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ORIGINAL COMMUNICATION

Head tremor at disease onset: an ataxic phenotype of cervical dystonia

Aristide Merola[1] · Alok K. Dwivedi[2] · Aasef G. Shaikh[3] · Tamour Khan Tareen[1] · Gustavo A. Da Prat[1,4] · Marcelo A. Kauffman[5] · Jennie Hampf[6] · Abhimanyu Mahajan[1] · Luca Marsili[1] · Joseph Jankovic[7] · Cynthia L. Comella[8] · Brian D. Berman[9] · Joel S. Perlmutter[10] · Hyder A. Jinnah[11] · Alberto J. Espay[1]

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Abstract

Background Cervical dystonia (CD) can present with head tremor. It is unclear whether ataxic features are differentially associated with this phenotype at onset of CD.

Objectives We sought to evaluate: (1) the demographic features of CD patients with (Tr-CD) and without head tremor (nTr-CD) at onset, and (2) the differential ataxic features between these CD subtypes.

Methods For the first objective, we compared demographic data in Tr-CD versus nTr-CD subtypes in the entire cohort of CD subjects enrolled in the Dystonia Coalition Natural History and Biorepository studies ($n=1608$). For the second objective, we rated the standardized videos from consecutively enrolled Tr-CD subjects ($n=50$) and age-, gender-, and disease duration-matched nTr-CD subjects ($n=50$) for ataxia severity scoring using the Scale for the Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS); and for dystonia severity using the Toronto Western Spasmodic Torticollis Rating Scale section-I (TWSTRS) and the Global Dystonia Rating Scale (GDRS).

Results Of 1,608 subjects, 18.1% ($n=291$) were classified as Tr-CD and 81.9% ($n=1317$) as nTr-CD. The Tr-CD cohort was older, predominantly female, and had longer disease duration than the nTr-CD cohort ($p=0.01$). Compared to nTr-CD, Tr-CD subjects had worse generalized ataxia, speech, and gait and posture scores. High ataxia severity with low dystonia severity distinguished Tr-CD from nTr-CD with high accuracy (area under the curve, 0.91 (95% CI 0.85–0.97).

Conclusions Head tremor at disease onset represents a clinically distinguishable subtype of cervical dystonia affecting predominantly older women, with worse ataxia and milder dystonia than the non-tremulous dystonic phenotype.

Keywords Dystonia · Tremor · Ataxia · Cerebellum · Head tremor

Introduction

Head tremor has long been recognized as one of the early presentations of cervical dystonia (CD) [1–3]. The classic tonic phenotype is sustained turning (torticollis), tilting toward a shoulder (laterocollis), head flexion (anterocollis), extension (retrocollis), or combinations thereof, without tremor (NTr-CD). Tremor-dominant CD (Tr-CD) can manifest as "no–no", "yes–yes" or mixed jerky head oscillations [4–6]. These patients seek attention because of the tremor rather than the posturing.

Head tremor can also be a manifestation of acute or chronic cerebellar dysfunction [7, 8]. The cerebellum is a critical pathophysiologic node in the generation and expression of tremor and dystonia, and CD in particular [9–12]. Neuroimaging functional studies documented increased activation of the anterior cerebellar regions ipsilateral to the direction of head rotation and reduced activation in the posterior cerebellar regions [13, 14]. Symptomatic CD can occur after cerebellar stroke or hemorrhage [15, 16], and dystonic features improve after deep-brain stimulation of the anterior lobe of the cerebellum [17]. Finally, post-mortem pathological studies have shown patchy loss of cerebellar Purkinje cells, as well as areas of focal gliosis and torpedo bodies (fusiform swelling of Purkinje cell axons) in patients with CD [18]. The extent to which cerebellar dysfunction

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✉ Aristide Merola
merolaae@ucmail.uc.edu

Extended author information available on the last page of the article

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might underlie the tremor and tremorless clinical phenotypes of CD remains to be clarified.

We sought to fulfill two research objectives: (1) to compare the demographic features of patients with and without head tremor at onset in a large CD cohort, and (2) to determine whether ataxic features are differentially associated with Tr-CD and NTr-CD.

