Clinical and Demographic Characteristics Related to Onset Site and Spread of Cervical Dystonia

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Author Contributions

Scott Norris performed all statistical analyses, wrote the first draft and revised the final version critically for important intellectual content. Alberto Espay contributed to generation of figures. Joel Perlmutter and H. A. Jinnah conceived the Dystonia Coalition and managed activities and supervised clinical data collection for this study. All authors contributed to data collection, data analysis, drafting, and/or revising the manuscript critically for important intellectual content, and approved the final version of the manuscript. All collaborators in the Dystonia Coalition contributed to data collection and site investigators assisted with data analysis.

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Abstract

Background—Clinical characteristics of isolated, idiopathic cervical dystonia such as onset site and spread to and from additional body regions have been addressed in single-site studies with limited data and incomplete or variable dissociation of focal and segmental subtypes.
Objectives—To characterize clinical characteristics and demographics of isolated, idiopathic cervical dystonia in the largest standardized, multicenter cohort.

Methods—The Dystonia Coalition, through a consortium of 37 recruiting sites in North America, Europe and Australia recruited 1477 participants with focal (60.7%) or segmental (39.3%) cervical dystonia on examination. Clinical and demographic characteristics were evaluated in terms of the body region of dystonia onset and spread.

Results—Site of dystonia onset was: a) focal neck only (78.5%), b) focal onset elsewhere with later segmental spread to neck (13.3%), and c) segmental onset with initial neck involvement (8.2%). Frequency of spread from focal cervical to segmental dystonia (22.8%) was consistent with prior reports, but frequency of segmental onset with initial neck involvement was substantially higher than 3% previously reported. Cervical dystonia with focal neck onset, more than other subtypes, is associated with spread and tremor of any type. Sensory tricks were less frequent in cervical dystonia with segmental components, and segmental cervical onset occurred at an older age.

Conclusions—Subgroups had modest but significant differences in the clinical characteristics that may represent different clinical entities or pathophysiologic subtypes. These findings are critical for design and implementation of studies to describe, treat, or modify disease progression in idiopathic isolated cervical dystonia.

Keywords
Spasmodic torticollis; focal; segmental; geste antagoniste; neck

Introduction

Isolated, idiopathic dystonia (previously known as primary dystonia) includes a heterogeneous group of disorders characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. What factors differentiate subtypes of dystonia and which different pathological mechanisms influence clinical features or variability in therapeutic response remain to be determined. In an attempt to study demographic and clinical characteristics, previous efforts focused on increasingly homogenous subgroups to clarify demographics and clinical characteristics of isolated, idiopathic cervical dystonia (CD). However, these smaller single-site studies did not distinguish CD that began in the neck from that which started elsewhere and spread to the neck.

Most reports of CD have focused on dystonia that begins in the neck and may spread to contiguous body parts. Occasionally, CD begins as a component of segmental dystonia or develops after dystonia emerged in another body part. Several studies report that site of onset, presence of tremor, disease duration, family history and age of onset affect the risk of spread of dystonia to other body parts. These clinical and demographic features are critical for understanding disease progression and, potentially, response to treatment. Previous large studies of CD either focused mostly on genetic aspects or did not address progression. Thus, none of these studies distinguished various clinical characteristics of CD across onset type including focal (with or without later
spread), segmental, or appearance after dystonia began elsewhere. These clinical characteristics may be essential for design and implementation of future studies that aim to describe, treat or modify disease progression in those with idiopathic isolated CD. The primary purpose of this work was to characterize the clinical characteristics and demographics of isolated, idiopathic CD in the largest standardized, multicenter cohort reported to date. We focused on CD since this is the most common isolated focal dystonia and represents the largest group in the Dystonia Coalition clinical database (70%). This large sample permits examination of demographic and clinical characteristics across the entire phenotypic spectrum of CD, including focal and segmental forms and spread to or from other body regions.

Methods

Data were obtained from the Dystonia Coalition clinical database for Project 1 (Natural History and Biorepository subprojects). Thirty-seven institutions across 7 countries contributed to the database using a common consent, data intake form and examination protocol. All subjects gave written informed consent at the recruiting site according to the Declaration of Helsinki and The Common Rule. Analysis of de-identified aggregate data was further exempted by the Emory University Human Subjects Review Board and the Human Research Protection Office at Washington University. All data from January 5, 2011 (study onset) through September 30, 2015 were used. We only included data from the first visit if a participant had additional follow up visits.

