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ARTICLE

Dystonia and Tremor

A Cross-Sectional Study of the Dystonia Coalition Cohort

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Abstract

Objective

To assess the clinical manifestations and predictors of different types of tremors in individuals with different types of isolated dystonia.

Methods

Clinical manifestations of tremor were assessed in a multicenter, international cross-sectional, cohort study of 2,362 individuals with all types of isolated dystonia (focal, segmental, multifocal, and generalized) recruited through the Dystonia Coalition.

Results

Methodical and standardized assessments of all participants in this cohort revealed the overall prevalence of any type of tremor was 53.3%. The prevalence of dystonic tremor varied from 36.9% to 48.4%, depending on criteria used to define it. To identify the factors associated with tremors in dystonia, the data were analyzed by generalized linear modeling and cluster analyses. Generalized linear modeling indicated 2 of the strongest factors associated with tremor included body region affected by dystonia and recruitment center. Tremor was also associated with severity of dystonia and duration of dystonia, but not with sex or race. The cluster analysis distinguished 8 subgroups within the whole cohort; defined largely by body region with dystonia, and secondarily by other clinical characteristics.

Conclusion

The large number of cases evaluated by an international team of movement disorder experts facilitated the dissection of several important factors that influence the apparent prevalence and phenomenology of tremor in dystonia. These results are valuable for understanding the many differences reported in prior studies, and for guiding future studies of the nosology of tremor and dystonia.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BFM = Burke-Fahn-Marsden Dystonia Rating Scale; **GDRS** = Global Dystonia Rating Scale; **MDS** = Movement Disorders Society; **TAWD** = tremor associated with dystonia.

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive and patterned, movements or postures.[1] In contrast, tremor is defined as a disorder characterized by rhythmical oscillations of a body region.[2]

Although dystonia and tremor are distinct disorders, they are closely related. Individuals diagnosed with dystonia frequently have tremor, with reported prevalence rates ranging from 14% to 90%.[3] Conversely, many individuals diagnosed with tremor disorders also have dystonia, with coprevalence rates of 1%–27%.[3] The wide variations in coprevalence rates for dystonia and tremor reflect multiple issues including clinical and etiologic heterogeneity among different cohorts, how dystonia and tremor were assessed, and varied interests of investigators conducting the studies.

In addition to uncertainties about coprevalence rates for dystonia and tremor, these 2 disorders can sometimes be difficult to distinguish clinically. Dystonic movements occasionally have a tremor-like appearance because they can be repetitive and oscillatory. These tremor-like movements of dystonia have been termed dystonic tremor. However, operational definitions for dystonic tremor have varied considerably over the years.[4–8] To address these differences, an expert panel recently released a consensus statement,[2] but disagreements have persisted.[9–13]

A better understanding of the relationships between dystonia and tremor will ultimately require expert opinion be supported by empirical evidence. To this end, the current study takes advantage of a large cohort of 2,632 patients with various forms of isolated dystonia to delineate the prevalence and manifestations of different tremor phenomenologies.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

We received institutional approval from an ethical standards committee on human experimentation for any experiments using human participants. All participants (patients) in the study provided written informed consent. This study is not a clinical trial, hence public trials registry or clinical trial identifiers are not applicable.

Participants and Recruitment

Participants were recruited by 37 sites participating in the Dystonia Coalition, a part of the NIH Rare Diseases Clinical Research Network (rarediseasesnetwork.org/cms/dystonia). The majority of the sites were distributed across North America (United States and Canada), with 4 in Europe (France, Germany, Italy, United Kingdom) and 1 in Australia.

To be included, participants had to be at least 18 years of age and have a diagnosis of isolated dystonia (previously known as primary dystonia) according to current criteria.[1] Any region of the body could be affected, alone or in various combinations (focal, segmental, multifocal, and generalized). The vast majority of cases were idiopathic, but a small fraction had known genetic defects.[14] The study excluded dystonia syndromes combined with other neurologic features (previously known as dystonia-plus syndromes or heredodegenerative dystonias), acquired dystonias (such as tardive syndromes or encephalitis), and functional (psychogenic) dystonia. Participants treated with botulinum toxin were not excluded, although all participants were to be enrolled when the movement disorder was apparent, which was typically at least 3 months following treatment, and never less than 2 months following treatment. Prior surgery for dystonia is not an exclusion criterion for the Dystonia Coalition cohort, but all such cases were excluded from this study to avoid inclusion of cases where surgery might result in atypical residual manifestations. The study included 2,362 participants recruited from December 2009 to December 2015. Table 1 summarizes inclusion and exclusion criteria.

Clinical Assessment of Dystonia and Tremor

All investigators collected clinical data using a standardized data elements form that was developed in collaboration with investigators in North America and Europe, along with representatives from the Office of Rare Diseases Research at National Center for Advancing Translational Sciences, the National Institute of Neurological Disorders and Stroke, and the Coriell Institute for Medical Research.[15] All cases were to be evaluated by individuals with expertise in movement disorders. The neurologic examination was standardized and structured specifically to elicit dystonia by merging previously published protocols used for different types of focal or generalized dystonias.[15] The severity and body distribution of dystonia were assessed via the Burke-Fahn-Marsden Dystonia Rating Scale (BFM) and the Global Dystonia Rating Scale (GDRS).[16] However, because the BFM is nonlinear and applies different weights to different body regions, only the GDRS scores were used here.

