DYSTONIA

June

Dystonia and Tremor

Issue Editors

Aparna Wagle Shukla
University of Florida, United States

Pattamon Panyakaew
Chulalongkorn University, Thailand

frontiers | Publishing Partnerships

Dystonia and Tremor

ISSN 2813-2106
ISBN 978-2-8325-6551-3
DOI 10.3389/978-2-8325-6551-3

Tremor is a common co-occurring feature in individuals diagnosed with dystonia, particularly in those with focal cervical dystonia—the most prevalent form of the disorder. Unlike parkinsonism or myoclonus, tremor is now increasingly understood as an intrinsic component of dystonia itself. While our understanding of the mechanisms linking tremor and dystonia continues to evolve, this relationship has spurred significant research interest worldwide.This eBook brings together eight contributions from the Special Issue Dystonia and Tremor, highlighting recent progress in the clinical characterization, electrophysiological features, and therapeutic management of tremor in dystonia. The collection includes original research on tremor subtypes and treatment outcomes, reviews of pathophysiological mechanisms, and perspectives on future clinical and research directions. Together, these articles offer a timely overview of this complex clinical entity and aim to support continued advances in evidence-based care and mechanistic understanding.

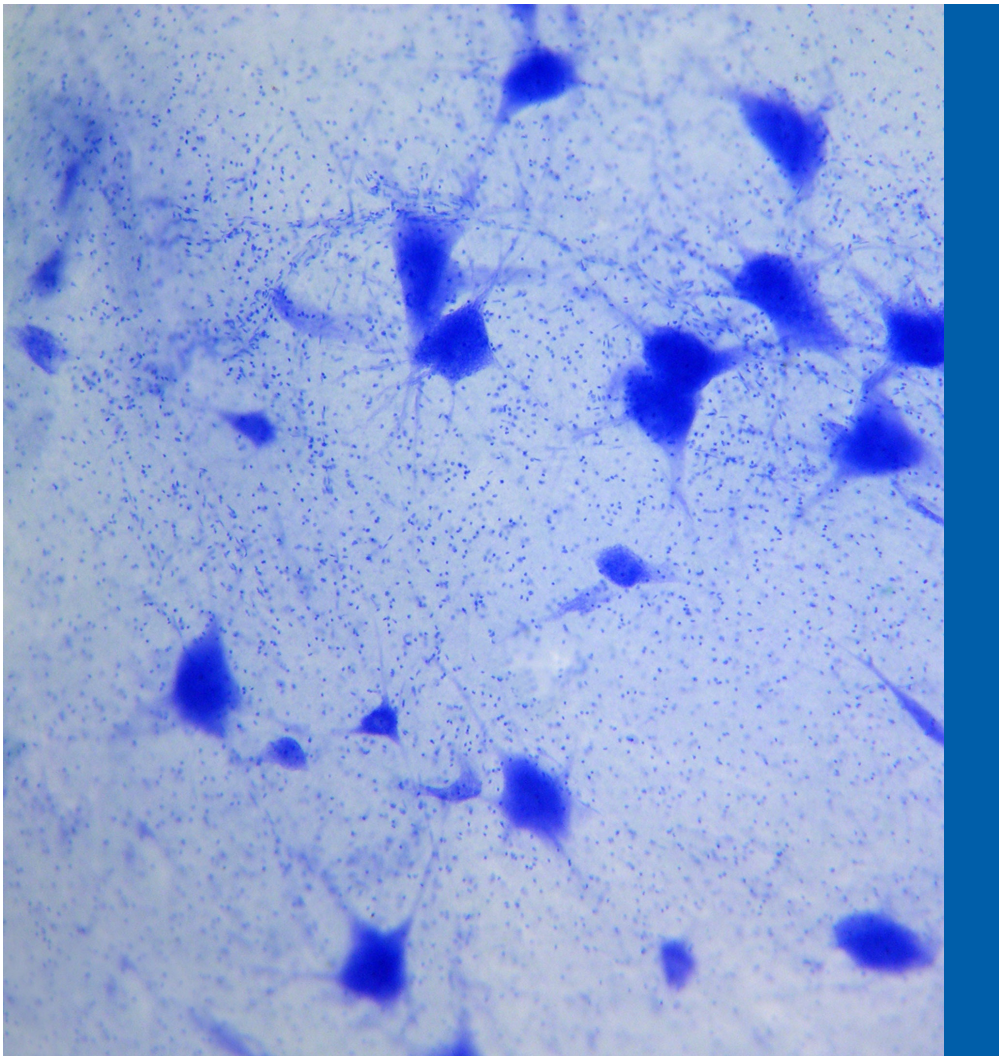

Table of contents

DYSTONIA

TYPE Special Issue Editorial
PUBLISHED 21 May 2025
DOI 10.3389/dyst.2025.14589

OPEN ACCESS

EDITED BY
Aasef Shaikh,
Case Western Reserve University,
United States

*CORRESPONDENCE
Pattamon Panyakaew,
ppa@chulapd.org

RECEIVED 06 March 2025
ACCEPTED 28 April 2025
PUBLISHED 21 May 2025

CITATION
Panyakaew P and Wagle Shukla A (2025) Editorial: Dystonia and tremor.
Dystonia 4:14589.
doi: 10.3389/dyst.2025.14589

Editorial: Dystonia and tremor

Pattamon Panyakaew[1]* and Aparna Wagle Shukla[2]

[1]Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn Excellence Centre on Parkinson's Disease and Related Disorders, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand, [2]Norman Fixel Institute for Neurological Diseases, College of Medicine, University of Florida, Gainesville, FL, United States

KEYWORDS

dystonia, tremor, dystonic tremor, task-specific tremor, dystonic tremor syndrome

Editorial on the Special Issue
Dystonia and tremor

The definition of "Dystonia and tremor" is heterogeneous and has been recently revisited in 2024 by an expert panel of the MDS Dystonia Study Group and the Dystonia Coalition. It has now been explicitly redefined to refer only to rhythmic oscillatory movements in dystonia. In contrast, the arrhythmic jerky movements seen in dystonia, which were also previously classified as dystonia and tremor, should now be renamed as jerky repetitive dystonia and not be included in the dystonia and tremor category [1–3]. This may help to create more standardized terminology in research and clinical practice. The studies in this special issue of *Dystonia and Tremor* provide updated insights into dystonia and tremor, particularly in isolated focal dystonia, with detailed characterization of the clinical features and physiological aspects of isolated cervical dystonia (CD) and task-specific dystonia (TSD) presenting with tremor. This issue also advances the understanding of gait and balance impairments in CD patients with tremor, and nonmotor symptoms in children and adults with dystonia underscoring the importance of multidisciplinary care for this patient population.

Beylergil et al. determined the prevalence of tremor in CD patients enrolled in the Dystonia Coalition cohort. The study found that approximately 45% of patients, particularly women, experienced head tremor, with nearly 75% exhibiting irregular head tremor (better classified as jerky dystonia) and 25% presenting with regular head tremor. Predictors of head tremors included increased disease severity, increased disease duration, and increased age, in this order, whereas the presence of regular head tremor was associated with decreased disease severity and older age. This underpins that jerky dystonia and regular head tremor seen in CD should be regarded as distinct entities.

Jabarkheel and Wagle Shukla prospectively compared the electrophysiologic characteristics of head and arm tremor in patients with focal CD vs segmental dystonia. While the mean frequency of the head tremor was observed to be low (4.3 ± 0.9; range 3.5–6 Hz), the arm tremor had a slightly higher frequency (5.5 ± 0.6; range 3.5–7 Hz). The frequency of head tremor was higher in younger participants than in older participants, as previously described in patients with essential tremor (ET). When comparing focal vs. segmental dystonia, the head tremor in CD had a lower peak frequency and amplitude with a longer EMG burst duration. Arm tremor in patients grouped as focal dystonia (CD plus arm tremor without dystonic features) had a lower amplitude compared to segmental dystonia (CD plus arm tremor with

dystonic features). Head and arm tremor tended to be less severe in patients who reported alcohol responsiveness. The study concluded that the physiological characteristics of tremor in focal and segmental dystonia differ to some extent, indicating that the progression of dystonia symptoms across body regions may influence the underlying physiology of co-occurring tremor.