Eligibility for Dystonia Coalition studies required a diagnosis of isolated, idiopathic dystonia and age greater than 17 years. A standard clinician administered questionnaire (supplemental figure 1) and video protocol was collected for each participant at the time of enrollment; the latter is kept in a video repository available to investigators with institutional review board and Dystonia Coalition approval. Specifically, the questionnaire accounted for each participants’ account regarding dystonia onset site and improvement of dystonia (not tremor) following alcohol ingestion. Thus, these particular data were collected retrospectively. All participants were evaluated by movement disorders specialists either in person or by video to identify all body regions affected by dystonia, to complete rating scales, and to identify presence or absence of tremor. Specifically, the examiner noted involvement of each affected body region (upper face, lower face, jaw, tongue, neck, shoulder, upper arm, hand, trunk, pelvis, upper leg, foot), documented the affected side of the body, and indicated presence or absence of tremor in each of the body regions. In addition, video recordings included each participant's demonstration of an attempted sensory trick, and this remains documented in the Dystonia Coalition video repository. Symptom severity was rated using the Global Dystonia Rating Scale (GDRS) and Burke-Fahn Marsden rating (BFM) for all enrolled participants. Final classification of dystonia into focal, segmental, multifocal or generalized was based on documented examination findings. Shoulder involvement was included as a component of focal CD. Tremor affecting dystonic regions was distinguished from tremor affecting regions without dystonia. All participants had cervical dystonia; some had tremor of the neck and some had tremor of other body parts that may or may not have had dystonia. Tremor alone was not
rated as dystonia in the absence of dystonic posture of a body region. All examinations were performed at least two months after botulinum toxin injections or when symptoms returned. In this study, exclusion criteria include patients with CD secondary to known causes such as medication-induced dystonia, parkinsonian syndromes, and those with orthopedic procedures that may affect neck movement. For data presented here, videos were reviewed and new exam ratings generated only if clarification regarding location or type of dystonia was necessary, otherwise exam ratings by recruiting investigators were used. Details regarding the Dystonia Coalition can be found at https://www.rarediseasesnetwork.org/cms/dystonia/.

All statistics were completed with IBM SPSS Statistics for Windows, Version 23.0. Two-tailed unpaired t-tests and one-way analysis of variance (ANOVA) were used to test group differences in continuous data, including age of onset, dystonia duration, GDRS, and BFM score comparison. When significance was demonstrated by ANOVA, post-hoc Tukey-Kramer statistics were used for pairwise comparisons. Multinomial logistic regression was performed to account for covariates when assessing the main effect association of clinical characteristics with dystonia subtype. The first regression model contained dependent variables (dystonia subtypes), independent variables (clinical characteristics: presence of sensory trick, presence of tremor affecting a dystonic region, presence of tremor affecting a non-dystonic region) and covariates (sex, age at onset, duration of dystonia, and neck dystonia severity as measured by GDRS and BFM). Regression was repeated with each dependent variable as reference. Response of dystonia to alcohol was omitted from the first regression model due 724 missing cases (only 51% of all participants responded with a known effect to alcohol). We then repeated a similar multinomial logistic regression model, including response of dystonia to alcohol included as an independent variable, which resulted in 753 valid cases. Chi-square tests were used to test differences in frequency distribution of dystonia response to alcohol across tremor groups (tremor affecting a dystonic body region or tremor affecting a non-dystonic body region) with the null hypothesis of no association following Bonferoni correction. All statistics were considered significant with p<0.05.

Results

Data from 1582 participants with CD were extracted from a pool of 2257 consecutively enrolled participants in the Dystonia Coalition project 1. Subgroup analyses were performed on 1477 participants with focal (60.7%) and segmental (39.3%) dystonia at study enrollment (Figure 1). This analysis excluded subgroups with numbers too small for meaningful interpretation (see below). Thirty-seven international institutions in Australia (1), Europe (4), and North America (3 in Canada, 29 in the USA) recruited and enrolled participants for this study. Median contribution per institution of those with cervical dystonia was 25.5 participants (interquartile rage, 42; range 4-196). Regarding intercontinental recruitment, 1337 participants were recruited in North America, 226 in Europe, and 17 in Australia.