Consistent with current criteria for diagnosis of isolated dystonia,[1] cases with coexisting tremor were not excluded. Dystonia Coalition investigators therefore also collected information regarding tremor. The structured examination included many of the same items recommended for the assessment of tremors using The Essential Tremor Rating Assessment Scale (TETRAS) tremor rating scale.[17] In addition, of particular relevance for the

current study, investigators were asked to report whether the tremor was irregular and jerky, or regular and sinusoidal, in keeping with the original definition of dystonic tremor proposed by Fahn.[4] They also recorded tremor according to body region, making it possible to determine whether tremor corresponded to body regions affected with dystonia, in keeping with the definitions of dystonic tremor provided by the 2018 tremor consensus panel.[2] Results for voice tremors are included for some analyses, but distinctions between irregular/jerky and regular/sinusoidal tremor were not made for voice tremor, because voice experts do not traditionally acknowledge a voice tremor that is predominantly irregular/jerky. Such patients are typically diagnosed as having spasmodic dysphonia, not tremor.

Investigators also recorded whether participants had tremor-dominant dystonia, a term used when tremulous movements are more prominent than twisting movements or abnormal postures. There are no formal diagnostic criteria for this entity, so investigators were asked to make their own judgement. To provide a real-world picture of assessments conducted at different centers, evaluations of investigators at each site were used directly, rather than conducting a centralized reassessment. Investigators also recorded their overall diagnosis such as focal cervical dystonia, focal hand dystonia, segmental dystonia, multifocal dystonia, or generalized dystonia. However, because of varying interpretation of diagnostic criteria for these groups, most analyses here were based on the dystonia examination recorded rather than the investigator diagnosis.

Data Analyses

Table 1 summarizes the analytical approach. Descriptive statistics are provided as means, standard errors, and ranges.

Table 1 Inclusion/Exclusion Criteria and Basic Methodology

Inclusion criteria
- ≥18 years of age
- Diagnosis of isolated dystonia (previously known as "primary" dystonia[1]) affecting any region of the body or their combination

Exclusion criteria
- Dystonia syndromes combined with other significant neurologic features (previously known as "dystonia-plus syndromes" or "heredodegenerative dystonias")
- Acquired dystonias including tardive syndromes, posttraumatic dystonia, encephalitis
- Functional (psychogenic) dystonia

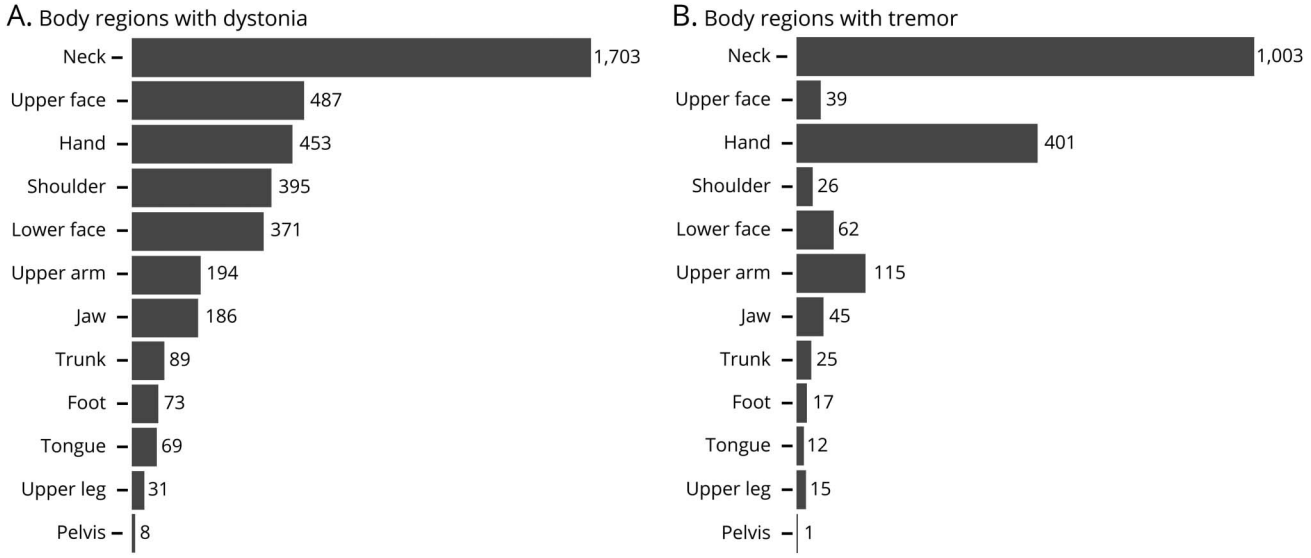
Other points of consideration
- Botulinum toxin treatment was not an exclusion criteria, but all enrolled patients had such treatment at least 2 months prior to data collection
- Surgical therapy for dystonia (such as deep brain stimulation) is not an exclusion criterion for the Dystonia Coalition cohort, but such cases were excluded from this study

Total participants: 2,362; total sites: 37; recruitment duration: December 2009 through December 2015