Materials and methods

Patients

Objective 1: full-cohort analysis

We reviewed all CD patients from the Dystonia Coalition Natural History and Biorepository studies [19, 20] from over 2000 patients with dystonia recruited from 37 Centers in the United States, Canada, Europe, and Australia. Initial analysis evaluated the clinical and demographic features (age, disease duration, and gender) for the entire cohort classified into Tr-CD or NTr-CD as per this item of the Dystonia Coalition data collection form: "Is this patient's dystonia dominated by tremor more than tonic or twisting movements?" In addition to tremor "dominance" from the Biorepository data set, we also captured whether tremor was the "initial" feature from the Natural History data set. Exclusion criteria were generalized, multifocal, or segmental dystonia and use of medications known to be associated with tremor, such as neuroleptics, antidepressants, and mood stabilizers.

Objective 2: video rating

50 consecutive Tr-CD subjects ($n = 15$ from the Natural History and $n = 35$ from the Biorepository study, proportionate to their different sample sizes) were individually gender-, age-, and disease duration-matched with consecutively selected 50 NTr-CD subjects from the same data sets. We chose consecutive patients for both groups to minimize selection bias in sampling of video segments used for ataxia and dystonia scoring. All subjects must have had focal dystonia predominantly affecting the cervical region and age ≥ 18 years. Videos were rated for ataxic and dystonic features by two blinded evaluators, naïve to the study hypothesis. Each video, lasting approximately 10–15 min, was collected in accordance with the Dystonia Coalition protocol and included a standardized battery of 32 tasks assessing patients while seating, standing, and walking, and including tasks that can be amenable for rating of cerebellar features using standardized scales. Given the heterogeneous presentation of dystonia, which may involve different body segments, the video protocol was specifically designed with the aim of providing a comprehensive neurological examination, including tasks required for the rating of intention and action tremor, ataxia, and speech (Online Resource 1) [19].

Clinical scales for video rating

Ataxia assessment

Ataxia severity was rated using the 8-item Scale for the Assessment and Rating of Ataxia (SARA [range 0–40]) [21] and the 19-item International Cooperative Ataxia Rating Scale (ICARS [range 0–100]), which while not validated for use in appendicular tremor has been validated for the assessment of cerebellar impairments in hereditary ataxias, strokes, and tumors, among others [22]. Speech, gait, and postural ataxia were rated using the 2-items ICARS Speech Disorder (range 0–8) and the 7-item ICARS Gait and Posture (range 0–34), which are both independently validated subscales of the ICARS [22]. Higher scores mean worse ataxia severity in all scales. Associated appendicular tremor was rated on a scale of 0–32, as the composite score of items 9–14 of the ICARS, using the following tasks from the Dystonia Coalition video protocol: write "Today is a nice day" three times with the dominant and non-dominant hand; draw Archimedes' spiral with the dominant and non-dominant hand; hold tip of pen over dot for 10 s, as close as possible, with the dominant and non-dominant hand; and hold up written page with extended arms/hands supinated for 5 s; extended arms/hands pronated for 5 s; and flex elbows and hold hands/arms steady without touching in front of chest for 5 s; and perform the finger-to-nose test slow enough to capture accuracy five times for each hand.

Dystonia assessment

Dystonia severity was rated using the 10-item Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) section-I (Torticollis Severity Scale [range 0–35]) [23] for cervical involvement and the 14-item Global Dystonia Rating Scale (GDRS [range 0–140]) [24] for generalized involvement. Higher scores in both scales mean worse dystonia severity.

Sample size and power analysis for video rating

In the absence of prior studies assessing ataxic and dystonic differences between Tr-CD and NTR-CD phenotypes, a formal sample size computation could not be carried out. However, we sought to determine a moderate Cohen's effect size ($d = 0.50$) for all chosen ataxia scales between Tr-CD and NTr-CD groups. Using this information, a sample size of 48 per group was found to be sufficient to detect significant moderate effect sizes with power greater than 85% at the 1% level of significance using unpaired t-tests. The

level of significance was adjusted to 1% due to multiple comparisons.