The effects of botulinum toxin (BoNT) injection on the regularity of head oscillation in CD were investigated in a small sample size (N = 8 with documented head movements by the magnetic search coil) Agharazi et al. The regularity of head tremor was quantified by calculating the dispersion of head movements in time series values. BoNT injection could change the regularity of head tremor to a certain "set-point" in the oscillatory network possibly by modulating proprioceptive feedback to the head neural integrator [4]. In addition, the randomness of head movements was not changed by BoNT injection, supporting that the head movements in this study were consistent with jerky dystonia rather than tremor based on the current viewpoint. Overall, the amplitude and frequency of head movements decreased with BoNT injection, with a pronounced reduction in head orientation in patients with high-intensity head oscillation prior to the injection.

Whether task-specific tremor (TST) should be classified as a form of task-specific dystonia (TSD) or a variant of ET remains unclear. The electrophysiology of TST is poorly characterized. Kuo and Chen reviewed the current evidence on the underlying physiology of TST. The majority of the studies were conducted in patients diagnosed with primary writing tremor and TST presenting in musicians. Electromyographic results showed co-activation between the antagonist pairs and overflow muscle activities to the adjacent muscles, similar to dystonia. However, the loss of inhibition at the spinal, brainstem, and cortical levels was not identical to dystonia. Reciprocal inhibition, the physiological technique to assess spinal inhibition, was normal in TST. GABAergic cortical inhibition was slightly impaired, while the cortical silent period was within the normal range. Functional imaging revealed reduced functional connectivity between the cerebellum and other parts of the brain, but less widespread compared to dystonia. Taken together, TST may be a subtype of dystonia and tremor rather than ET. Nevertheless, it may be a separate entity since it is not entirely congruent with the physiology of dystonia and tremor.

Zhou et al. compared the prevalence of non-motor features such as depression, anxiety, fatigue, and sleep disturbances in pediatric-onset versus adult-onset dystonia. As expected, pediatric-onset dystonia was more commonly associated with the generalized form, whereas adult-onset dystonia tended to present as focal dystonia. Interestingly, aside from a lower rate of sleep disturbances in children, the prevalence of fatigue, anxiety, and depression was comparable between pediatric and adult patients with dystonia.

Finally, gait and balance problems have been identified in patients with CD. However, these aspects have never been addressed in CD with head tremor. Wagle Shukla et al. investigated the clinical and spatiotemporal parameters of gait in this specific group. They demonstrated that nearly half of the patients with CD and tremor experienced clinical gait and balance difficulties, including slower walking speed and impaired performance on the Berg Balance Scale. In their assessments, more than 20% of patients had a shorter step length, wider stride width, and increased double support time when walking on a gait mat compared to healthy individuals, suggesting that an abnormal cerebellar network contributes to these findings. However, when compared with ET and patients with orthostatic tremor, the dystonia and tremor group exhibited less pronounced abnormalities in objective gait and balance variables, suggesting that a relatively lower degree of dysfunction within the cerebellar network was present. The study also highlighted that gait and balance dysfunction in CD with head tremor may also stem from factors beyond cerebellar dysfunction, including impairments in vestibular and proprioceptive pathways due to abnormal head positioning and constant head shaking. Reduced control of voluntary neck movements may further hinder navigation in complex environments. These findings emphasize the importance of incorporating rehabilitation strategies into outpatient management plans for dystonia and tremor.

In summary, this Special Issue of *Dystonia and Tremor* emphasizes the clinical characteristics, physiological aspects, and pathophysiological understanding of dystonia and tremor. The repetitive jerky movements of a specific body part in dystonia should no longer be classified as a tremor. Physiological findings can offer clinicians valuable insights to improve diagnosis and patient management while also guiding researchers in designing more robust studies. The implementation of more precise definitions for dystonia and tremor represents an essential advance in generating more homogenous evidence in this field.

Author contributions

Equal contribution for writing and critique. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

References

1. Lalli S, Albanese A. Dystonic tremor: time to change. *Mov Disord Clin Pract* (2024) 11(6):605–12. doi:10.1002/mdc3.14010

2. Shaikh AG, Fasano A, Pandey S, Helmich RC, Albanese A, Vidailhet M, et al. Challenges in describing tremor and dystonia. *Neurology* (2025) 104(2):e210209. doi:10.1212/WNL.0000000000210209

3. Shaikh AG, Jinnah HA. Interdisciplinary insights into tremor in dystonia: navigating clinical controversies, definitional challenges, and pathophysiological complexities. *Parkinsonism Relat Disord* (2024) 122:106068. doi:10.1016/j.parkreldis.2024.106068

4. Shaikh AG, Zee DS, Crawford JD, Jinnah HA. Cervical dystonia: a neural integrator disorder. *Brain* (2016) 139(Pt 10):2590–9. doi:10.1093/brain/aww141

DYSTONIA

TYPE Case Report
PUBLISHED 30 June 2023
DOI 10.3389/dyst.2023.11363

OPEN ACCESS

EDITED BY
Pattamon Panyakaew,
Chulalongkorn University, Thailand

*CORRESPONDENCE
Aparna Wagle Shukla,
aparna.shukla@neurology.ufl.edu

RECEIVED 15 March 2023
ACCEPTED 23 May 2023
PUBLISHED 30 June 2023

CITATION
Wagle Shukla A, Chitnis S, Malaty IA and Zeilman P (2023), Case Report: Bilateral globus pallidum internus DBS for treating tremor and dystonia in spinocerebellar ataxia 17: a thirteen-year follow-up.
Dystonia 2:11363.
doi: 10.3389/dyst.2023.11363

Case Report: Bilateral globus pallidum internus DBS for treating tremor and dystonia in spinocerebellar ataxia 17: a thirteen-year follow-up

Aparna Wagle Shukla[1]*, Shilpa Chitnis[2], Irene A. Malaty[1] and Pam Zeilman[1]

[1]Department of Neurology, Fixel Institute for Neurological Diseases, University of Florida, Gainesville, FL, United States, [2]UT Southwestern Medical Center, Dallas, TX, United States

Background: Spinocerebellar ataxia 17 (SCA17) is a rare autosomal dominant trinucleotide disorder. There are no effective therapies for addressing the clinical symptoms of SCA17.

Case report: We describe a 46-year-old male who presented with symptoms of generalized dystonia and focal arm tremors manifesting during adolescence. He underwent bilateral globus pallidus (GPi) DBS surgery that led to notable improvements in dystonia and tremor symptoms, impacting his quality of life. At the time of surgery, he did not show cerebellar ataxia features; however, these began to manifest 2 years after DBS surgery. He subsequently underwent genetic testing that confirmed the SCA17 diagnosis. Currently, at 13 years of follow-up, although the ataxia has continued to worsen, DBS therapy has led to persistent improvements in dystonia, tremor, and many aspects of quality of life.

Discussion: The current case indicates that DBS is a promising symptomatic therapy for dystonia and tremor in SCA17.

KEYWORDS

dystonia, tremor, deep brain stimulation, SCA17, globus pallidus

Introduction

Spinocerebellar ataxia (SCA) 17 is a rare form of autosomal dominant cerebellar ataxia resulting from an abnormal CAG expansion of the TATA-binding protein gene. In addition to the core symptoms of progressive cerebellar ataxia, the clinical phenotype can include dementia, epilepsy, psychosis, Parkinsonism, dystonia, and chorea [1]. Currently, there are no effective treatments for clinical symptoms of SCA17. We report a case of SCA17 presenting with generalized dystonia and bilateral arm tremors who demonstrated long-term improvements with deep brain stimulation (DBS) targeted to bilateral globus pallidus (GPi).