Demographic data for all subjects with CD are reported in Table 1 (column 1). The mean age for all participants at study enrollment was 59.8 ± 12.4 years; 86.8% were right-handed and 2.5% were ambidextrous.
Focal neck onset was reported by 1160 participants (78.5%), and 896 of these (77.2%) remained focal with no spread while 264 (22.8%) later spread to a contiguous body region, thereby defining segmental dystonia. Segmental cervical onset was reported in 121 (8.2%) and focal onset elsewhere (in another body region) that later spread to neck in 196 (13.3%). Thirteen subjects had segmental onset without neck involvement (that subsequently spread to neck), but were excluded from the final pool of 1477 participants since this number was too small for meaningful interpretation. The excluded subgroup included 8 with cranial (5 with blepharospasm-oromandibular, 2 with blepharospasm-lingual-oromandibular, and 1 with blepharospasm-lingual dystonia), 3 with cranial-laryngeal, and 2 with cranial-upper limb segmental onset that later spread to involve the neck. Thus, 86.7% of all participants with focal or segmental CD reported symptom onset involving the neck. Data regarding onset site, body regions affected at onset (segmental cervical onset and focal onset elsewhere that later spread to neck), and examination findings at intake (focal neck onset with segmental spread) are displayed in Figure 2.

Age of onset, dystonia duration, global dystonia rating scale total, global dystonia rating scale neck, Burke-Fahn-Marsden total, and Burke-Fahn-Marsden neck scores significantly differed across onset types. Post-hoc comparisons revealed significantly older age of onset and shorter dystonia duration in segmental cervical onset compared to all other subgroups; the focal neck onset with segmental spread group had a longer dystonia duration. Global dystonia rating scale and Burke-Fahn-Marsden total scores also significantly differed between focal neck onset and either segmental cervical onset or focal onset elsewhere that later spread to neck. Global Dystonia rating scale and Burke-Fahn-Marsden neck scores differed across all three groups. For those with segmental dystonia (i.e. focal neck onset with segmental spread, segmental cervical onset, focal onset elsewhere that later spread to neck) and tremor affecting a dystonic body region (N=798), dystonic body regions include the upper face (14.7%), lower face (12.9%), upper arm (8.6%), hand (20.1%), tongue (1.6%), jaw (5.5%), and larynx (13%). In the same group, tremor affected the upper face (2.2%), lower face (2.5%), upper arm (5.4%), hand (14.6%), tongue (0.3%), jaw (1.8%), and neck (92.6%). In contrast, for those with segmental dystonia and tremor affecting non-dystonic regions (N=134), dystonia affected the upper face (12.6%), lower face (13.4%), upper arm (2.4%), hand (3.1%), tongue (3.1%), jaw (6.3%), and larynx (14.2%). In this group, tremor affected the upper face (7.1%), lower face (11.0%), upper arm (22.0%), hand (81.9%), tongue (3.1%), and jaw (8.7%). Any hand tremor (dystonic or other) was present in 15.3% of all participants (regardless of the body region affected by dystonia), and significantly associated with onset site and spread ($\chi^2 = 49.1, p<0.01$). Specifically, hand tremor was less frequent in focal neck onset with no spread and more in focal neck onset with segmental spread and segmental cervical onset subgroups. Duration of dystonia was significantly shorter for those enrolled with segmental cervical onset and longer in those with focal neck onset with segmental spread compared to all other subgroups. Table 1 summarizes demographic and clinical characteristics for the onset type subgroups. Cross-sectional multinomial logistic regression (excluding the independent variable response of dystonia to alcohol) of the association between clinical characteristics (excluding response of dystonia to alcohol) and dystonia subtype indicated statistically significant covariate contributions to the model. Specifically, dystonia duration ($X^2 = 13.8, p < 0.01$), global dystonia rating scale
total ($X^2 = 177.6, p < 0.01$), global dystonia rating scale neck ($X^2 = 69.8, p < 0.01$), Burke-Fahn-Marsden total ($X^2 = 53.2, p < 0.01$), and Burke-Fahn-Marsden neck ($X^2 = 57.6, p < 0.01$) contributed but not age at dystonia onset, handedness and sex. The Nagelkerke R2 indicated that the model accounted for 61.4% total variance. Presence of sensory trick, tremor of a non-dystonic body region, and tremor of a dystonic region were associated with dystonia subtype; significant associations are summarized in table 2. In summary, sensory trick was more likely in focal neck onset with no spread (Wald = 12.4, $p < 0.01$) and focal neck onset with segmental spread (Wald = 8.5, $p < 0.01$) compared to focal onset elsewhere that later spread to neck, tremor of a dystonic region was more likely in focal neck onset with segmental spread than focal onset elsewhere that later spread to neck (Wald = 9.6, $p < 0.01$), and tremor of a nondystonic region was more likely in focal neck onset with no spread than focal neck onset with segmental spread (Wald = 23.9, $p < 0.01$), segmental cervical onset (Wald = 29.7, $p < 0.01$), and focal onset elsewhere that later spread to neck (Wald = 7.5, $p < 0.01$). A separate multinomial logistic regression including response of dystonia to alcohol resulted in significant association with focal neck onset with segmental spread and segmental cervical onset, where response of alcohol to dystonia was more likely in focal neck onset with segmental spread (OR=1.3, Wald = 6.4, $p < 0.01$). There was no association of dystonia response to alcohol and type of tremor (i.e. tremor of a dystonic body region or tremor of a non-dystonic body region, $X^2=2.0, p = 0.16$).