Data analysis

We assessed the demographic variables for Tr-CD and NTr-CD (age, gender distribution, and disease duration) from the entire Dystonia Coalition cohort of CD patients meeting all of the inclusion and none of the exclusion criteria ($n=1608$), and the ataxia (ICARS, SARA) and dystonia severity (TWSTRS, GDRS) for the subgroups of Tr-CD and NTr-CD (50 each). The consensus scores from the two raters were obtained and analyzed. Continuous data were expressed as mean and standard deviation (SD), while categorical data were reported as frequencies and compared using unpaired *t* test or Fisher's exact test, as appropriate. The clinical scores were compared between Tr-CD and NTr-CD groups using logistic regression analysis after accounting for clustering effect. The clustering was due to matching Tr-CD subjects with NTr-CD subjects based on age, gender, disease duration, and study type. The robust variance using the Huber sandwich method was used to adjust for within-cluster correlation in analysis. The results of logistic regression analysis were reported using odds ratio (OR) along with 95% confidence interval (CI) and *p* value. In addition, some items of SARA scale were also compared between the two groups using Wilcoxon signed-rank tests due to matched study design and validated with paired t-test analysis. Further, multiple logistic regression analysis accounting for clustering effect was used to determine independent ataxic and dystonic scores associated with Tr-CD compared to NTr-CD. Significant variables from the univariate analysis were included in the multivariable analysis. The model discriminatory performance was measured using area under the curve (AUC) along with 95% CI. A receiver operating characteristic (ROC) curve was constructed to demonstrate accuracy of the developed regression model. *p* values less than 1% were considered as significant. All statistical analyses were carried out using STATA version 13 (STATA Corp., Texas, USA). This study was approved by the University of Cincinnati Institutional Review Board, and the Dystonia Coalition Executive Committee reviewed and approved the protocol and provided access to the database for analysis. All patients gave written informed consent.

Results

Full cohort

Of 1608 CD patients included in the Dystonia Coalition databases (Table 1), 18.1% ($n=291$) were classified as Tr-CD and 81.9% ($n=1317$) as NTr-CD. Tremor was a presenting symptom in 50% of Tr-CD cases included in the Natural History Dystonia Coalition study, from which these data were available. The Tr-CD cohort was older ($p=0.01$), had longer disease duration ($p<0.001$), and was predominantly female ($p=0.006$) compared with the nTr-CD cohort.

Video-based cohort

The blinded-rated cohort of 50 age-, sex-, and disease duration-matched Tr-CD and 50 NTr-CD patients consisted of 43 women and 7 men for each group (Table 1). There were no differences between cohorts in use of medications with potential influence on ataxia rating scales, including benzodiazepines (Tr-CD = 15 vs. NTr-CD = 19; $p=0.437$), topiramate (Tr-CD = 1 vs. NTr-CD = 1; $p=1$), primidone (Tr-CD = 3 vs. NTr-CD = 0; $p=0.242$), and gabapentin (Tr-CD = 1 vs. NTr-CD = 3; $p=0.343$).

Ataxia severity in video cohort

Total ICARS (12.68 ± 7.86 vs. 5.64 ± 6.08) and SARA scores (5.34 ± 4.08 vs. 2.16 ± 2.50) were greater in Tr-CD than NTr-CD (ICARS OR, 1.2; 95% CI 1.04–1.38; $p=0.012$; SARA OR, 1.45; 95% CI 1.10–1.91; $p=0.009$) (Fig. 1). Speech, gait, and postural ataxia were worse in Tr-CD

Table 1 Dystonia coalition cervical dystonia cohorts: clinical and demographic data

	Dystonia coalition full cohort			Video-rated cohort		
	NTr-CD ($n=1317$)	Tr-CD ($n=291$)	*p* value	NTr-CD ($n=50$)	Tr-CD ($n=50$)	*p* value
Age (years)	59.0 (12.7)	62.9(12.6)	0.01	62.2 (11.3)	62.2 (11.4)	N/A*
Age at onset (years)	45.1 (15.1)	44.0 (17.3)	0.2602	49.4 (14.5)	49.4 (14.4)	N/A*
Disease duration (years)	13.9 (11.9)	18.9 (14.5)	<0.0001	12.8 (10.9)	12.8 (10.8)	N/A*
Gender (women/men)	941/376 (71.4%)	231/60 (79.4%)	0.006	43/7 (86%)	43/7 (86%)	N/A*

Results are reported as average values (standard deviation), unless specified differently. *p* value statistical differences between groups (unpaired *t* test or Fisher's exact test). *NTr-CD* non-tremor-dominant cervical dystonia, *Tr-CD* tremor-dominant cervical dystonia; % express the ratio (women/men)