Logistic regression analysis 1	Logistic regression analysis 2	Logistic regression analysis 3	K-means clustering analysis
• Goal: To identify important clinical characteristics that are present in patients with tremor of any type	• Goal: To delineate the clinical variables associated with irregular/jerky tremor, according to the Fahn definition of dystonic tremor[4]	• Goal: To determine the variables associated with concordance of tremor with dystonia in the same body region, according to the 1998 and 2018 MDS definition of dystonic tremor[2,5]	• Goal: To identify whether there are meaningful subgroups within the entire cohort
• Assessed measures: age at the time of evaluation, duration of dystonia, dystonia severity (measured with total GDRS score), primary body region affected by dystonia, sex, race, recruitment site	• Assessed measures: age at the time of evaluation, duration of dystonia, dystonia severity (measured with total GDRS score), primary body region affected by dystonia, sex, race, recruitment site	• Assessed measures: age at the time of evaluation, duration of dystonia, dystonia severity (measured with total GDRS score), primary body region affected by dystonia, sex, race, recruitment site	• Measures of interest: age at the time of evaluation, duration of dystonia, dystonia severity (measured with total GDRS score), and primary body region affected by dystonia
• 2,243 participants analyzed	• 1,045 participants with tremor: 737 had irregular and 386 had regular tremor	• 1,074 participants with tremor; dystonia was concordant with tremor in 998 and discordant in 76 participants	• 2,243 participants analyzed
• Criteria/number for excluded cases: 18 participants with missing GDRS scores, 3 with missing durations, 87 from sites that collected fewer than 20 participants, and 11 with trunk/pelvis as the primary body region affected were excluded	• Criteria/number for excluded cases: 10 participants with missing GDRS scores, 1 with missing duration, 61 from sites that collected fewer than 20 participants, and 5 with trunk/pelvis as the primary body region affected were excluded; voice tremor was not evaluated	• Criteria/number for excluded cases: 10 participants with missing GDRS scores, 1 with missing duration, 169 from sites that collected fewer than 20 participants, and 5 with trunk/pelvis as the primary body region affected were excluded; voice tremor was not evaluated	• Criteria/number for excluded cases: 18 participants with missing GDRS scores, 3 with missing durations, 87 from sites that collected fewer than 20 participants, and 11 with trunk/pelvis as the primary body region affected were excluded

Abbreviations: GDRS = Global Dystonia Rating Scale; MDS = Movement Disorders Society.

Figure 1 Prevalence of Dystonia and Tremor According to Body Regions Among All 2,362 Patients



The totals for individual body regions with dystonia (A) and tremor (B) sum to more than the total number of participants because many participants had more than one body region affected. The numbers in the figures show the actual numbers of participants with each region affected.

Where appropriate, groups were compared using the χ^2 statistic. A logistic regression was used to identify important clinical characteristics associated with tremor. The clinically relevant regressors selected for this analysis included age at the time of evaluation, duration of dystonia, dystonia severity (total GDRS score), body region affected with dystonia, sex, race, and recruitment center. The body region affected by dystonia was evaluated as a categorical variable with 4 groups based on the highest regional GDRS score: cranial (upper and lower face, tongue, and jaw), neck, larynx, limbs (upper and lower combined, including shoulder). For the categorical value of race, a group "other" (n = 70) was created for participants who were neither White (n = 2,056), nor Black (n = 94), nor Asian (n = 23). Age at onset was excluded due to strong correlations with age (Pearson r = 0.66) and duration of dystonia (r = −0.58). Family history was not considered in the regression model. We excluded 18 participants with missing GDRS scores, and 3 participants with missing durations. To ensure sufficient data with a minimum n = 20 for each test variable in the regression analysis, the regression analysis excluded data from 87 participants from recruitment centers with fewer than 20 participants each, as well as the data of 11 participants where trunk/pelvis was the main body region affected. These criteria left 2,243 participants across 28 different sites. The model was fitted to the data set using R Core Team, 2017. To assess the contribution of individual predictors in our logistic regression model, a Wald χ^2 test was used.

Logistic regression was also used to delineate the clinical variables associated with irregular/jerky tremor, according to the Fahn definition of dystonic tremor.[4] Measures assessed were age at the time of evaluation, duration of dystonia, severity of dystonia, body region affected with dystonia, sex, race, and recruitment center. The model considered 1,123 participants with either regular (n = 386) or irregular tremor (n = 737). A total of 1,045 participants were assessed for this analysis after excluding 61 cases from recruitment centers with less than 20 participants, 10 participants with missing GDRS scores, 6 participants where trunk/pelvis was the main body region affected, and 1 participant with missing duration.

Logistic regression was next used to determine the variables associated with concordance of tremor with dystonia in the same body region, according to the 2018 tremor panel's definition of dystonic tremor.[2] This analysis excluded 169 participants from recruitment sites with fewer than 20 participants, 10 participants with missing GDRS scores, 5 participants where trunk/pelvis was the main site affected, and 1 participant with missing duration. The race groups of "other" and "Asian" were merged, due to the small numbers in the latter. Measures evaluated included age at the time of evaluation, duration of dystonia, severity of dystonia, body region affected, sex, race, and recruitment center. Participants who had tremor combined with dystonia in at least one of the body regions in the GDRS (upper face, lower face, shoulder, upper arm, hand, upper leg, foot, tongue, jaw, neck, trunk, pelvis) were defined as having dystonia concordant with tremor (n = 998). Participants who had no overlap between their dystonia and tremor body regions were defined as discordant cases (n = 76). For participants in whom laryngeal dystonia was the major problem, concordant/discordant tremor was observed in at least one of the evaluated body regions (voice tremor was not evaluated).