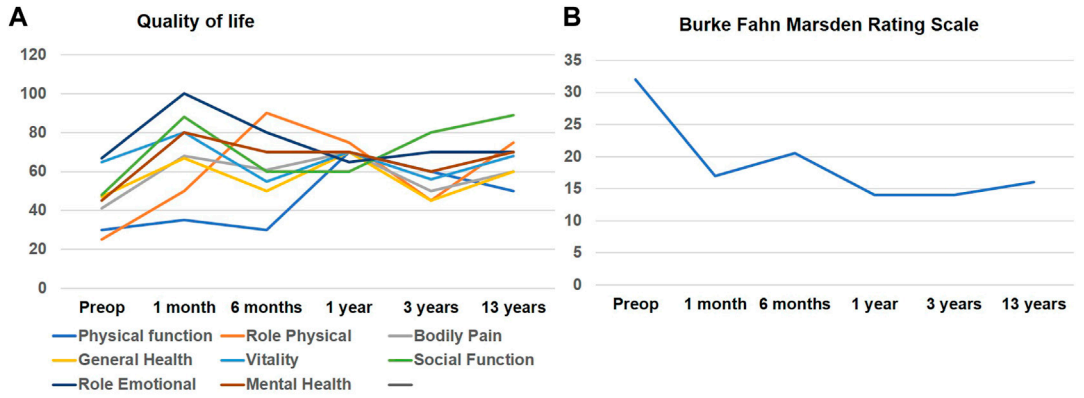

FIGURE 1
(A) illustrates line graphs of individual domain scores for SF-36 quality-of-life assessment that was recorded longitudinally after DBS surgery. Physical Function; Role physical and Social Function domains showed initial improvement which seemed to diminish over time however remained higher than scores before surgery. **(B)** illustrates the Burke-Fahn-Marsden dystonia rating scale assessed at multiple time intervals after DBS surgery.

Case report

A 46-year-old right-handed white male presented to our center with adolescent-onset symptoms of painful posturing of the neck, arms, trunk, and toes. He had tremors affecting his arms that interfered with writing, eating, drinking, and dressing activities. With progression, he began to experience symptoms of chronic anxiety, depression, and panic attacks. He reported an awkward "lazy gait" but denied falls. Physical examination revealed that the neck was deviating to the left almost 30° and tilting to the right 20°, with some overall forward pulling. The wrist exhibited mild posturing, the trunk had right latero-flexion, the feet had plantar-flexion and inversion, and the toes (left > right) involuntarily flexed when walking. He had mild-moderate symmetric arm tremors, mainly kinetic, with minimal resting and no intentional components. There was no dysmetria/dysdiadochokinesis present on rapid repetitive movements. The spiral drawing task revealed a moderate amplitude jerky tremor with no axis. The remaining parts of the examination were unremarkable, including cognition, eye movement assessment, and motor system testing. His workup, such as MRI brain testing for Wilson's disease and dystonia gene panel, was unremarkable. He received trials of trihexyphenidyl, levodopa-carbidopa, clonazepam, baclofen, and multiple rounds of botulinum toxin injections to the neck muscles with no improvements, deeming symptoms to be medication-refractory. Therefore, he underwent bilateral GPi DBS surgery to address the symptoms of dystonia and dystonic tremor. DBS leads were confirmed to be well placed postoperatively. The arm tremors responded soon after surgery; however, symptoms of dystonia required trials of wide monopolar and bipolar configurations at higher pulse widths of 450 μs and a range of frequencies (60 Hz–180 Hz). After 6 months of continued programming, he finally improved on the monopolar settings of 2 V amplitude, 120 μs pulse width, and 130 Hz frequency. The neck dystonia became less problematic, and he could ambulate more effectively in public spaces. Physical examination conducted at one and 6 months after DBS with the help of Burke Fahn Marsden rating scale, demonstrated improvements. The quality of life tracked with the SF-36 quality of life scale also revealed improvement in many domains (Figure 1). At the 1-year visit, he had some persistent difficulties with gait (Supplementary Video S1 reveals video collected with DBS turned off and on), despite reporting improvements in dystonia severity. About 2–3 years after surgery, he noticed significant impairments in speech and gait regardless of whether DBS was turned on or off (Supplementary Video S1 segment). Physical examination at this point revealed clear dysmetria in both arms and significant gait ataxia. These new features prompted a further workup, including serum levels for alpha-fetoprotein, albumin, amino acid, cholesterol, very long chain fatty acid, ammonia, transferrin factor, paraneoplastic antibodies, heavy metals, vitamin E, and ceruloplasmin. The urine was checked for elevated levels of organic acid, phytanic acid, frataxin, and lactic acid. Genetic testing was pursued to investigate a possible genetic form of ataxia, although the family history was negative. SCA panel revealed an unstable CAG trinucleotide expansion mutation coding for polyglutamine tracts in the TBP. There was one allele with 22 repeats and the other allele with 43 repeats. The findings of the testing were consistent with a diagnosis of SCA17. At 13 years of follow-up, even though ataxia symptoms progressed, the patient endorsed enduring improvements in dystonia and tremor with DBS turned on (Left GPi, C+ 1-, 3 V, 180 PW, 60 Hz; Right GPi, C+ 1-, 3 V; 180 PW; 60 Hz). Some DBS programming studies have found clinical benefits for dystonia when using low frequencies [2]. At this follow-up visit, we conducted an accelerometer-based electrophysiological testing of the tremor that revealed a 3 Hz low-frequency band with a slightly

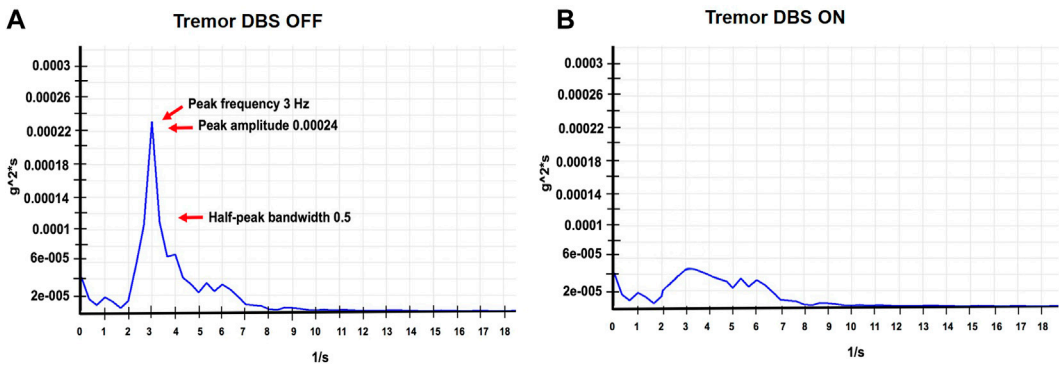

FIGURE 2
(A,B) represent accelerometer-based tremor recordings with DBS OFF, and DBS ON DBS (Left GPi, C+ 1-, 3V, 180 PW, 60 Hz; Right GPi, C+ 1-, 3V; 180 PW; 60 Hz), wash-out and wash-in intervals were 30 min respectively. These recordings were performed at the last follow-up visit. The figure illustrates the power spectrum analysis of the tremor signal. The raw signal was digitized, filtered (0–50 Hz) and was subjected to a fast fourier transform (FFT) analysis to generate the frequency peak. We first divided the selected data series (10 s) into overlapping sections of a specified window length, and window overlap and the squared FFT magnitude of each section was averaged and zero-padded to identify the dominant frequency peak. The tremor amplitude was calculated as a square root of the summated power of the frequency peaks recorded along the x, y, and z-axes. The width of the spectral peak at one-half the peak amplitude in the power spectrum was calculated to determine the cycle-to-cycle variability in the frequency (half peak bandwidth > 2 Hz indicates a more irregular tremor).

broad half-peak bandwidth. Importantly the tremor peak was observed to go away when the DBS was turned on (Figure 2). He reported that his activities of daily living were easier with DBS turned on due to effective tremor control. He found that the quality of life compared to before surgery was better in domains pertaining to social functions, and physical and mental health.

Discussion

We report long-term outcomes of bilateral GPi DBS therapy in a patient with SCA17. Unlike previous SCA17 reports of focal dystonia (writer's cramp and cervical dystonia) [3], the current case presented with dystonia generalized in distribution. The cerebellar ataxia symptoms manifested two decades after the initial symptoms, highlighting the wide variability in the phenotypic spectrum and disease course reported in the literature. While the CAG repeats cut-off for symptomatic manifestation is 43, many recent publications have reported clinical symptoms even with lower repeat expansion numbers [4]. Literature has only a few cases that reported DBS outcomes for genetic ataxia, such as SCA1, SCA 2, and SCA3. In recent series of SCA3 patients, the dentate nucleus of the cerebellum was targeted with DBS to improve ataxia symptoms. DBS was observed to be safe and well tolerated but did not improve ataxia symptoms [5]. With regards to dystonia, one report of SCA1 demonstrated partial benefit [6] In another report of patients with SCA2 and SCA3, there was some improvement in dystonia with bilateral GPi stimulation [7]. DBS outcome for the current case was earlier reported at a 1-year follow-up [8]. Although the patient continued to improve for another year, he later began to report clinical worsening mainly related to the emergence of ataxia over 20 years into his disease. DBS improved arm tremors, maintained at 13 years of follow-up with electrophysiological assessment revealing the tremor peak to suppress in response to DBS turning on. While the diagnosis for SCA17 was indeed delayed, our current case demonstrated that DBS could lead to long-term symptom-specific benefits, accompanied by improvement in the activities of daily living and quality of life. Whether cerebellar ataxia was unmasked with improvement in tremor and dystonia or DBS therapy acted as a trigger for delayed presentation of ataxia symptoms a few years later is unclear.