*By design, the cohorts for video rating were matched for age, gender, and disease duration

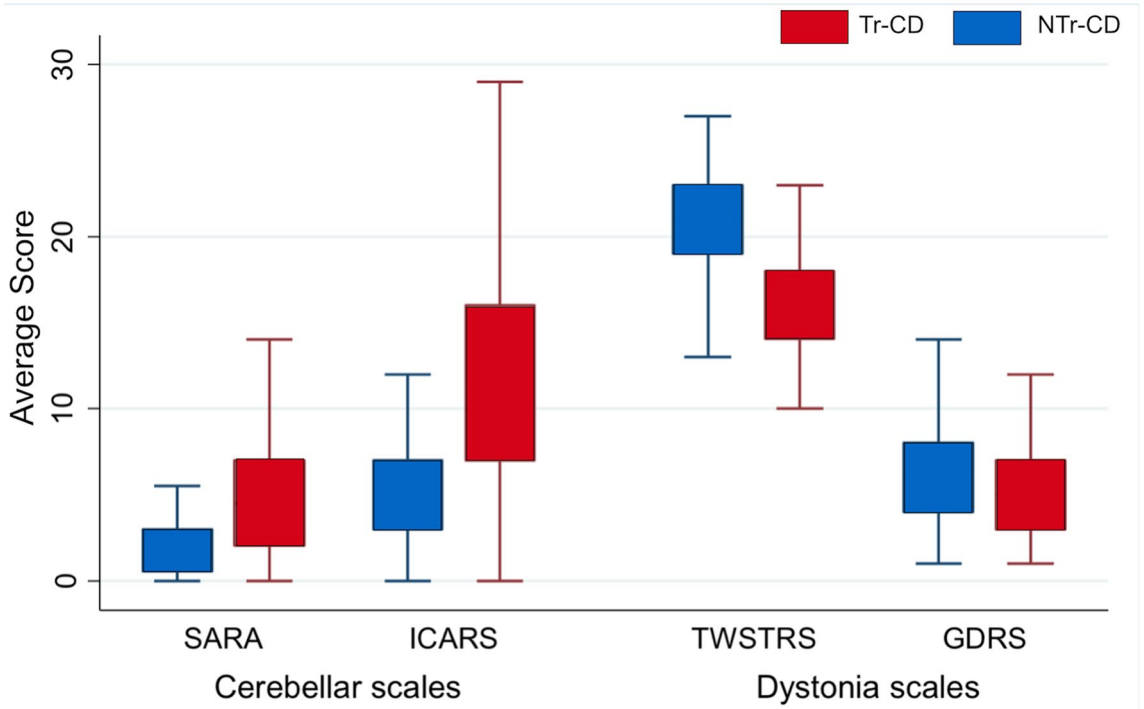

Fig. 1 Comparison of ataxia and dystonia scores in CD subtypes. *NTr-CD* non-tremor-dominant cervical dystonia, *Tr-CD* tremor-dominant cervical dystonia, *SARA* scale for the assessment and rating of ataxia, *ICARS* international cooperative ataxia rating scale, *TWSTRS* Toronto Western spasmodic torticollis rating scale, *GDRS* global dystonia rating scale