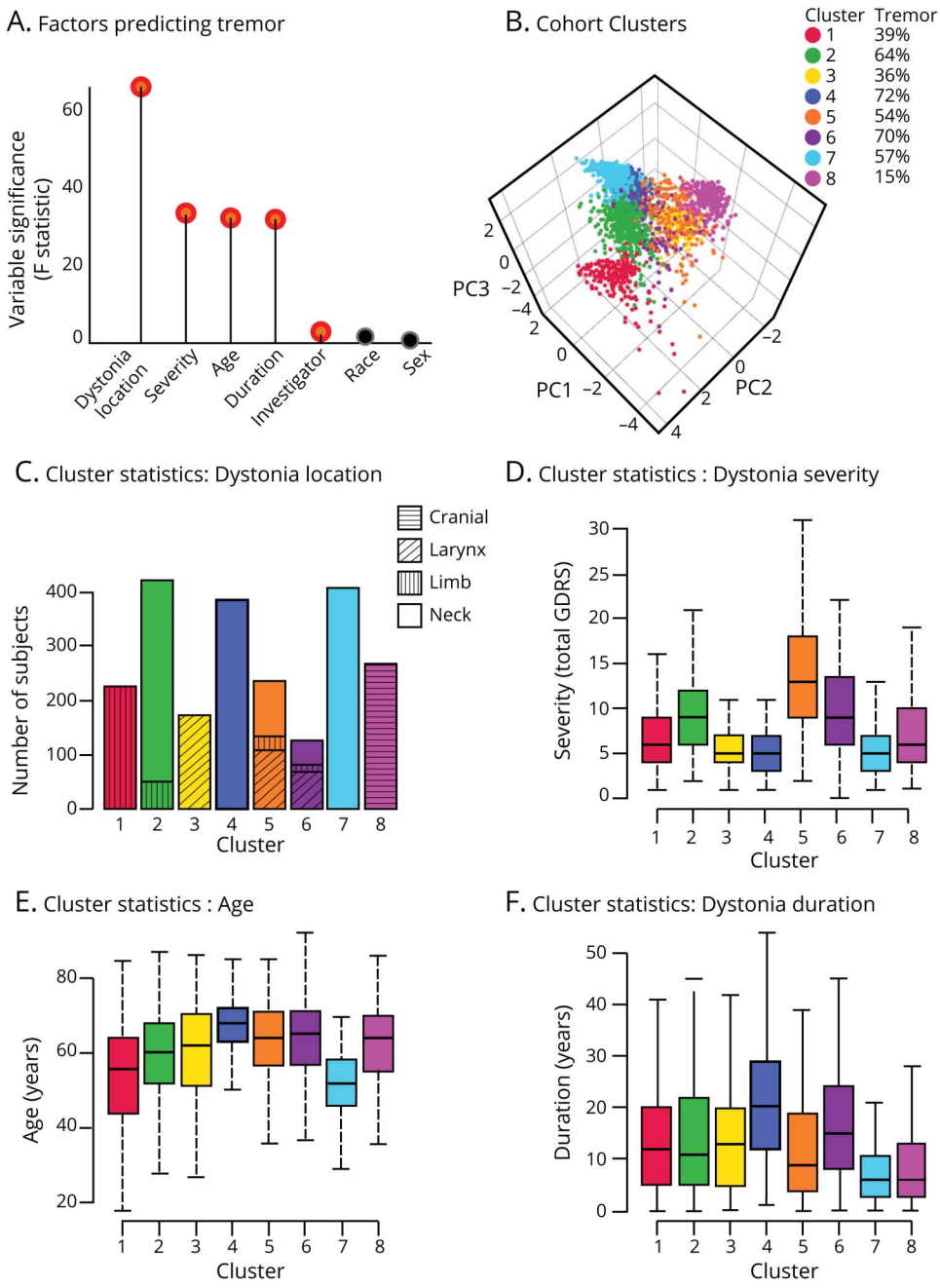
Table 2 Binomial Multiple Logistic Regression Analyses

Predictor	OR (95% CI)	*p* Value
Any tremor		
Dystonia location (reference: neck)		
Cranial	0.15 (0.27–0.48)	<0.001
Larynx	0.33 (0.11–0.19)	<0.001
Limb	0.36 (0.24–0.45)	<0.001
Dystonia severity (total GDRS)	1.04 (1.03–1.06)	<0.001
Age (per 1 year of age)	1.02 (1.01–1.03)	<0.001
Duration (per 1 year of duration)	1.02 (1.01–1.03)	<0.001
Investigator site (reference: median site with 51.7% prevalence rate)		
Site A	0.31 (0.12–0.73)	<0.05
Site B	0.34 (0.13–0.87)	<0.05
Site C	0.24 (0.08–0.67)	<0.05
Dystonic tremor: Fahn criteria (irregular/jerky)		
Dystonia location (reference: neck)		
Cranial	0.75 (0.40–1.46)	0.40
Larynx	0.38 (0.21–0.68)	<0.05
Limb	0.42 (0.24–0.70)	<0.05
Dystonia severity (total GDRS)	1.06 (1.03–1.10)	<0.001
Age, y	0.98 (0.96–0.99)	<0.05
Duration, y	1.02 (1.01–1.04)	<0.05
Investigator site (reference: median site with 75% irregularity rate)		
Site C	27.51 (3.93–556.18)	<0.05
Site F	0.06 (0.01–0.17)	<0.001
Dystonic tremor: MDS criteria (concordant with dystonia body location)		
Dystonia location (reference: neck)		
Cranial	0.11 (0.04–0.27)	<0.001
Larynx	0.06 (0.02–0.11)	<0.001
Limb	0.88 (0.23–3.01)	0.74
Dystonia severity (total GDRS)	1.13 (1.05–1.22)	<0.001
Sex (reference: male)	1.90 (10.99–3.59)	0.05
Investigator site (reference: median site with 98.4% concordance rate)		
Site F	0.09 (0.005–0.54)	<0.05

Abbreviations: CI = confidence interval; GDRS = Global Dystonia Rating Scale; MDS = Movement Disorders Society; OR = odds ratio.
This table summarizes the results of logistic regression analyses for factors that predict any type of tremor, dystonic tremors categorized as irregular/jerky according to the Fahn criteria, and dystonic tremors that were combined with dystonia in the same body region according to the MDS criteria. The ORs are expressed as categorical values (body region, sex, investigator site) or continuous values (age, duration, severity), sometimes adjusted for duration. As an example of the latter, an OR of 1.02 for duration means a 20% increase in risk of tremor for every 10 years.