Our case had some additional unique features. Unlike previous cases that selected the thalamus to control tremors [9], our patient with a tremor in the setting of dystonia revealed benefits with GPi stimulation. None of the previous cases reports or case series reported electrophysiological characterization of tremor in SCA17 or has provided data on long-term follow-up. We recognize that the symptomatic improvement seen in our case of SCA17 cannot be generalized to all other forms of inherited ataxias. Our case presentation does not include video recordings for all time points. More cases with blinded assessments will be needed. We recognize that DBS cannot address all features of an ataxia syndrome. Nevertheless, DBS in SCA17 has shown a promising potential to address specific extrapyramidal features such as tremors and dystonia.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The authors confirm that the patient provided formal written consent for this work. Because this article is a case report, no IRB approval was necessary. We have also blurred the facial features to protect patient identity. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

Research project: AW and PZ, conception. AW and SC, organization. AW and SC, execution. Manuscript preparation: AW and PZ, writing of the first draft. IM and PZ, review and critique. AW, IM, and PZ, writing of the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/dyst.2023.11363/full#supplementary-material

References

1. Toyoshima Y, Takahashi H. Spinocerebellar ataxia type 17 (SCA17). *Adv Exp Med Biol* (2018) 1049:219–31.

2. Velez-Lago FM, Oyama G, Foote KD, Hwynn N, Zeilman P, Jacobson C, et al. Low-frequency deep brain stimulation for dystonia: Lower is not always better. *Tremor Other Hyperkinet Mov (N Y)* (2012) 2:tre-02-55-272-1. doi:10.7916/D85X27PH

3. Hagenah JM, Zühlke C, Hellenbroich Y, Heide W, Klein C. Focal dystonia as a presenting sign of spinocerebellar ataxia 17, Movement disorders. *Mov Disord* (2004) 19(2):217–20. doi:10.1002/mds.10600

4. Park H, Jeon BS, Shin JH, Park SH. A patient with 41 CAG repeats in SCA17 presenting with parkinsonism and chorea. *Parkinsonism Relat Disord* (2016) 22:106–7. doi:10.1016/j.parkreldis.2015.11.011

5. Cury RG, França C, Duarte KP, Paraguay I, Diniz JM, Cunha P, et al. Safety and outcomes of dentate nucleus deep brain stimulation for cerebellar ataxia. *Cerebellum* (2021) 21(5):861–5. doi:10.1007/s12311-021-01326-8

6. Copeland BJ, Fenoy A, Ellmore TM, Liang Q, Ephron V, Schiess M. Deep brain stimulation of the internal globus pallidus for generalized dystonia associated with spinocerebellar ataxia type 1: A case report. *Neuromodulation* (2014) 17(4):389–92. doi:10.1111/ner.12081

7. Beaulieu-Boire I, Aquino CC, Fasano A, Poon YY, Fallis M, Lang AE, et al. Deep brain stimulation in rare inherited dystonias. *Brain Stimul* (2016) 9(6):905–10. doi:10.1016/j.brs.2016.07.009

8. Oyama G, Thompson A, Foote KD, Limotai N, Abd-El-Barr M, Maling N, et al. Deep brain stimulation for tremor associated with underlying ataxia syndromes: A case series and discussion of issues. *Tremor Other Hyperkinet Mov (N Y)* (2014) 4:228. doi:10.7916/D8542KQ5

9. Hashimoto T, Muralidharan A, Yoshida K, Goto T, Yako T, Baker KB, et al. Neuronal activity and outcomes from thalamic surgery for spinocerebellar ataxia. *Ann Clin Transl Neurol* (2018) 5(1):52–63. doi:10.1002/acn3.508

DYSTONIA

TYPE Original Research
PUBLISHED 14 August 2023
DOI 10.3389/dyst.2023.11231

OPEN ACCESS

EDITED BY
Pattamon Panyakaew,
Chulalongkorn University, Thailand

*CORRESPONDENCE
Aparna Wagle Shukla,
aparna.shukla@neurology.ufl.edu

RECEIVED 30 January 2023
ACCEPTED 27 July 2023
PUBLISHED 14 August 2023

CITATION
Wagle Shukla A, Gurrala A and Vedam-Mai V (2023), Gait and balance in cervical dystonia and dystonic head tremor.
Dystonia 2:11231.
doi: 10.3389/dyst.2023.11231

Gait and balance in cervical dystonia and dystonic head tremor

Aparna Wagle Shukla*, Anjela Gurrala and Vinata Vedam-Mai

Department of Neurology, Fixel Institute for Neurological Diseases, University of Florida, Gainesville, FL, United States

Background: Previous studies have found gait and balance abnormalities in patients with cervical dystonia. However, the characteristics of gait and balance in cervical dystonia with head tremors have not been ascertained. A midline constant head tremor when walking would likely render gait and balance more difficult. The pathophysiology of dystonia has also been increasingly linked with cerebellar function abnormality, commonly implicated in gait and balance disorders.

Methods: We examined the gait and balance characteristics of cervical dystonia presenting with head tremors. We used the timed up-and-go (TUG) walk test, 10 m walk test, Berg Balance Scale (BBS), and Gait and Freezing questionnaire. We then assessed the gait on an instrumented walkway system to capture spatiotemporal measures such as speed, cadence, step time, step length, stride width, swing%, stance%, single support%, double support%, and gait variability index (GVI). We also assessed whether the gait in dystonic tremor (DT) differed from essential tremor (ET) and orthostatic tremor (OT), as these tremor disorders share the cerebello-thalamo-cortical pathway as the common pathological pathway.

Results: 50 participants comprising DT (20 patients), ET (15 patients), and OT (15 patients) were enrolled. While the gait abnormalities were subclinical, 11/20 DT patients (55%) walked at a slower speed on the TUG, 11/20 (55%) had reduced scores on the BBS, 9/20 (45%) had increased step time, 4/20 (20%) had reduced step length, 4/20 (20%) had wider stride width, 9/20 (45%) spent greater time during double support and 8/20 (40%) patients had an abnormal GVI. Comparisons of DT with healthy control data revealed a slower gait velocity ($p = 0.001$) and a reduced step length ($p = 0.001$). Compared to DT, the ET group revealed a reduced cadence ($p = 0.04$) and the OT group revealed an increased TUG time ($p = 0.03$), reduced BBS scores ($p = 0.02$), reduced step length ($p = 0.02$), reduced cadence ($p = 0.03$), reduced GVI ($p = 0.01$), and increased double support phase ($p = 0.045$).

Conclusion: DT is accompanied by multiple abnormalities affecting gait and balance, albeit subclinical and less pronounced than ET and OT, possibly related to more effective compensatory mechanisms. Nevertheless, these abnormalities indicate that rehabilitative measures warrant consideration when managing in clinical settings.

KEYWORDS

dystonia, dystonic tremor, gait, walkway, essential tremor

Introduction

Gait and balance difficulties can be seen in many tremor disorders, such as essential tremor (ET), Parkinson's disease tremor, and orthostatic tremor (OT) [1–4]. The pathophysiology of these tremor disorders is linked with abnormalities of cerebellar functions, which are critical for gait and balance [5, 6], There is mounting evidence that the cerebellum is a key pathophysiological substrate in dystonia [7–9], thus implying that gait and balance could potentially be compromised in this patient population. As such, previous studies have found subclinical and clinical gait abnormalities in some forms of dystonia such as cervical dystonia [10]. It has been reported that these patients walk at slower speeds than healthy controls [11], and that they report a lower level of fall self-efficacy and balance confidence [11, 12]. However, to our knowledge, there are no studies that have ascertained and characterized the gait abnormalities in cervical dystonia when there is a co-occurring tremor affecting the head, referred to as the dystonic tremor (DT). A midline body tremor, especially a constant head tremor when walking, would plausibly render gait, balance and equilibrium more difficult.