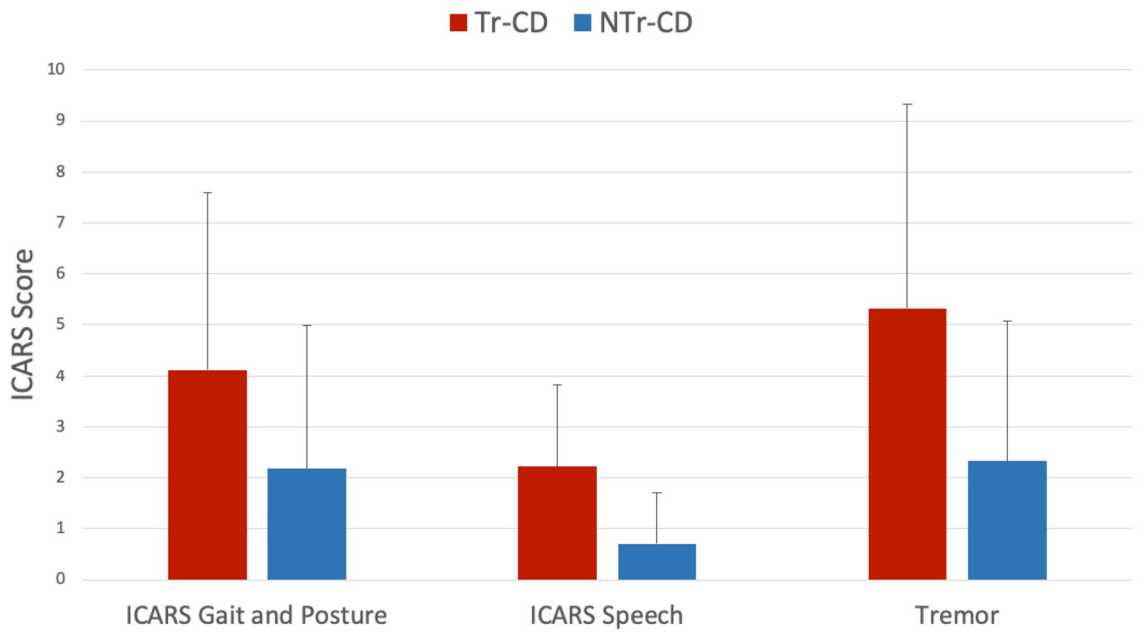

Fig. 2 Ataxia and tremor sub-scores in CD Subtypes. *NTr-CD* non-tremor-dominant cervical dystonia, *Tr-CD* tremor-dominant cervical dystonia, *ICARS* international cooperative ataxia rating scale, *Tremor* composite score of items 11–14 of the ICARS; $*p < 0.05$

than NTr-CD (ICARS Speech Disorder: 2.22 ± 1.61 vs. 0.7 ± 1.02; $p < 0.001$; ICARS Gait and Posture: 4.12 ± 3.48 vs. 2.18 ± 2.8; $p = 0.003$) (Fig. 2). The absolute Cohen's effect size varied between 0.61 and 1.13, which was greater than the expected effect size used for sample size computation (0.5). Appendicular tremor was also more severe in Tr-CD than NTr-CD (Fig. 2; $p < 0.001$).

Dystonia severity in video cohort

TWSTRS score was lower in Tr-CD than NTr-CD (16.44 ± 4.20 vs. 20.30 ± 3.64; OR = 0.78; 95% CI 0.69–0.88; $p < 0.001$) and GDRS score was moderately reduced in Tr-CD than NTr-CD (5.64 ± 3.59 vs. 7.42 ± 5.80; OR = 0.91; 95% CI 0.81–1.02; $p = 0.09$). As measure of overall dystonia severity, GDRS was relatively low in both groups preselected for cervical involvement, but with a trend for even lower overall severity in Tr-CD (Fig. 1). Neither age at onset nor disease duration correlated with dystonia severity (TWSTRS and GDRS).

The combination of low TWSTRS (less severe CD; OR = 0.70, 95% CI 0.60–0.81; $p < 0.001$) and high ICARS (more severe ataxia; OR = 1.29, 95% CI 1.04–1.60; $p = 0.021$) differentiated Tr-CD from NTr-CD with an AUC of 0.91 (95%CI: 0.85–0.97) (Fig. 3).

Discussion

We found that (1) tremor-dominant CD was more prevalent in older women in a large CD cohort and (2) was associated with more severe ataxia, milder dystonia, and longer disease duration compared to non-tremor-dominant CD.

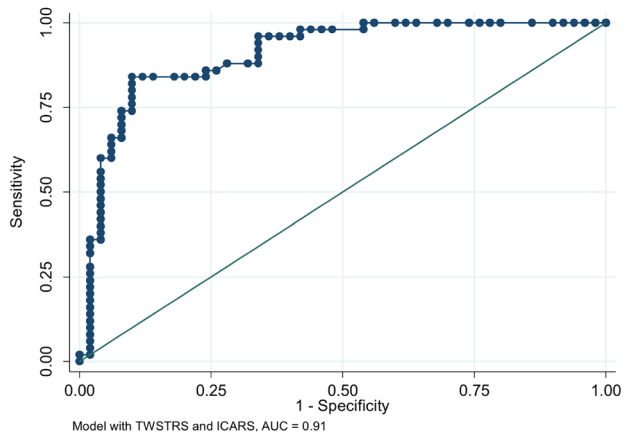

Fig. 3 Receiver operator curve. Sensitivity and specificity values in differentiating Tr-CD and NTr-CD using the combination of TWSTRS and ICARS. *ROC* receiver operator curve, *AUC* area under the curve, *ICARS* international cooperative ataxia rating scale, *TWSTRS* Toronto Western Spasmodic torticollis rating scale

