] However, timely and accurate diagnosis of FD can open the door to starting appropriate treatment, a very different management pathway from OD. FND care involves the multidisciplinary involvement of neurologists, psychiatrists, psychotherapists (cognitive/behavioral therapy), and rehabilitation clinicians (physical, occupational, and speech therapy).[7,17] A specialist FND clinic can be utilized in complex or difficult to diagnose cases, if available.[49]

Additionally, we acknowledge that being on or pursuing disability is a complex issue, which is not relevant for children; it was felt, however, important to include as this variable was a major discriminating factor between the matched dystonia groups. Firstly, with children excluded, the prevalence of being on or pursuing disability in adults with FD was significantly higher than in OD. We also assessed associations with overall severity of functional disability (as measured by the mRS) and disease duration, two factors strongly associated with being unable to work and applying for disability benefits. Unsurprisingly, the mRS score was higher in both adult FD and adult OD patients on or seeking disability; however, there was no significant relationship between disability and disease duration in FD. This further underscores the importance and relevance of being on or pursuing disability in our prediction algorithm, given that this data point represents an easily ascertained marker of high functional disability, which can be asked on the initial clinical visit and serves as a proxy for the degree of functional impairment seen in patients with FD. Nonetheless, we do not in any way suggest that the clinician should infer from medical disability status that patients are consciously seeking secondary gain, as FMD patients are frequently more debilitated than some other movement disorders, which makes their disability claims legitimate and appropriate.

Subjective symptom count (an approximate measure of symptom burden) was higher in FD vs. OD. It is not unusual for FND patients to have a "pan-positive" review of systems (ROS).[50] However, there is disagreement regarding whether somatic symptom count can distinguish patients with FND vs. other medical conditions: a prospective study of neurology outpatients showed a lack of discriminatory ability for FND,[51] whereas a retrospective study of epilepsy patients found that a ROS questionnaire was a useful predictive tool for dissociative seizures.[50] Additionally, a worse mRS-based functional status was predicted by more functional examination features, being unemployed/not attending school, number of medication allergies, and a lower age of first visit.

FD patients underwent a diagnostic odyssey, akin to those with rare neurological disorders (despite FMD being common). FD patients had a higher number of neurological consultations than OD patients prior to visiting our specialist dystonia clinic, including one patient who saw an astounding 14 different neurologists. FD had considerably higher rates of diagnostic testing prior to their visit, as well as repeated imaging, owing to persistent, worsening, or changing symptoms. This diagnostic odyssey continued even after their Dystonia Center consultation, with over one third of FD patients seeking additional neurological consultations following their assessment.

Outcome assessment was limited owing to limited patient follow-up. Based on available data, FD had low levels of symptom improvement, consistent with prior studies.[1] Although the standards of FND care have changed over the span of our data (2005-2017), over 60% of FD patients were referred for rehabilitative treatment and over 50% were referred for mental health treatment for their symptoms, including referral to the specialist MGH FND Clinic, consistent with the multidisciplinary care suggested for FND patient management.[7,17]

Over the course of their illness, FD had a higher rate of medical procedures and surgeries. Additionally, FD had roughly three times as many ED presentations and six times as many nonelective hospitalizations related to their symptoms, in the 6 months before or after their first clinic visit. Taken together, the greater number of medical and neurological opinions, investigations, greater ED visits/hospitalizations, and medical procedures demonstrate greater health-care utilization and economic burden.[21,52]

Therefore, early diagnosis may save costs, underscoring the potential benefit of our prediction algorithm.