Thus, in this study, we sought to characterize the gait in cervical dystonia patients presenting with dystonic head tremor. We used standardized clinical assessment questionnaires and scales for assessment of gait and balance and an instrumented walkway system for capturing individual spatiotemporal gait measures and compared these measures with data collected from age matched healthy controls. We ascertained whether the clinical features in patients with DT, such as the age, gender, disease duration, cognition, botulinum doses or head tremor severity, were related to the gait measures. We also assessed whether the gait characteristics in DT differed from those seen in patients with ET and OT as the cerebello-thalamo-cortical pathway was common and implicated in the pathophysiology for these tremor disorders.

Methods

We prospectively enrolled DT, ET and OT patients in an IRB approved study who consecutively presented to our Movement Disorders Center at the University of Florida between 2019 and 2020. Diagnosis of DT, ET and OT was confirmed with clinical criteria following recommendations of the Movement Disorders Society [13]. We only enrolled those patients who were able to perform gait tasks comfortably and could walk on an instrumented walkway system while off medications and at least 3 months past their last botulinum toxin injections. We excluded patients with substantial arthritis, spinal disease and deformities, substance abuse, neuropathy symptoms and visual difficulties.

Study protocol

Upon obtaining an informed consent, participants underwent a detailed clinical history assessment, and a complete tremor pertaining physical examination by a movement disorders specialist at the Fixel Movement Disorders Center. For the gait and balance component, participants were assessed with the following scales, tests and questionnaires: (1) Berg Balance scale (BBS); a 14-item objective measure for assessment of static balance and risk of falls in adults. BBS is used to objectively determine the subject's ability (or inability) to safely balance during a series of predetermined tasks. Each item on the 14-item list consists of a five-point ordinal scale ranging from 0 to 4, with 0 indicating the lowest level of function and 4 indicating the highest level of function. The scale does not include the assessment of gait. High scores (50 and above) indicate normal balance (2) Time Up and Go (TUG) test; a test that captures transfers, gait, and turning movements used for the assessment of mobility, balance, walking ability, and fall risk. The test involves standing and sitting from a chair as well as walking a 3-meter distance. These components of the test allow examination of gait, turns, sit to stand, and turn to sit transitions. Most healthy controls need 10 s or less to complete the TUG test (3) 10 m walk test; a performance measure employed to assess walking speed measured in meters per second over a short distance. A gait speed < 1.1 m per second (m/s) is accepted to fall in the normal range. It can be used as a measure of functional mobility and gait. (4) Gait and Freezing Questionnaire (GFQ); a 6-item survey used to assess gait and freezing. The scale has two items specifically for assessment of gait. Response to each item is a 5-point interval scale ranging from 0 for the absence of symptoms to 5 for the highest severity of symptoms. Higher scores indicate an increased severity of impairment (5) Montreal Cognitive Assessment (MoCA); a screening technique designed to detect mild cognitive dysfunction. An impaired cognition can be seen in tremor disorders [14] and that can impact gait and balance.

Participants were then instructed to walk on a Zeno™ Walkway mat (ProtoKinetics, Havertown, PA) [20-foot-long x 4-foot-wide pressure sensor]. They were asked to sit with both feet placed on the ground on a chair that was 42 cm high was placed at the end of the gait mat. In response to an auditory cue, participants stood up and walked twice on the mat. Participants walked on the gait mat back and forth without breaks unless symptoms of unsteadiness precluded completion of the task. Four passes were recorded, and for each walking trial, data was collected at a sampling rate of 120 Hz (4 bits) for assessment of spatiotemporal parameters. Data was captured using the electronic, pressure-sensing walkway and analyzed using the ProtoKinetics Movement Analysis Software (PKMAS). The following gait outcome measures were collected and analyzed: speed (cm/s), distance traveled over time; cadence (steps/min), total number of steps per time period taken during a given time;

TABLE 1 Clinical characteristics of the DT cohort.

Pt	Age in yrs	Sex	Disease duration in yrs	Body region affected by dystonia	Body region affected by tremor	Head tremor severity	Oral medications	BoNT	BoNT dose in units	Gait & freezing questionnaire	TUG time (s)	10 m walk (m/s)	MoCA	Berg balance test
1	75	F	25	neck	head, arms	3	clonazepam, gabapentin	y	160	12	16.3	0.6	25	47
2	79	M	15	neck, jaw	head, jaw, arms	2	metoprolol, alprazolam	n	0	0	10.3	1.2	24	53
3	73	F	4	neck	head	1	THP MT	n	0	14	12.1	0.8	22	52
4	60	M	5	head, neck	head	1	eszopiclone, paroxetine, clonazepam	Y	300	6	8.8	1.3	24	55
5	82	F	22	neck, eyes	head	2	clonazepam	y	200	14	12.2	0.9	26	47
6	80	F	15	neck	head	1	primidone, propranolol	y	200	6	8.4	1.3	27	49
7	50	F	2	neck	head	1	none	y	200	0	8.3	1.2	27	56
8	85	F	20	neck, larynx	head, voice, arms	3	primidone, propranolol	y	225	4	12.5	0.8	24	46
9	65	F	14	neck	head, arms	2	alprazolam, metoprolol	y	260	1	9.15	1.2	26	49
10	67	F	12	neck	head, arms	2	propranolol	y	200	8	12.5	0.9	27	47
11	63	M	4	neck	head	1	clonazepam	y	300	7	14.3	0.9	25	44
12	71	F	12	neck, jaw, arms	head, arms	1	zolpidem, metoprolol, CBZ	y	400	14	13.1	0.8	29	45
13	69	F	5	neck	head	1	none	y	250	0	11.7	1.2	23	39
14	55	M	25	neck	head	2	gabapentin	n	0	3	8.4	1.3	24	54
15	61	M	50	neck, larynx	head, voice	3	clonazepam, zolpidem, propranolol	y	400	7	9.9	1.1	25	55
16	64	F	16	neck	head	2	primidone, propranolol, clonazepam	y	380	7	15.7	0.7	25	45
17	66	F	3	neck	head	1	primidone, propranolol, clonazepam, benztropine	y	200	2	10.7	1.1	22	49
18	66	F	50	neck	head	2	clonazepam, tizanidine	y	255	5	8.6	1.1	20	55
19	64	F	24	neck	head, arms	2	baclofen, clonazepam	y	400	0	8.5	1.2	27	53
20	41	F	20	neck	head	2	CBZ	y	300	0	6.6	1.4	28	56

THP, trihexyphenidyl.
CBZ, cyclobenzaprine.
MT, methocarbamol.

10.3389/dyst.2023.11231

step duration (s), time between the first contact of one foot; step length (m or cm), distance between two consequent footprints (heel) and stride width, distance between the feet while walking is the perpendicular distance between the line connecting the two ipsilateral foot heel contacts (stride) with the contralateral heel contact between those events (cm). Normal gait consists of two phases: the swing phase (40% of the gait cycle; when the foot first touches the ground and ends when the same foot leaves the ground) and the stance phase (60% of the gait cycle; when the foot first leaves the ground and ends when the same foot touches the ground again). These phases are divided into sub-phases; single limb support % involving mid and terminal stance subphase and double limb support % involving initial contact, loading, and pre-swing subphase. Finally, the gait variability index (GVI), a measure to quantify the variability in spatiotemporal variables, was collected (a score ≥100 indicates values similar to healthy controls, whereas a lower score denotes increased gait variability).

Statistical analysis was performed using IBM SPSS Statistics 27 (Armonk, NY). Demographics, baseline clinical measures, and gait assessments were compared between DT vs. healthy controls, DT vs. ET and DT vs. OT using Mann-Whitney U tests or $\chi 2$ tests as appropriate. In the DT group, continuous clinical measures were correlated with gait measures using the Spearman correlation test and the categorical predictors were analyzed with the help of Mann Whitney U test. The threshold for significance was set at p-value <0.05 and the Holm-Bonferroni method was used to correct for type I error rates for multiple comparisons.

Results

50 participants comprising of DT (20 patients), ET (15 patients), and OT (15 patients) were enrolled.