Discussion

Using the latest consensus criteria\(^1\), we report demographic and clinical characteristics from the largest multicenter, international cohort of patients to date with CD. Of those enrolled with focal or segmental dystonia that included CD, the majority reported only neck involvement at onset (focal neck onset), of which 77.2% did not have segmental spread 14.3±11.8 years after onset; whereas 22.8% eventually spread (focal neck onset with segmental spread). The frequency of focal neck onset with segmental spread supports prior reports\(^11, 13, 14, 16, 34\) but accounts for just 45% of participants with segmental CD. The remaining participants with segmental CD either started with segmental cervical onset, or started focally in another body region (focal onset elsewhere that later spread to neck). The former group (8.2% of all participants) is higher than the 3% previously reported\(^16\). The current data demonstrate that clinical characteristics of CD, including presence of an effective sensory trick, response of dystonia to alcohol and presence of tremor affecting dystonic regions differ based on onset site and spread, and thus may represent distinct clinical entities. Specifically, CD with focal neck onset and segmental spread may be more likely to respond to sensory tricks, and involve tremor any type than CD with focal onset elsewhere and segmental spread to the neck. Sensory tricks are less frequent in CD with segmental components, and segmental cervical onset tends to occur at an older age. These findings address the issue of spread not addressed in a subset of similar participants previously reported in a study focusing on genetics\(^27\) and are particularly critical for design and implementation of any studies to describe, treat or modify disease progression in those with idiopathic isolated CD.
Cervical Dystonia: Demographics

Demographic characteristics of CD depended upon onset region and spread. The current data support prior studies reporting predominance in women and the typical age of onset, about 42 years-old.\textsuperscript{7,8,10} Age of onset in the segmental cervical onset group appears higher and may reflect the large representation (55%) in this group of participants with blepharospasm. Blepharospasm is a dystonia subtype with older age of onset than CD\textsuperscript{14} but little is known regarding the frequency in which blepharospasm begins focally compared to beginning as segmental dystonia.

Clinical characteristics based on onset site and spread

Focal and segmental subtypes account for 94.1\% (N=1477) of all study participants with CD in our cohort. As a group, those with focal or segmental CD report an effective sensory trick (68.7\%), response of dystonia to alcohol ingestion (17.8\%), and tremor affecting a dystonic region (54.0\%) or non-dystonic region (9.1\%). Clinical traits (specifically presence of sensory trick, response of dystonia to alcohol and tremor affecting dystonic regions) differed within focal and segmental subtypes based on onset and spread characteristics.