Also, Tr-CD patients were more frequently affected by concomitant appendicular tremor. The combination of minimal dystonic features and greater ataxia scores reliably distinguished Tr-CD from NTr-CD with high sensitivity and specificity, supporting the concept of Tr-CD as a unique clinical phenotype.

Tr-CD may be in the spectrum of the emerging "dystonia plus ataxia" syndrome [12]. Multiple clinical observations have shown that cerebellar lesions can be associated with, or even cause CD [25, 26] and that hereditary cerebellar diseases, including but not limited to spinocerebellar ataxia types 1, 2, 3, 6, 14, 17, and 35 may present with prominent dystonic features [10, 27–30]. One study evaluating clinical and neuroimaging data from 188 patients with cervical and segmental dystonia documented cerebellar atrophy on neuroimaging in 9% ($n = 17$) [10]. Over 80% of the 17 cases with cerebellar atrophy had CD (82.4%; $n = 14$), of whom 71.4% ($n = 10$) were women and 78.6% ($n = 11$) presented with a Tr-CD phenotype. Together with our findings, these data argue in favour of Tr-CD representing a distinguishable nosological entity characterized by potentially greater cerebellar dysfunction compared to NTr-CD.

Head tremor has been previously suggested to represent a subtype of CD [11, 31, 32], although with the confusing caveat that the spectral frequency of head tremor resembles that of "essential tremor," and that dystonia and pure tremor disorders might co-aggregate or cluster in families [33]. While the occurrence of isolated head tremor in familial tremor disorders has never been described [34–36], CD patients presenting with head tremor often have a family history of tremor or other movement disorders and may be misdiagnosed as essential tremor [32, 37]. The loss of Purkinje cells and torpedo bodies reported in the granule cell layer of the cerebellum in brains of both CD and pure tremor disorders have led some authors to speculate on a possible association between the two conditions [11, 18, 38]. Our data, however, suggest that head tremor appearing at disease onset might represent a clinical subtype of CD, characterized by both ataxic and dystonic features. Future assessments of the Natural History Dystonia Coalition cohort may serve to determine whether ataxia progresses among the Tr-CD subtype and to examine its neurophysiologic, genetic, and neuropathologic underpinnings.

Some limitations temper the strength of our conclusions. First, our conclusions were based on a cross-sectional observational study, which might overlook potential confounders and selection biases inherent to tertiary referral centers from which subjects were recruited. These types of studies are, however, important to create new hypotheses, investigate rare outcomes, and identify associations that can then be more rigorously studied using a prospective cohort study [39, 40]. Second, the ataxia assessments were based on video material captured with a protocol aimed at documenting

dystonic features rather than ataxia. While the video protocol was not designed for SARA or ICARS rating, many of the examination tasks overlap with those recommended for evaluating ataxia, including tasks associated with a comprehensive neurological examination. Of note, every potential shortcoming of this approach to measure ataxia on video material would have influenced both groups equally, which may have attenuated the effect size of the difference but with low likelihood it affected the direction of the results. Appendicular tremor, which was more frequently observed in the Tr-CD group, might also have impacted the final score of the rating scales. However, an accurate estimate of this effect is not possible since dystonia and ataxia scales are not validated for the assessment of tremor severity. Third, neuroimaging measures of the cerebellum were not available. Thus, we could not examine whether Tr-CD patients had greater cerebellar atrophy than NTr-CD, as suggested by the clinico-neuroimaging series from Queen Square [10]. Fourth, while we confirmed that there was no effect of medications on ataxia and tremor, we cannot exclude that a small proportion of patients included in this study had atypical presentations of hereditary cerebellar pathologies, since no genetic evaluations were performed. Examiner-confirmed data related to the initial presence of tremor were available only in the Natural History database, while data from the Biorepository database (with subjects having greater than 5 years of disease duration) may have been affected by recall bias given the longer duration of symptoms at enrollment. Fifth, differences in disease duration may be dependent on variability in time to diagnosis in different CD phenotypes. Only 40% of patients with CD pursue medical care within the first 6 months and fewer than 10% receive a diagnosis [41]. Thus, the possibility exists that Tr-CD might have been diagnosed earlier than nTr-CD due to their prompt referral to specialists' care. Finally, this cross-sectional analysis cannot serve to estimate the progression of cerebellar disability in the two cohorts of patients, although the longer disease duration despite mild dystonia severity in the Tr-CD cohort suggests this subtype may possibly be neurodegenerative in nature.