Demographics and clinical features of the DT cohort

15 females and 5 males participated. Mean age for the participants was 66.8 ± 10.8 (standard deviation or SD) years. Mean disease duration was 17.1 ± 13.2 years. Clinical characteristics of the DT cohort are presented in Table 1. All participants had a diagnosis of cervical dystonia with head tremor and except four participants, none endorsed clinical gait difficulties. Video segments of gait recorded for 2 DT patients is presented in Supplementary Information. Three DT patients had dystonia symptoms affecting the arm, two patients had laryngeal involvement, two had jaw and one patient had dystonia involving the eyes along with the neck. The mean severity of head tremor (based on the item 4 of Fahn Tolosa Marin tremor rating scale used routinely in our clinic) was noted to be 1.8 ± 0.6. Six participants had arm tremor, two had voice tremor and one had jaw tremor in addition to their head tremor. All participants except three were receiving botulinum toxin injections with mean dosage 231.5 ± 124.2 units. Gait assessment was performed when the participants were at least 3 months past their botulinum toxin injections and oral medications had been held off for at least 12 h. Thirteen patients were receiving benzodiazepines and two patients were receiving anticholinergics for dystonia. Nine patients were receiving betablockers and four patients were receiving primidone for treatment of tremor.

In the GFQ questionnaire, 4/20 patients (20%) were found to have abnormally elevated scores indicating that these patients reported some difficulties with walking. In the assessment of TUG time, a cut-off value of 12 s that has been found to differentiate fallers from non-fallers among the community-dwelling elders was used [15, 16]. We found with this cut-off, 8/20 participants (40%) needed more than 12 s and 3/20 (15%) patients needed more than 13.5 s to complete the task. 11/20 patients obtained slightly lower scores on the BBS test and in the 10 m walk test, 8/20 (40%) patients were observed to walk slow when a cut off score of 1.1 m/sec was used [17].

DT gait on the instrumented walkway system

Table 2 presents data for individual DT participants. The Supplementary Table presents data for age- and sex-matched healthy controls (n = 46). The minimum and maximum values for data collected from healthy controls within a specific age range is plotted in the Supplementary Table. When comparing against these values for healthy control data, 11/20 DT participants (55%) were identified to walk at a slower speed, 9/20 (45%) walked with increased step time; 4/20 (20%) walked with shorter step length; 4/20 (20%) had wider stride width, 6/20 (30%) participants had shorter time spent during the swing phase; 7/20 (35%) had reduced time spent during single support, 9/20 (45%) spent greater time during double support and 8/20 (40%) patients had an abnormal gait variability index. Cadence was affected only in 3/20 (15%) patients and the time spent during stance phase was observed to be within normal limits for all participants. However, in the statistical analysis comparing the mean values for the two groups using the Mann Whitney U test (adjusted for multiple comparisons), only the gait velocity (mean 99.1 ± 26.3 vs. 124.1 ± 20.3; p = 0.001) and reduced step length (mean 57.2 ± 10.6 vs. 70.2 ± 10.3; p = 0.001) were significantly different in the DT group compared to healthy controls (Figure 1).

Clinical features of DT participants and relationship with gait findings

Age of the DT participants was found to correlate significantly with their TUG time (r = .49; p = 0.01), 10 m

gait speed (r = −.473; $p = 0.015$), score on the BBS (r = −.537; $p = 0.015$) and the gait velocity (r = - 0.479; $p = 0.018$) measured on the walkway system. However, gender, disease duration, head tremor severity, presence of axial tremors such as jaw tremor and voice tremor, MoCA score and botulinum doses did not impact the gait findings measured with clinical scales (GFQ, BBS, 10 m walk and TUG time) as well as the instrumented walkway system (velocity, cadence, step time, step length, stride width, percentage of time spent during swing and support phase, single support phase and double support phase and the gait variability index ($p > 0.05$).

Comparisons of DT vs. ET and DT vs. OT

Demographics and gait findings of ET and OT groups are presented in Table 3. The ET group consisting of patients with bilateral arm tremors also had five patients with additional head tremors. In the OT group, 4 participants complained of bilateral arm tremors, and none had a head tremor. There were more females in the DT group compared to ET (17 vs. 6; $p = 0.01$) and the OT group (17 vs. 10; $p = 0.04$). There were no significant differences in age and MoCA scores. Disease duration was significantly longer for the OT group than the DT group (29.6 ± 8.3 vs. 17.6 ± 9.1; $p = 0.04$). In the gait and balance testing, time needed to complete the TUG testing was longer (13.6 ± 3.5 vs. 10.7 ± 2.3; $p = 0.03$) and scores recorded on the BBS were reduced (45 ± 4.7 vs. 50.1 ± 4.5; $p = 0.02$) in the OT group compared to the DT group. In the instrumented gait analysis, the cadence was reduced in ET (95.1 ± 11.2; $p = 0.04$) and OT (89.3 ± 9.8; $p = 0.03$) compared to DT (103.4 ± 10.3). The step length (51.4 ± 6.7 vs. 56.7 ± 7.8; $p = 0.02$) and GVI (89.1 ± 7.1 vs. 118.4 ± 8.7; $p = 0.01$) were reduced, and the time spent during the double support phase (35.9 ± 15.1 vs. 32.1 ± 15.2; $p = 0.045$) was increased in OT compared to DT (Figure 1).

Discussion

Our study demonstrates that cervical dystonia patients with co-occurring head tremors display a number of spatiotemporal abnormalities related to gait. Although it has been previously suggested that gait impairments can be seen in cervical dystonia, the inclusion of head tremors as a clinical presentation has not been taken into account [18, 19]. The DT group in our study walked slower with shorter steps and with a broader base, and spent relatively greater amounts of time during the double limb support phase of the gait cycle. Many DT patients revealed that the gait variability was increased. Although the BBS scores for balance assessment were mainly within normal limits, nearly 40% of patients needed more time to complete the TUG test. Our study also found that among the tremor disorders, the most impressive number of abnormalities were present in the OT group compared to DT and ET. Patients with OT needed the highest amount of time on TUG, had relatively worsened BBS scores, walked slower with shorter steps, spent much more time during the double support phase, and had a higher gait variability. These findings support the shared link to the cerebellum as the source of tremor pathogenesis and gait dysfunction and emphasize the need for involving rehabilitation care when managing patients with tremor disorders in clinical settings.

Three-fourths of our DT cohort were females, which is not surprising as cervical dystonia affects females more frequently [20]. An increased preponderance of head tremors is also observed in females with cervical dystonia [21–23]. The findings of increased TUG seen in the DT cohort raise concerns that there is decreased control of mobility, transfers, and balance and they may be an increased risk of falls. Indeed, patients with cervical dystonia have been found to display deficits in balance, gait, and stepping reactions and they have expressed a higher fear of falling [12, 24]. In our study, many DT patients were observed to have an increase in step time, stride width, and time spent during double support to attempt increasing the stability during walking [25]. A lower walking speed in our cohort may have allowed the patients to maximize the sensory feedback from the lower limbs to aid in stability and balance. These natural adaptations have been noted to commonly occur in many other neurological populations such as multiple sclerosis [25, 26]. We also observed that as the age of DT patients increased, there was further lowering of gait speed and a concomitant increase in the time needed to complete the TUG task. We believe, a worsened age may have accelerated the progression of pathological changes in the tremor network leading to worsening of findings. Similar to our findings, a previous study in cervical dystonia found subclinical abnormalities such as increased gait variability and lower gait velocity [10]. However, it was not clear whether the patients in that study had a head tremor in addition to abnormal neck posturing.