Sensory trick

With regard to differences in specific clinical characteristics, the percentage of subjects reporting effective sensory tricks differed based on dystonia subtype, but this appeared driven by lower frequencies in focal onset elsewhere that later spread to neck subgroups compared to focal neck onset with segmental spread and focal neck onset with no spread. This indicates that effectiveness of a sensory trick in CD may reflect, in part, onset site in the neck rather than dystonia distribution or spread. Several factors likely contribute to the discrepancy between the current data and prior studies examining sensory tricks in CD.\textsuperscript{6} First, the current data reflect participant surveys rather than examination findings. Project 2 of the Dystonia Coalition focused on 154 people with CD and identified sensory tricks in 83\% of participants based upon investigator review of videos\textsuperscript{35} suggesting that patients themselves may under-report this phenomenon. Second, successful sensory tricks are reported less in those with more body regions affected, with the exception of focal neck onset with segmental spread. Thus, while the former study focuses on participants with focal neck onset with no spread and focal neck onset with segmental spread, one might anticipate higher reported rates of a sensory trick in a smaller sample size.

Tremor

Our data indicating that tremor was present in 63.0\% of all participants with isolated focal or segmental CD are consistent with prior reports.\textsuperscript{5,7} Prevalence of tremor affecting dystonic regions varied based on onset site within the segmental dystonia group, and was highest in focal neck onset with segmental spread compared to focal onset elsewhere that later spread to neck. Furthermore, prevalence of tremor affecting regions without dystonia remains modest across all sites of onset regardless of spread. Thus, these data support prior reports that spread of dystonia more commonly occurs in those with tremor compared to those without tremor.\textsuperscript{36} Specifically, the current data indicate that spread of dystonia from the neck to other body regions is associated more with tremor affecting the dystonic part than tremor.
in another region of the body. Such observations may impact counseling patients regarding symptom progression and in clinical trial design. While hand tremor occurred more often in all three segmental groups compared to focal neck onset with no spread, this did not directly translate to increased prevalence of tremor affecting regions without dystonia and thus indicate a higher prevalence of dystonic hand involvement in these groups. Indeed, participants with associated arm and hand dystonia had more tremor in a dystonic region than those with upper face involvement (e.g. blepharospasm) which may account for some group differences. Regardless, these observations may explain discrepancies of tremor prevalence across various studies of dystonia that did not account for dystonia onset and spread.\textsuperscript{17, 36-38} Our data are limited to prior classification schemes of tremor affecting dystonic regions for this analysis, but future efforts with objective tremor measures may help to further distinguish relevance of tremor to dystonic phenotypes.\textsuperscript{31} The video repository in the Dystonia Coalition dataset may allow for improved objective measures for better characterizing tremor in the future.\textsuperscript{30}

In a limited sample analysis, we did not observe a difference in dystonia responsiveness to alcohol across tremor groups including tremor affecting the part of the body with or without dystonia. But, both tremor groups reported higher response rate to alcohol than participants without tremor. Alcohol responsiveness may reflect participants that have dystonia and an action tremor in parts of the body not affected by dystonia.

**Response of dystonia to alcohol**

There are few prior reports involving a small number of participants documenting a response of CD to alcohol that include direct observation of improvement following intravenous alcohol infusion\textsuperscript{39, 40} and survey results demonstrating 56.5\% of patients with laryngeal dystonia self-reported improvement following alcohol (independent of the presence of tremor).\textsuperscript{40} Current data support a smaller percentage of individuals who report benefit from alcohol with CD, but there may be some bias as only 51\% of all participants responded with a known effect (i.e. the remaining reported “unknown”) and recall of tremor response to alcohol shares additional reliability issues. Despite the observation that both groups with tremor reported higher response rate of dystonia to alcohol, future studies are thus necessary to objectively quantify the relationship of alcohol responsiveness in CD while considering onset site.

**Study limitations**

All exam data were collected prospectively, but the retrospective cross-sectional nature of historical data points may contribute to recall bias in participant recollection of dystonia onset, response of dystonia to alcohol or presence of sensory trick. Additionally, the population readily available for study may not reflect subcategories of dystonia that lack response to botulinum toxin since recruitment at our center may be biased to those patients that return for chemodenervation. Similarly, those with mild disease that are either under recognized or not seeking treatment will less likely attend one of our recruiting centers. With regards to botulinum toxin administration, examinations were performed at least two months after botulinum toxin injection, but data regarding the distribution of this variable are not available for many of the participants and thus could confound presence of tremor in a
dystonic region and/or severity of neck dystonia. It also remains possible that the relative extent of cervical dystonia may independently influence comparability between and within groups (i.e. the neck is more affected in focal cervical dystonia than segmental dystonia, partially reflected by global dystonia rating scale and Burke-Fahn-Marsden scores in table 2). Validated interval severity rating scales to objectively compare severity of dystonia across body regions remain elusive, and future efforts should continue to develop such scales. Finally, due to the exploratory nature of analyses, strict multiple comparisons were not addressed in statistical analyses across groups that may produce additional false positive statistical errors.