Conclusions

Taking into account the above limitations and pending future neurophysiological, neuroimaging, neuropathological, and genetic studies, we propose that dystonic head tremor at disease onset may represent a unique nosological subtype of combined dystonia of the cervical region with ataxic features, disproportionately affecting older women, and which may become more apparent after several years of progression. Whether this subtype represents a form of primary cerebellar degeneration will require dedicated longitudinal studies.

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Author contributions Research project: A. Conception; B. Organization; C. Execution. Statistical Analysis: A. Design; B. Execution; C. Review and Critique. Manuscript Preparation: A. Writing of the first draft; B. Review and Critique. Dr. Merola: 1A, 1B, 1C, 2A, 2B, 3A. Dr. Dwivedi: 1B, 2A, 2B, 3B. Dr. Shaikh: 1A, 2C, 3B. Dr. Tareen: 1B, 1C, 3B. Dr. Da Prat: 1B, 1C, 3B. Dr. Kauffman: 1A, 2C, 3B. Dr. Hampf: 1A, 2C, 3B. Dr. Mahajan: 1A, 2C, 3B. Dr. Marsili: 1A, 2C, 3B. Dr. Jankovic: 1A, 2C, 3B. Dr. Comella: 1A, 2C, 3B. Dr. Berman: 1A, 2C, 3B. Dr. Perlmutter: 1A, 2C, 3B. Dr. Jinnah: 1A, 2C, 3B. Dr. Espay: 1A, 1B, 1C, 2A, 2C, 3B. All the co-authors listed above gave their final approval of this manuscript version.

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Data access and responsibility statement Dr Merola had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical standards The study has been approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave written informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study have been omitted.

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Affiliations

Aristide Merola[1] · Alok K. Dwivedi[2] · Aasef G. Shaikh[3] · Tamour Khan Tareen[1] · Gustavo A. Da Prat[1,4] · Marcelo A. Kauffman[5] · Jennie Hampf[6] · Abhimanyu Mahajan[1] · Luca Marsili[1] · Joseph Jankovic[7] · Cynthia L. Comella[8] · Brian D. Berman[9] · Joel S. Perlmutter[10] · Hyder A. Jinnah[11] · Alberto J. Espay[1]

1 Department of Neurology, Gardner Family Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, Cincinnati, OH, USA

2 Division of Biostatistics and Epidemiology, Department of Biomedical Sciences, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center (TTUHSC), El Paso, TX, USA

3 Department of Neurology, University Hospitals and Cleveland VA Medical Center, Case Western Reserve University, Cleveland, OH, USA

4 Departamento de Neurologia, Sanatorio de la Trinidad Mitre, Buenos Aires, Argentina

5 Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y División Neurología, Hospital JM Ramos Mejía, Facultad de Medicina, UBA, and Programa de Medicina de Precision y Genomica Clinica, Instituto de Investigaciones en Medicina Traslacional, Facultad de Ciencias Biomédicas, Universidad Austral-CONICET, Buenos Aires, Argentina

6 Institute of Neurogenetics, University of Luebeck, Luebeck, Germany

7 Department of Neurology, Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, TX, USA

8 Rush University Medical Center, Chicago, IL, USA

9 Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

10 Neurology, Radiology, Neuroscience, Physical Therapy and Occupational Therapy, Washington University School of Medicine, St. Louis, MO, USA

11 Department of Neurology, Human Genetics and Pediatrics, Emory University, Atlanta, GA, USA