Many potential hypotheses could be conjectured to explain the gait and balance findings observed in our DT cohort. A sustained, aberrant neck position appears to reduce the reliability of visual cues for postural control which, in turn, negatively impacts balance and balance related confidence [24]. As such, an abnormal head posture in cervical dystonia has also been found to impact vestibular functions [27] and proprioceptive capabilities [28, 29]. Another consideration is related to cervico-collic and tonic neck reflexes which may be affected and these factors could influence head, eye, and postural stability [30, 31]. In keeping with this hypothesis, a previous study found that patients with cervical dystonia have an increase in postural sway when standing [26]. In one study, a reduced range of motion for the cervical spine was found to correlate with balance and stepping reaction time in cervical dystonia [11]. A number of studies have also drawn attention to the orthopedic and spinal cord complications emerging from chronic mechanical stress of cervical dystonia related to constant twisting motion [32, 33]. Reduced control over voluntary neck movements is expected to render navigating

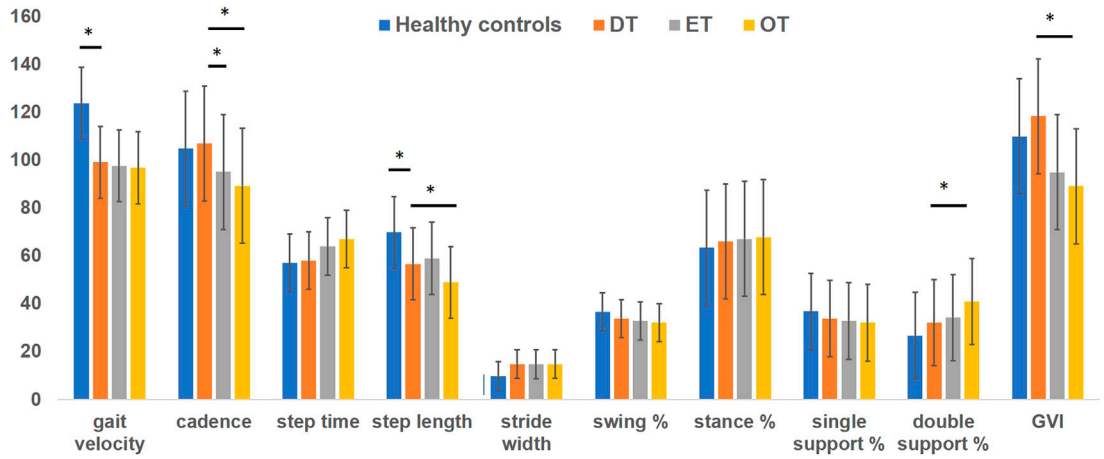

FIGURE 1
Bars represent mean values for gait data collected on instrumented walkway system. Absolute values of step time were multiplied by 100 to plot on the y axis (marked by asterisk). Blue bars represent gait data for healthy controls, orange represent gait data for DT cohort, grey represent gait data for ET cohort and yellow represent gait data for OT cohort. Error bars represent standard errors of mean. Stars placed between the bars in the data for gait velocity and step length illustrate significant differences between healthy control data and DT group.

TABLE 2 Gait data for DT recorded with instrumented walkway system.

Pt	Age in yrs	Velocity cm/sec	Cadence steps/min	Step time (sec.)	Step length (cm.)	Stride width (cm.)	Swing %	Stance %	Single support %	Total D. support %	GVI
1	75	**54.9**	**85.3**	**0.72**	**38.6**	8.8	**32.2**	68.7	**31.6**	**36.6**	**138.9**
2	77	113.7	103.2	0.53	67.2	**18.2**	**32.9**	63.5	36.6	29.3	**130.8**
3	71	**69.6**	103.8	**0.67**	**42.3**	10.9	**30.9**	68.8	**31.4**	**37.9**	**130.3**
4	60	**95.8**	98.0	**0.69**	56.7	12.1	34.9	65.3	35.0	30.8	110.2
5	80	**126.5**	117.0	0.53	63.8	10.5	37.8	63.6	36.6	25.8	117.0
6	50	**115.9**	110.5	0.54	63.9	12.0	34.7	64.8	35.3	30.1	110.0
7	85	**78.7**	103.7	0.61	48.5	13.8	32.5	64.1	36.5	30.9	**131.1**
8	65	117.0	102.2	0.60	69.7	11.4	34.5	66.5	33.2	**32.4**	113.2
9	67	**87.9**	100.9	**0.64**	56.6	**17.0**	**29.5**	69.4	**30.8**	**38.9**	**136.5**
10	63	**78.7**	**87.0**	**0.72**	54.1	14.4	34.0	67.7	**32.5**	**33.8**	119.9
11	71	**72.9**	101.5	**0.68**	**42.8**	13.4	33.2	68.2	**31.7**	**34.7**	**132.2**
12	69	**93.8**	106.5	**0.66**	52.5	**15.8**	**32.3**	65.7	33.9	33.6	**132.7**
13	55	**91.1**	100.1	0.62	52.9	10.2	**32.0**	66.9	33.3	32.9	118.5
14	61	101.6	96.8	0.61	60.9	**18.6**	34.6	65.4	34.6	30.5	111.0
15	64	**78.7**	103.0	**0.66**	**46.3**	10.7	33.4	69.7	**30.5**	**36.3**	**135.6**
16	66	**77.0**	91.3	**0.73**	49.4	9.1	31.6	67.7	**32.2**	**36.1**	107.3
17	66	121.6	114.9	0.52	64.9	10.2	34.3	65.7	34.4	31.0	100.0
18	64	138.2	126.3	0.54	66.7	8.6	35.6	63.6	36.4	27.8	97.6
19	41	137.0	113.4	0.55	73.8	12.8	37.8	62.3	37.8	24.7	100.0
20	65	131.8	107.4	0.61	74.3	9.1	36.7	62.8	37.2	25.8	97.6

Bold values are abnormal values for individuals when comparing to age and sex matched healthy control values.

complex environments challenging While the presence of head tremors and the resulting mechanical instability is undoubtedly important, previous research supports a pathogenic role of the cerebellum, particularly in the context of DT [34]. Many participants in our DT cohort walked with a slower speed, revealed an increased stride width, and spent more time in the double support phase of the gait cycle, findings similar to those seen in patients with cerebellar dysfunction [9, 35]. Thus, many

TABLE 3 Comparisons of gait data in DT with ET and OT cohorts.

	Dystonic tremor (DT)	Essential tremor (ET)	Orthostatic tremor (OT)	DT vs. ET (*p*-value)	DT vs. OT (*p*-value)
Number of participants	20	15	15		
Age in years (mean ± SD)	66.5 ± 8.9	68.8 ± 7.8	70 ± 6.5	$p = 0.71$	$p = 0.23$
Sex (Male: Female)	3:17	9:6	5:10	**p = 0.01**	**p = 0.02**
Disease duration in years (mean ± SD)	17.6 ± 9.1	22.5 ± 8.9	29.6 ± 8.3	$p = 0.06$	**p = 0.04**
MOCA score	24.4	23.1	28.5	$p = 0.56$	**p = 0.04**
Gait and freezing questionnaire total score (mean ± SD)	4.2 ± 1.4	4.8 ± 1.5	4.5 ± 2.1	**p = 0.057**	$p = 0.63$
TUG walking time in seconds (mean ± SD)	10.7 ± 2.3	12.8 ± 3.1	13.6 ± 3.5	**p = 0.05**	**p = 0.03**
10 m walk (speed) in m/seconds (mean ± SD)	0.9 ± 0.2	0.9 ± 0.2	0.7 ± 0.3	$p = 0.82$	$p = 0.13$
Berg Balance total score (mean ± SD)	50.1 ± 4.5	48.9 ± 4.6	45 ± 4.7	$p = 0.47$	**p = 0.02**
Gait velocity in cm/seconds (mean ± SD)	99.1 ± 9.1	97.6 ± 8.4	96.8 ± 8.9	$p = 0.78$	$p = 0.67$
Cadence in steps/minute (mean ± SD)	103.4 ± 10.3	95.1 ± 11.2	89.3 ± 9.8	**p = 0.04**	**p = 0.03**
Step time in seconds (mean ± SD)	0.68 ± 0.2	0.64 ± 0.2	0.81 ± 0.5	$p = 0.71$	**p = 0.06**
Step length in cm (mean ± SD)	56.7 ± 7.8	59.0 ± 9.1	51.4 ± 6.7	**p = 0.13**	**p = 0.02**
Stride width in cm (mean ± SD)	12.4 ± 4.5	14.8 ± 5.6	14.9 ± 6.9	$p = 0.28$	$p = 0.16$
Swing % (mean ± SD)	33.8 ± 12.1	32.8 ± 11.4	32.1 ± 13.4	$p = 0.68$	$p = 0.79$
Stance % (mean ± SD)	66.1 ± 12.3	67.2 ± 13.4	67.9 ± 12.5	$p = 0.77$	$p = 0.62$
Single support % (mean ± SD)	33.9 ± 14.1	32.9 ± 13.1	32.1 ± 14.6	$p = 0.71$	$p = 0.17$
Double support % (mean ± SD)	32.1 ± 15.2	34.3 ± 13.4	35.9 ± 15.1	**p = 0.12**	**p = 0.045**
Gait variability index (GVI) (mean ± SD)	118.4 ± 8.7	95.1 ± 8.6	89.1 ± 7.1	**p = 0.04**	**p = 0.01**

Bold values indicate significant *p* values.

factors in varying combinations can potentially explain the gait and balance findings in our DT cohort.