Dystonia Coalition investigators may enter data from direct examinations of participants or from standardized video recordings. To determine whether the direct or video-based evaluations affected results, we evaluated method of evaluation in separate logistic regression analysis for a subset of the cohort (n = 1,044) where this information was available.

Figure 2 Clustering of Dystonia Cohort Based on Similarities in Significant Predictors of Tremor Prevalence



(A) Significant features predicting tremor as determined by Wald tests. Significant measures (shown in red) are significantly different from 0, and produce a statistically significant decrease in the accuracy of the predictive model once removed. The effect of each parameter is estimated by the length of the line. Nonsignificant factors are shown in black. (B) The K-means cluster analysis revealed 8 subgroups, which are displayed in different colors according to the first 3 principal components. Recruitment site was not included in this analysis because it is not a participant characteristic relevant to dystonia. Tremor prevalence rates of the different clusters are shown as percentages and varied between 15% and 72%. (C) Stacked bar plot shows the major dystonia location distribution of the 8 clusters. These clusters were defined predominantly by body region affected: cluster 1 (limbs), cluster 3 (larynx), cluster 8 (cranial), clusters 4 and 7 (neck), cluster 2 (neck and limbs), cluster 3 (neck and larynx). (D–F) For each separate cluster, boxplots show the median values, interquartile ranges (marked by the box edges), and ranges (shown by whiskers) for dystonia severity (total Global Dystonia Rating Scale), age, and dystonia duration.

Evaluation method was indeed a significant factor for the diagnosis of any type of tremor (direct: video = 1.77, p = 0.03). However, the final outcomes were not influenced by evaluation type, with one exception that the difference in tremor prevalence between cervical and laryngeal dystonia became of borderline significance (z = 1.38; p = 0.06) after including evaluation method as a covariate. On the other hand, there was no significant effect of evaluation method on the most relevant clinical variables associated with irregular/jerky tremor (z = 0.25; p = 0.79), or concordance of tremor with dystonia (z = 1.54; p = 0.12). As a result, we present overall results for all cases, regardless of whether their evaluation was direct or video-based.

Finally, because of the large amount of data available, cluster analyses were explored as a means to identify meaningful subgroups in the cohort. A K-means clustering analysis was applied, based on the clinical features that were found to be statistically associated with occurrence of tremor in the regression analysis. Although recruitment center was a significant measure associated with tremor in the regression, it was not included in the cluster analysis, which aimed to include

phenotypically relevant patient characteristics related to dystonia. The body region expressing dystonia was based on GDRS scores for cranial area (upper and lower face, tongue, and jaw), larynx, limbs (upper and lower combined), and neck. Individual region scores were divided by the total GDRS score to give a body distribution as a percentage. Participant age, duration, and overall severity were the other measures used in the cluster analysis.

Data Availability

Data from the Dystonia Coalition are available to any qualified investigator by request with appropriate institutional review board approval.

Results

Characteristics of Participants With Dystonia

The clinical characteristics of all 2,362 participants in the cohort were similar to other large series. The average age at evaluation was 59.8 ± 12.4 years (median 61, range 18–92). The average age at onset was 45.9 ± 14.8 years (median 47, range 0–82), with an average illness duration of 13.8 ± 11.9 years (median 10, range 0–74). Women (n = 1,692) outnumbered men (n = 670) by a ratio of 2.5 to 1. Most were White, with smaller numbers of patients who were Black or Asian.

The majority of participants were diagnosed with isolated focal dystonia (n = 1,801) but some had segmental dystonia (n = 426), multifocal dystonia (n = 76), generalized dystonia (n = 42), or hemidystonia (n = 10). A significantly greater proportion of patients had dystonia of the neck, followed by the upper limb and face; relatively smaller numbers of patients had involvement of the tongue, jaw, and trunk (figure 1A; $\chi^2_{11,\ n\ =\ 4,059} = 5{,}925.1$, $p < 0.0001$).

Overall Prevalence of Any Tremor

The overall prevalence of any type of tremor (regular or irregular) in any body region was 53.3% (n = 1,258). The majority of patients had tremor of the neck, followed by the upper limbs; fewer patients had tremor of the lower limb, trunk, or pelvis (figure 1B; $\chi^2_{11,\ n\ =\ 1,761} = 5{,}346.4$, $p < 0.0001$). Logistic regression followed by Wald χ^2 tests revealed that statistically significant features associated with any tremor included the following, in order of effect: body region affected by dystonia, dystonia severity, age at evaluation, duration of dystonia, and recruitment site (table 2 and figure 2A). For example, participants in whom the neck had the highest dystonia scores had the highest likelihood of tremor, whereas participants with cranial dystonia had the lowest likelihood of tremor. Race and sex did not influence the likelihood of tremor.

Considering the entire cohort, cluster analysis revealed the optimum number of distinct groups to be 8. A 3D scatterplot of the first 3 principal components (figure 2B) illustrates the 8 clusters with prevalence of tremor varying from 15% (cluster 8) to 72% (cluster 4). Most clusters were defined by body region affected, confirming that the most prominent feature related to tremor in dystonia was body region. For example, the lowest prevalence of tremor (15%) was cluster 8 (n = 268), which had only cranial dystonia. The second lowest tremor rate (36%) was observed in cluster 3 (n = 172), which had only laryngeal dystonia. The highest rates of tremor were observed for patients who had cervical dystonia. There were 2 clusters with isolated focal cervical dystonia distinguished by age and duration of dystonia (cluster 4 with n = 385 and 72% tremor; cluster 7 with n = 408 and 57% tremor) and 3 clusters where cervical dystonia was combined with other body regions in segmental or multifocal patterns (cluster 2 with n = 420 and 64% tremor, cluster 5 with n = 237 and 54% tremor, and cluster 6 with n = 127 and 70% tremor). Body regions for each cluster are shown in figure 2C. The cluster distributions for the other 3 measures (age, duration, and severity) are displayed in figures 2, D–F. The cluster analysis therefore confirmed body region affected by dystonia to be one of the most influential variables affecting the presence of tremor, with subgroups further divided according to dystonia severity, age, and duration of dystonia.