We found high levels of autonomic symptoms, including gastroparesis and POTS, in FD but not OD. POTS shares a similar problem with FND, with an often considerable diagnostic odyssey,[53] and association with FSD including IBS, fibromyalgia, and chronic fatigue syndrome,[53] which were more common in FD. FD were also more likely to have a history of an eating disorder, as has been described in a study of pediatric FD.[54] Eating disorders may be associated with increased somatic symptoms.[55-57] Potential associations between FD and abnormal eating behaviors require further study, including investigating if shared involvement of impaired autonomic and interoceptive mechanisms may help explain these co-occurrences.[58]

Limitations include the retrospective design, that the prediction algorithm does not directly lead to a FD diagnosis but instead prompts the clinician to assess for specific functional neurological clinical signs (when historical factors indicate a higher likelihood of FD), and limited data regarding clinical outcomes. There was also imperfect age matching that was somewhat unavoidable, as the goal was to match distribution first. Probing for psychologically sensitive content (such as abuse or post-traumatic stress disorder) likely did not occur consistently across initial clinical encounters (and would likely not have been asked in OD patients) and hence this could not be adequately assessed in our study. We acknowledge that the high prescription of controlled drugs in the FD patients may reflect the higher rates of pain in this population, as well as at times of inadequate treatment in the community of chronic, intractable pain. Furthermore, the prescription of opiates/benzodiazepines in patients with FD speaks to a larger issue beyond FD itself, which is the misuse of these medications in the management of chronic pain, which may be particularly resistant to treatment in FD with concurrent CRPS.[12,13] Although we assessed multiple EMRs, potentially relevant records were not always available, which may have precluded full identification of investigations prior to the first visit, and neurological consultations following their assessment at the MGH Dystonia Center. We were also unable to accurately record data regarding adherence to treatment recommendations (PT/OT/SLP and mental health care), as patients frequently engaged in treatment outside of our medical center or shared EMR record access. As such, additional prospective outcome and treatment studies in FD are needed. Given the specialist nature of our clinic, with straightforward dystonia presentations commonly managed locally, complex cases are disproportionately referred, particularly FD, which may limit generalizability. Patients with other neurological disorders and concurrent FD were included to be representative of real-life practice.[31] We used 2020 U.S. costs for investigations performed in the cohort to approximate the economic impact of diagnostic workups; further detailed econometric assessment comparing FD to OD is required.

Conclusions

We identified several historical features that differentiated FD from OD in our specialist dystonia clinic population. FD patients were more debilitated than OD, less able to work, and more frequently requiring disability benefits. We developed a practical prediction algorithm, based on historical characteristics, as an aid to clinicians to raise their index of suspicion for FD and to subsequently probe for diagnostic examination features. Of concern, FD patients were more likely to be prescribed controlled drugs, increasing the risk of dependence and substance abuse. FD also had a considerable diagnostic odyssey and high health-care utilization. Taken together, these underscore the need for continued research into timely and accurate diagnosis in FD – including prospectively validating the proposed prediction algorithm.

Author Contributions

C.S. prepared the first draft of the manuscript. C.S. and N.S. contributed to the conception and design of the study. C.S. contributed to the acquisition of the data. C.S., D.L.P., L.C., and N.S. contributed to the analysis and interpretation of the data. C.S., D.L.P., L.C., and N.S. performed critical revision of the manuscript for important intellectual content.

Conflict of Interest

The authors describe no conflict of interest relevant to the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplemental Figure S1. Decision trees with prediction algorithm for the adult and pediatric subcohorts using historical features to aid in diagnosis of functional dystonia. Adult (A) and pediatric (B) decision trees are shown. The sensitivity and specificity of the prediction algorithm for detect functional dystonia in the adult and pediatric subcohorts are as follows: Adult cohort (n = 165) sensitivity 89.4%, specificity 91.3%, pediatric cohort (n = 33), sensitivity 85.7%, specificity 94.7%.

Supplemental Figure S2. Number of different neurological consultations seen prior to first visit in functional dystonia vs. other neurological causes of primary dystonia. The chart depicts the histograms and overlaid frequency curves for the number of independent neurological opinions prior to the first MGH Dystonia Center visit in the functional dystonia (FD) and other primary dystonia (OD) cohorts. Abbreviations: No.: number.