Conclusions

Data from the largest standardized multi-center collection of CD data demonstrate modest but significant differences in clinical characteristics across subgroups based on onset site and spread. The differences in presence of sensory trick, response of dystonia to alcohol, and tremor affecting dystonic regions may represent distinct clinical entities for which future studies need to consider for proper experimental design and implementation. Consideration of such features may be necessary for accurate description, pathophysiologic categorization, prognosis, treatment, or modification of disease progression in those with idiopathic isolated CD. The Dystonia Coalition clinical database provides a means to collect prospective data that will allow improved data analyses along these lines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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She received grants from the following patient associations: APTEES (tremor) and AMADYS (dystonia). Dr. Roze is in scientific advisory boards for Orkyn, Arguettant, Ultragenix, and Merz pharmaceuticals. He received honoraria from Orkyn, Arguettant, and Merz Pharmaceuticals. He had research grants from AP-HP, INSERM, CNRS, Orkyn, Arguettant, IP sante, Merz Pharmaceuticals, UltraGenix, UCB pharmaceuticals, and received travel grants from the movement disorder society, dystonia coaliton, dystonia medical research foundation, Orkyn, Arguettant, Abbvie, and Sanofi-Genyhone. Dr. Reich received grants from the NIH (NINDS), royalties from Informa and is a reviewer for UpToDate. Dr. Berman received grant support from NIH/CAT Colorado CTIS (KL2 TR001080), The Dana Foundation, NIH/NINDS R01 NS074343 (PI: Schenkman), NIH/NIHM R01 MH102224 (PI: Tregellas), NIH/NIDDK R01 DK103691 (PI: Tregellas). Dr. LeDoux consulted for Mayo Clinic Jacksonville, served on the scientific advisory boards for the National Spasmodic Torticollis Association, Spastic Paraplegia Foundation, received honoraria from Lundbeck. He had grants from NIH, Benign Essential Blepharospasm Reesarch Foundation, Omeros, Auspex, Teva, CHDI, US WorldMeds, and Accordia, received compensation for expert testimony for Starnes Davis Florie, and received royalties from Elsevier. Dr. Pirio Richardson received grant support (NCRR/CAT K2L2 TR001448-01) and royalties from Springer. Dr. Agerwal’s spouse holds stock in Exilexis, Pharmathens, Atossa Genetics, Pain Therapeutics, Antares, MEI Pharma, Marina Biotech, RxiPharmaceuticals. Dr. Agerwal consulted for Teva, Cynapsus, US world meds, UCB, Lundbeck, and Impax, served on scientific advisory boards for Teva, Cynapsus, US world meds, UCB, Lundbeck, and Impax, received honoraria from Teva, Lundbeck, US world meds, and Impax and has a grant funded by Astellas. Dr. Mari had grants from the NIH, NPF, MJFF, Avid, P-Cori and Abbvie. He is co-founder of NeuroTechno Inc (MD). Dr. Ondo served on scientific advisory boards for ACADIA, USWorldMeds, Lundbeck, received honoraria as a speaker for Lundbeck, Avanir, Xenoport, and TEVA, and received grants from Tremor Research Group, Huntington Study Group, Lundbeck, and Cynapsus. Dr. Shih was compensated by the Tremor Research Group as a video rater for a clinical trial sponsored by Insightec, Inc. Dr. Fox consulted for Lundbeck and Orion and received honoraria from the American Academy of Neurology and Movement Disorders Society. She had grants from