Prevalence of Dystonic Tremor

The prevalence and predictors for dystonic tremor varied according to how it was defined (table 2). When dystonic tremor was defined according to the original Fahn criteria as a jerky and irregular movement regardless of any coexisting dystonic posturing,[4] the overall prevalence among all 2,362 participants was 36.9%. The overall prevalence of regular/sinusoidal tremors was 21.2%, regardless of whether dystonia occurred in the same body part. A small portion of cases (1.9%) were judged to have a combination of irregular/jerky plus regular/sinusoidal tremors. Of those who had both types of tremor, 71.1% had both tremors simultaneously in the same body part, while 28.9% had irregular/jerky tremor in one body region combined with regular/sinusoidal tremor in another body region (table 2).

The variables associated with irregular/jerky tremor in order of impact included dystonia severity, recruitment center, duration of dystonia, body region affected by dystonia, and age (Wald χ^2 test, table 2 and figure 3A). Race and sex were not significantly associated with tremor irregularity. The odds ratios (table 2) showed that participants in whom the neck had the most severe dystonia had the highest likelihood of irregular tremor, compared to patients with dystonia in larynx or limb. The likelihood of irregular/jerky tremor decreased with age but increased with severity and duration of dystonia (table 2).

When dystonic tremor was defined instead by its co-occurrence with overt dystonia regardless of any irregular or jerky qualities according to the 2018 tremor panel criteria,[2] its overall prevalence among all 2,362 participants was 48.4%. Among these participants, 26.0% had a strict concordance of tremor with dystonia, while 22.4% had concurrent tremor and dystonia with the tremor affecting another body region that

was not dystonic. Only 4.3% of patients had tremor in a nondystonic body region without concurrent tremor in the dystonic body region (table 2).

Features significantly associated with concordant tremor included body region, dystonia severity, and sex (Wald χ^2 test, tables 2 and 3, and figure 3B). Age, duration of dystonia, recruitment site (except for one site where there was significantly lower concordance compared to the median), and race did not influence concordance. The odds ratios (table 3) indicated that patients with cervical dystonia were the most likely to have a concordant tremor, whereas patients with dystonia in larynx were the least likely to have a concordant tremor.

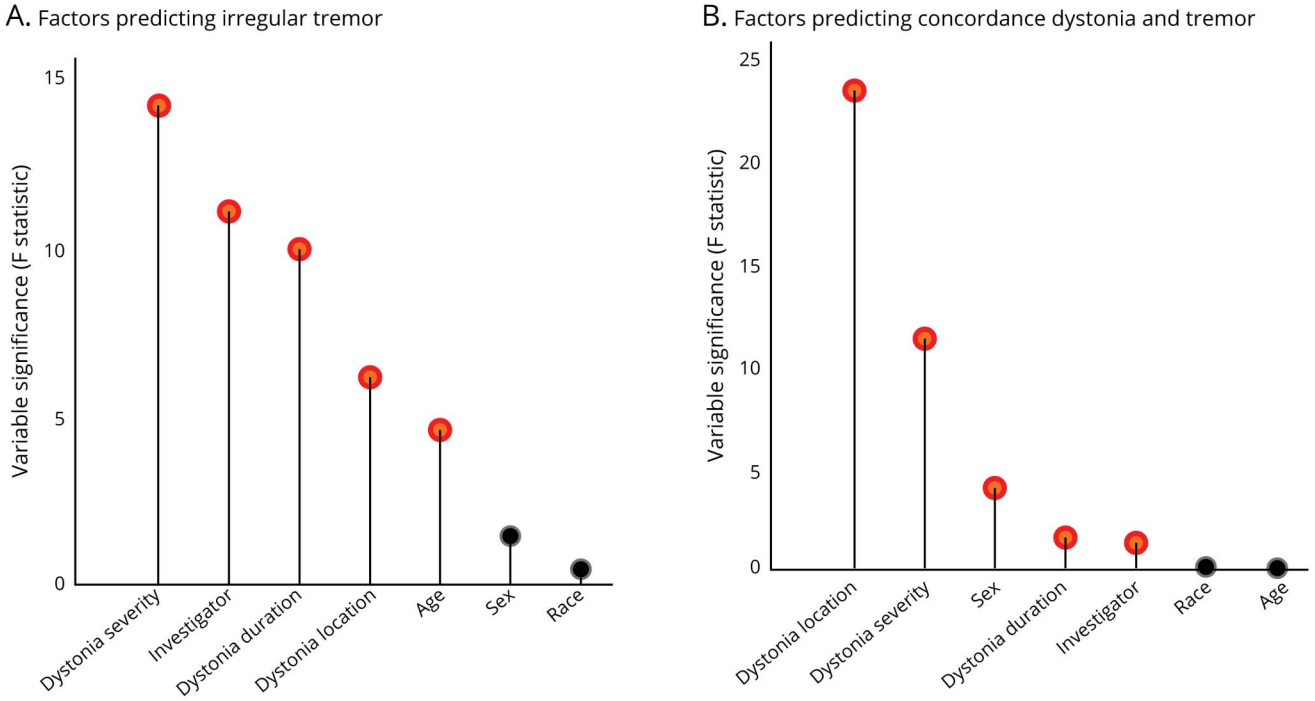
Tremor that was concordant with dystonia was further classified as irregular/jerky vs regular/sinusoidal. In these cases, 55.0% had irregular/jerky tremor, 43.4% had regular/sinusoidal tremors, and 1.5% were mixed. Mixed tremor was seen mostly in the neck. Tremor of a nondystonic part was also further classified as regular/sinusoidal (68.2%), irregular/jerky (27.7%), and mixed (4.1%). Among these cases, mixed tremor was mostly seen in the hand.