the NIH (Dystonia Coalition) and MJFF, contracts with Avanir, Kyowa, and Cynapsus and received royalties from Elsevier and Oxford University Press. Dr. Testa served on the scientific advisory boards for Lundbeck Pharmaceuticals (all honoraria was donated to Medical College of Virginia Foundation), received honoraria from MedLink Neurology (for updates to a comprehensive review), and she is co-PI on clinical trials funded by the Huntington Study Group and Ayspex Pharmaceuticals (a wholly owned subsidiary of Teva Pharmaceuticals), and is the site PI for Enroll-HD (sponsored by CHDI Foundation), PRIDE-HD and Open Pride (sponsored by Teva Pharmaceuticals). Dr. Berardelli had grants from Allergan and Chiesi. Dr. Fahab consulted for Cala Health, received honoraria from Teva, grants from Medtronic and royalties from Springer Publishing. Dr. Troung had grants from Auspex Pharmaceuticals Inc., Abbvie Inc., Ipen Pharmaceuticals, Merz Pharmaceuticals GmbH, NINDS, Adamsama Therapeutics, GE Healthcare, Kyowa Hakko Kirin Pharma Inc., Impax Pharmaceuticals Inc., Pfizer Inc., Osmotica Pharmaceuticals, CIVitas Therapeutics Inc., Cynapsus Therapeutics Inc., Revance Therapeutics Inc., Allergan Pharmaceuticals, NIH/NIND/ORDR. He has consulted for Ipen Pharmaceuticals and Merz Pharmaceuticals GmbH. Dr. Nahab consulted for Cala Health, received honoraria from Teva, grants from Medtronic, and royalties from Springer Publishing. Dr. Xie consulted for CVS/ Carmarck, received honoraria from Michael J Fox Foundation and Weston B. Michael J Fox Foundation, grants from Michael J Fox Foundation, NIH, GE Healthcare, and University of Chicago. Dr. Hallett received honoraria from Elsevier for editing an on-line neurology news service and had grants from UniQure for a clinical trial of AAV2-GDNF for Parkinson Disease, Merz for treatment studies of focal hand dystonia, and Allergan for studies of methods to inject botulinum toxins. He maintained intellectual property rights for US Patent #6,780,413 B2 (Issued: August 24, 2004): Immuno毒素 (MAB-Risin) for the treatment of focal movement disorders, and US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil) and received royalties from Brainway for US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for the same (H-coil). Ms. Rosen received salary support via the Dystonia Coalition, part of the RDCRN, funded by NCATS and NINDS grants U54NS065701 and US4TR001456 and by and Huntington Disease Society of America Center of Excellence grant. Dr. Perlmuter has received fees for medical legal consultations. He serves (unpaid) on the DMRF and APDA scientific advisor boards and received honoraria from University of Michigan, St. Louis University, Parkinson Disease Foundation, Harvard University, Columbia University, and the Indiana Neurological Society. He received research funding from the NIH (NINDS, NCATS), APDA, Greater St. Louis Chapter of the APDA; HDSA. Dr. Jinnah is PI for the Dystonia Coalition which receives the majority of support through NIH grant TR001456 from the ORDR, NCATS, and NS065701 from the NINDS. The Dystonia Coalition receives additional material or administrative support from industry sponsors (Allergan Inc. and Merz Pharmaceuticals) as well as private foundations (The American Dystonia Society, The Benign Essential Blepharospasm Foundation, Cure Dystonia Now, Dystonia Inc., Dystonia Ireland, The Dystonia Medical Research...
References