Discussion

This study provides results from an international, multicenter investigation of different types of clinically apparent tremors in a large and methodically evaluated cohort of participants with different types of isolated dystonia. The results demonstrate the overall prevalence of any type of tremor among the 2,362 participants in this cohort to be 53.3%. This study also reveals that the markedly varying estimates from the many prior smaller studies can be explained by several factors including the body regions affected by dystonia, age, duration of dystonia, severity of dystonia, and how different types of tremor are defined. Recruitment center had an unexpectedly large effect on both prevalence and type of tremor, implying significant differences in tremor ascertainment, even among experts. These conclusions derive from a large cohort of participants who were systematically evaluated by multiple investigators. As a result, conclusions are not likely to be heavily influenced by issues related to small and nonrepresentative cohorts, nonrepresentative types of dystonia or tremor, or idiosyncratic investigator habits for diagnosis and evaluation.

One of the most important factors influencing the prevalence of tremor was body region affected by dystonia. Body region was one of the most influential factors for both the regression and cluster analyses. An influence of body region on the prevalence of tremor may be related to prior observations that dystonia and tremor both vary according to body region. For essential tremor, the upper limbs are affected by definition, with commonly coaffected regions being the head/neck and voice.[18] For dystonia, the most commonly affected region is

Figure 3 Features Relevant for Dystonic Tremor



(A) Important features associated with irregular/jerky tremor defined according to the Fahn criteria.[4] (B) Important features associated with tremor concordant with dystonia, defined according to the Movement Disorders Society 2018 criteria.[2] In both panels, important measures (shown in red) create a statistically significant decrease in the accuracy of the predictive model once removed from the model.

Table 3 Characteristics of Participants With "Dystonic Tremor" According to Different Criteria

Characteristic	Original Fahn criteria		2018 MDS criteria	
	Regular or sinusoidal tremor (n = 385)	Irregular or jerky tremor (n = 736)	Tremor and dystonia concordant (n = 614)	Tremor associated with dystonia (n = 101)
Age at onset of dystonia, y	47.67 ± 15.39	44.14 ± 15.51	44.38 ± 14.95	47.47 ± 15.36
Age at evaluation, y	62.57 ± 11.80	60.51 ± 12.20	60.66 ± 11.96	63.02 ± 11.43
Duration of dystonia, y	14.89 ± 11.98	16.34 ± 13.10	16.29 ± 12.65	15.54 ± 12.05
GDRS score	7.66 ± 5.89	9.26 ± 7.69	6.72 ± 4.47	6.9 ± 5.09
BFM score	6.41 ± 5.16	7.71 ± 6.55	5.88 ± 4.40	5.46 ± 3.76
F:M	2.7:1	3:01	3.2:1	2.5:1
Body region affected	Neck > upper limb > face; $\chi^2_{10,\ n\ =\ 996} = 4{,}292$, $p < 0.0001$	Neck > upper limb; $\chi^2_{10,\ n\ =\ 462} = 1{,}354$, $p < 0.0001$	Neck > face > upper limb; $\chi^2_{10,\ n\ =\ 1{,}547} = 5{,}913.8$, $p < 0.0001$	Neck > upper limb; $\chi^2_{9,\ n\ =\ 308} = 898.5$, $p < 0.0001$

Abbreviations: BFM = Burke-Fahn-Marsden Dystonia Rating Scale; MDS = Movement Disorders Society.
This table summarizes patient results according to 2 definitions used for dystonic tremor. Results are given as mean ± SD. The table excludes participants who had both regular/sinusoidal tremor and irregular/jerky tremors as well as those who had tremor and dystonia concordant and tremor associated with dystonia.

the neck, followed by the face and the upper limbs.[19] The influence of body region may explain differences in prior studies, which were often dominated by a specific subtype of dystonia.

The prevalence of tremor also depended on age and duration or severity of dystonia. The increasing prevalence of tremor with older age and duration/severity of dystonia may reflect the progressive nature of many isolated dystonias.[20] These observations are important, because most studies attempting to document worsening of dystonia with time do not account for emergence or worsening of associated tremor.

Our study is unique in highlighting another factor influencing the apparent prevalence of tremor in dystonia: recruitment site. Because the vast majority of participants were recruited by a single investigator at each site, this factor most likely reflects different investigator thresholds for diagnosing tremor. Although we cannot rule out geographical or cultural differences influencing tremor prevalence, such differences are unlikely because they could also be observed among centers recruiting from geographically similar regions. Investigator differences may also explain the discrepancies among recent studies that included very similar cohorts of dystonia, using the same definitions for tremor.[21,22] These investigator differences highlight the subjective nature of the clinical ascertainment of tremor and its subtypes, and argue that more objective methods are needed.

Currently, there are no widely accepted diagnostic criteria for dystonic tremor. This entity was first recognized by Fahn, who emphasized 2 key features that distinguished dystonic tremor from more common tremors.[4] Dystonic tremor was viewed as being irregular in both frequency and amplitude, in contrast to other tremors that are usually regular. Dystonic tremor was also viewed as jerky, in contrast to other tremors that are typically sinusoidal. Occasional additional features of dystonic tremor included a geste antagoniste and a null point. Because an irregular and jerky tremor could sometimes be the sole manifestation of dystonia, a condition known as tremor-dominant dystonia, twisting movements, or postures were not a requirement for dystonic tremor.

Fahn's definition of dystonic tremor was revised by an expert committee of the Movement Disorders Society (MDS) in 1998.[5] The committee viewed irregular and jerky qualities required to define dystonic tremors to be too subjective to be reliable. Grossly irregular and jerky movements were easy to identify, but subtle irregularity or jerkiness were more difficult. Results from the current study demonstrating a significant effect of recruitment site confirm this concern (figure 3A). The committee sought to establish a more objective operational definition that could be more reliably applied in the clinic. The committee's new definition required dystonic tremors to be accompanied by more obvious twisting movements or postures in the same affected body region. They recognized that dystonic tremors were often irregular and jerky, but these qualities were no longer required. The committee also defined a new entity, tremor associated with dystonia (TAWD), to accommodate cases with dystonia in one body area plus tremor in body regions without dystonia.

The 1998 MDS definition for dystonic tremor was not universally adopted for several reasons. First, although irregularity and jerkiness are clinically subjective, the coexistence of twisting movements or abnormal postures is equally

subjective. In addition to the challenge of clinical diagnosis, another limitation of the 1998 definition was that it implied tremor and dystonia are mutually exclusive. By designating a distinct label of "dystonic tremor" for participants who have both tremor and dystonia, the definition implies that tremor and dystonia may not co-occur by chance or by some partly shared biological mechanism.

As a result of the disagreements in the nature and definition of tremulous movements in dystonia, some experts have preferred the original definition outlined by Fahn,[4] emphasizing the irregular and jerky quality, regardless of any co-occurrence of dystonia.[7,23–25] Others have used the definition provided by the 1998 MDS committee,[5] emphasizing any tremor that occurs in a dystonic body part, regardless of its irregular or jerky qualities.[7,26] Others have used different terminology, such as tremulous dystonia.[8] In 2018, a new proposal was provided by a second MDS committee.[2] This proposal retained the 1998 definitions for dystonic tremor and TAWD. It also divides upper limb action tremor into "essential tremor" as a relatively pure tremor syndrome and "essential tremor plus," which may have subtle dystonic posturing of uncertain clinical significance. Thus, individuals with dystonia combined with tremor might be diagnosed with dystonic tremor or essential tremor plus, depending on the opinion of the examiner. Although this report was published as a consensus statement, it led to much controversy, even among members of the panel that published it.[9–13]

The results from the current study are unique in simultaneously evaluating the prevalence of dystonic tremor according to both of the most widely used definitions for dystonic tremor. The results highlight the fact that these definitions yield different results. It is worth noting that the 1998 and 2018 MDS panels discarded Fahn's original focus on an irregular and jerky quality,[4] because it was viewed as too subjective to provide a reliable operational means to diagnose participants in the clinic.[2,5] However, defining dystonic tremor by the concordance of dystonia with tremor according to the MDS committee also appears to be too subjective to provide a reliable operational definition. The subjectivity of defining dystonic tremor based on concordance of tremor with dystonia is likely due to the absence of guidelines for defining mild dystonia. Some experts consider slight tilting of the head or minor spooning of a hand to be dystonia, while others consider these features to be potential variations of normal motor behavior. The literature contains numerous additional examples where cases are said to have been misdiagnosed with either tremor or dystonia based on subtle and often subjective findings.[27–31] Our results showing that investigators recruiting from different sites had a large influence on the overall prevalence of tremors as well as dystonic tremors imply that more objective measures are needed.

Some limitations of this study must be acknowledged. The most important is that thresholds for detection of tremor vary according to the methods used. Kinematic tools[32–34] or EMG[35,36] are more sensitive than the clinical examination.[37] As a result, the estimates for tremor provided here likely reflect an underestimate of the actual prevalence of tremor in dystonia. However, the current standard used in all large tremor studies involves clinical evaluation by an expert, since instrumented methods have not been fully validated for dystonia or tremor, and often show marked variance.[37]

The second limitation relates to ongoing debates regarding how "dystonic tremor" should be defined. The present study considered both commonly used definitions. Despite this more evidence-based approach, varying opinions among investigators influence their subjective impressions for labeling a tremor as "irregular" or "jerky." Varying opinions also influence diagnostic thresholds for labeling tremulous movements in body regions concordant with dystonia. Here again instrumentational measurement might be useful to discriminate these characteristics.[32,33]

The third limitation is that this study relied on data recorded by individual site investigators, without independent evaluation. Although all investigators used the same protocol for evaluation, thresholds for diagnosing tremor clearly varied among recruitment sites. This limitation is relevant for many prior large studies of tremor because the standard for evaluation typically relies on local experts. A fourth weakness is that the study did not account for medications that may cause or attenuate tremor, for example benzodiazepines. Despite these weaknesses, the results provide the most comprehensive picture of tremor in participants with dystonia seen by movement disorder experts currently available.

This study provides the largest and most comprehensive assessment of tremors in dystonia. Approximately half of all patients with dystonia have tremor. The actual frequency of tremor in dystonia depends on several factors including body regions affected by dystonia, duration and severity of dystonia, and how tremor is evaluated.

The high coprevalence rates for tremor and dystonia suggest they have overlapping biological mechanisms. In fact, there is ample additional evidence for shared biological mechanisms. For example, some individuals may start with tremor, followed years later by the development of dystonia.[21,38] Conversely, an individual with longstanding dystonia may later develop tremor.[21,38–40] Several dystonia genes have been linked with isolated tremor syndromes resembling essential tremor or parkinsonian tremor.[28,41–46] Additional evidence that dystonia and tremor are biologically related comes from studies addressing their neuroanatomical substrates. Both disorders have been linked with dysfunction of the cerebellum, although the nature of the dysfunction is not identical.[47,48]

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Continued

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