FIG. 1.
Study workflow (light gray boxes) to included (white boxes) and excluded participants (dark boxes). FNO-NS: focal neck onset, no spread; FNO-SS: focal neck onset, segmental spread; SNI: segmental onset with neck involvement, FOE-SS: focal onset elsewhere, segmental spread.
FIG. 2.
Cartoon depiction of body regions involved at onset and dystonia spread in all participants for A. FNO-NS (N=896, 60.7%) focal neck onset, no spread, B. FNO-SS (N=264, 17.9%) focal neck onset, segmental spread, C. FOE-SS (N=196, 13.3%) focal onset elsewhere with segmental spread to neck, and D. SNI (N=121, 8.2%) segmental neck involvement without spread.
Table 1

Demographic and clinical characteristics by dystonia site of onset and spread

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Focal</th>
<th>Focal-NS</th>
<th>Focal-SS</th>
<th>Segmental</th>
<th>SNI</th>
<th>FOE-SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>1477</td>
<td>896</td>
<td>264</td>
<td>121</td>
<td>196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right handed</td>
<td>1283 (86.9%)</td>
<td>789 (88.1%)</td>
<td>228 (86.4%)</td>
<td>105 (86.6%)</td>
<td>164 (83.7%)</td>
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<tr>
<td>Woman</td>
<td>1102 (74.6%)</td>
<td>661 (73.8%)</td>
<td>205 (77.7%)</td>
<td>91 (75.4%)</td>
<td>144 (73.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory trick</td>
<td>1015 (68.7%)</td>
<td>653 (72.9%)</td>
<td>189 (71.6%)</td>
<td>78 (64.2%)</td>
<td>101 (51.4%)</td>
<td></td>
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</tr>
<tr>
<td>Response to alcohol</td>
<td>263 (17.8%)</td>
<td>158 (17.6%)</td>
<td>66 (25.0%)</td>
<td>13 (10.4%)</td>
<td>28 (14.4%)</td>
<td></td>
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</tr>
<tr>
<td>Tremor of dystonic region</td>
<td>798 (54%)</td>
<td>467 (52.1%)</td>
<td>175 (66.1%)</td>
<td>67 (55.2%)</td>
<td>88 (45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor of nondystonic region</td>
<td>134 (9.1%)</td>
<td>88 (9.8%)</td>
<td>22 (8.5%)</td>
<td>9 (7.8%)</td>
<td>15 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of Onset (years)</td>
<td>45.8 ± 14.2</td>
<td>45.2 ± 13.5</td>
<td>45.0 ± 14.3</td>
<td>49.7 ± 15.0</td>
<td>46.6 ± 15.9</td>
<td></td>
<td></td>
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<tr>
<td>Dystonia Duration (years)</td>
<td>14.6 ± 12.0</td>
<td>14.3 ± 11.8</td>
<td>17.6 ± 13.0</td>
<td>11.0 ± 11.0</td>
<td>14.3 ± 11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDRS total</td>
<td>8.5 ± 6.0</td>
<td>6.2 ± 3.7</td>
<td>10.8 ± 5.9</td>
<td>12.9 ± 8.7</td>
<td>12.3 ± 7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDRS neck</td>
<td>4.8 ± 2.2</td>
<td>5.0 ± 2.1</td>
<td>5.1 ± 1.9</td>
<td>4.5 ± 2.2</td>
<td>3.5 ± 2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFM total</td>
<td>7.3 ± 5.3</td>
<td>4.6 ± 3.2</td>
<td>7.6 ± 6.1</td>
<td>9.0 ± 7.7</td>
<td>10.3 ± 8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFM neck</td>
<td>4.5 ± 2.1</td>
<td>4.6 ± 2.1</td>
<td>4.8 ± 1.9</td>
<td>2.9 ± 2.2</td>
<td>3.8 ± 2.1</td>
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<td></td>
</tr>
</tbody>
</table>

* Significant associations across all onset subtypes (FNO-NS, focal neck onset-no spread; FNO-SS, focal neck onset-segmental spread; SNI, segmental onset with neck involvement, FOE-SS, focal onset elsewhere-segmental spread). GDRS = Global dystonia rating scale; BFM = Burke-Fahn-Marsden scale
### Table 2

Significant associations of clinical characteristics with dystonia site of onset

<table>
<thead>
<tr>
<th>Sensory trick</th>
<th>Tremor of dystonic region</th>
<th>Tremor of nondystonic region</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNO-NS : FOE-SS</td>
<td>FNO-SS : FOE-SS</td>
<td>FNO-NS : FNO-SS</td>
</tr>
<tr>
<td>OR=2.4 (CI: 1.5-3.9)</td>
<td>OR=2.2 (CI: 1.3-3.5)</td>
<td>OR=1.4 (CI: 0.9-2.0)</td>
</tr>
<tr>
<td>FNO-SS : FOE-SS</td>
<td></td>
<td>FNO-NS : SNI</td>
</tr>
<tr>
<td>OR=2.0 (CI: 1.3-3.2)</td>
<td></td>
<td>OR=5.7 (CI: 3.0-10.5)</td>
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<tr>
<td></td>
<td></td>
<td>FNO-NS : FOE-SS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR = 2.5 (CI: 1.3-4.7)</td>
</tr>
</tbody>
</table>

*Significant associations (exponential logistic coefficient [odds ratio, OR] with confidence intervals (CI)) for clinical characteristics and dystonia subtype. FNO-NS, focal neck onset-no spread; FNO-SS, focal neck onset-segmental spread; SNI, segmental onset with neck.*