Interestingly, only 20% of our DT group reported clinical difficulties with gait and balance, indicating that the changes noted in our study were subclinical for most patients. Further, the severity of head tremors in the DT cohort was not found to predict gait and balance abnormalities. Our study cannot parse out whether the gait abnormalities are compensatory, or consequential. We also think that the relationship between cervical dystonia and gait is bidirectional, as sometimes, we observed a worsened dystonic posturing of the neck when the patients performed the gait task (Supplementary Video). Thus, it is possible that cervical dystonia leads to worsening of gait, and the performance of gait task exacerbates symptoms of cervical dystonia.

The cerebellum has been regarded as one of the key sources of pathogenic oscillations in other tremor disorders such as ET and OT [36–39]. In the context of ET, presence of head tremors has been found to predict gait dysfunction and balance abnormalities [40]. In a large study of ET patients, axial tremors, including the presence of head and jaw tremors, were associated with significant tandem gait disturbances [41]. Previous studies have reported that OT patients have abnormalities in postural balance assessments [42, 43], and spatial and temporal characterizations of gait [44]. With disease advancement, patients with OT have been observed to walk with shorter steps and a wider base, and spend more time during the double support phase. These patterns of gait abnormalities are similar to those seen in patients with cerebellar disorders [45]. Our study also found notable abnormalities in gait variability in OT patients. Gait variability, defined as the fluctuation in spatiotemporal characteristics between steps, is suggested to be a sensitive indicator of mobility deficits with pathological processes [46]. Some investigators report gait variability of spatial parameters, for example, the variability of the stride width to be a more important indicator of locomotion control than gait variability of temporal parameters. In our study, OT patients had greater gait and balance abnormalities compared to DT patients, which could be due to the fact that these patients are in general older in age and had longer disease duration.

We acknowledge that our study has limitations. While the DT group specifically had a head tremor, our control groups comprising OT and ET did not necessarily share the same phenotype (head tremor present only in a subgroup of ET). Further, the sample size for DT in our study was relatively small; we did not characterize and examine whether the severity of dystonia or electrophysiology of head tremor could impact the gait findings, we did not address the issues of postural sway and near falls, and we have not examined the gait under cognitive loading. We recognize that the intake of GABAergic medications by the patients in our study could have influenced our gait findings as these medications affect cerebellar functions. Although we did not specifically use a statistical model to adjust for medication doses, we collected all data when the patients were off medications to minimize the impact on data interpretation.

Nevertheless, our study has unique strengths as it is the first to focus on the presence of head tremors and their potential impact on gait and balance assessments in cervical dystonia. It compares these findings with other tremor disorders that share cerebellar pathology. Future studies with larger cohorts of dystonia patients with and without tremors as well as plans for longitudinal follow-up, are needed to confirm our findings. Future studies should involve EMG recordings from the neck and leg muscles in conjunction with the instrumented walkway system to understand the relationship between dystonia and gait. It would be interesting to investigate whether gait and balance abnormalities are unique to specific dystonia subtypes, as the pathogenic mechanism is quite heterogeneous. Studies with such designs and cohorts will advance our understanding of the cerebellum and its control over dystonia, tremor, and gait. Importantly, our study findings inform clinicians that rehabilitation strategies should be given due consideration for managing tremor disorders in the outpatient settings.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of Florida IRB. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Author contributions

AWS Research project: Conception, Organization, Execution, Manuscript preparation: Writing of the first draft, Writing of the final manuscript. AG Research project: Organization, Execution. VV-M Research project: Conception, Organization, Execution, Manuscript preparation: Writing of the first draft, Writing of the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

AWS reports grant support from the NIH R01NS122943 as PI and Ro1 NS121120-01 as a Co-I. She reports past funding from Benign Essential Blepharospasm Research foundation, Dystonia coalition, Dystonia Medical Research foundation, National Organization for Rare Disorders. AWS has received consultant fees from Merz, Jazz and Acadia. She is the current Vice President for the Tremor Research Group and recent advisor for Supernus and Biogen-Sage.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/dyst.2023.11231/full#supplementary-material

SUPPLEMENTARY VIDEO S1
A case of DT walking on the Zeno gait mat with significant torticollis to the right. The patient exhibits head tremors when walking. The patient voluntarily corrects his head position to the center as he pauses and takes a turn (segment 16 s to 19 s). His head remains stable for a few seconds, however, involuntarily pulls to the right as he continues to walk (segment 21 s to end).

SUPPLEMENTARY VIDEO S2
A case of DT with significant anterocollis and torticollis to the right. The video is recorded while performing the TUG task. Patient tends to take support from the wall as she walks towards the chair with slight unsteadiness (6 s to 7 s). She uses a sensory trick to steady her head (29 s to 32 s). However, as she continues to walk without using the trick (33 s onwards) her head posture worsens.

References

1. Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? *Brain* (2012) 135(11):3206–26. doi:10.1093/brain/aws023

2. Rao AK, Louis ED. Ataxic gait in essential tremor: a disease-associated feature? *Tremor Other Hyperkinet Mov (N Y)* (2019) 9. doi:10.5334/tohm.507

3. Helmich RC, Toni I, Deuschl G, Bloem BR. The pathophysiology of essential tremor and Parkinson's tremor. *Curr Neurol Neurosci Rep* (2013) 13(9):378. doi:10.1007/s11910-013-0378-8

4. Opri E, Hu W, Jabarkheel Z, Hess CW, Schmitt AC, Gunduz A, et al. Gait characterization for patients with orthostatic tremor. *Parkinsonism Relat Disord* (2020) 71:23–7. doi:10.1016/j.parkreldis.2020.01.007

5. Louis ED. Essential tremor and the cerebellum. *Handbook Clin Neurol* (2018) 155:245–58. doi:10.1016/B978-0-444-64189-2.00016-0

6. Cinar N, Sahin S, Okluoglu Onay T, Karsidag S. Balance in essential tremor during tandem gait: is the first mis-step an important finding? *J Clin Neurosci* (2013) 20(10):1433–7. doi:10.1016/j.jocn.2013.01.013

7. Prudente CN, Hess EJ, Jinnah HA. Dystonia as a network disorder: what is the role of the cerebellum? *Neuroscience* (2014) 260:23–35. doi:10.1016/j.neuroscience.2013.11.062

8. Tsuboi T, Jabarkheel Z, Zeilman PR, Barabas MJ, Foote KD, Okun MS, et al. Longitudinal follow-up with VIM thalamic deep brain stimulation for dystonic or essential tremor. *Neurology* (2020) 94(10):e1073–84. doi:10.1212/WNL.0000000000008875

9. DeSimone JC, Archer DB, Vaillancourt DE, Wagle Shukla A. Network-level connectivity is a critical feature distinguishing dystonic tremor and essential tremor. *Brain* (2019) 142:1644–59. doi:10.1093/brain/awz085

10. Esposito M, Dubbioso R, Peluso S, Picone A, Corrado B, Servodio Iammarone C, et al. Cervical dystonia patients display subclinical gait changes. *Parkinsonism Relat Disord* (2017) 43:97–100. doi:10.1016/j.parkreldis.2017.07.005

11. Barr C, Barnard R, Edwards L, Lennon S, Bradnam L. Impairments of balance, stepping reactions and gait in people with cervical dystonia. *Gait Posture* (2017) 55: 55–61. doi:10.1016/j.gaitpost.2017.04.004

12. Zetterberg L, Urell C, Anens E. Exploring factors related to physical activity in cervical dystonia. *BMC Neurol* (2015) 15:247. doi:10.1186/s12883-015-0499-6

13. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From the task force on tremor of the international Parkinson and movement disorder society. *Mov Disord* (2018) 33(1): 75–87. doi:10.1002/mds.27121

14. Wagle Shukla A. Diagnosis and treatment of essential tremor. *Continuum (Minneap, Minn)* (2022) 28(5):1333–49. doi:10.1212/CON.0000000000001181

15. Bischoff HA, Stähelin HB, Monsch AU, Iversen MD, Weyh A, von Dechend M, et al. Identifying a cut-off point for normal mobility: A comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women. *Age Ageing* (2003) 32(3):315–20. doi:10.1093/ageing/32.3.315

16. Herman T, Giladi N, Hausdorff JM. Properties of the 'timed up and go' test: more than meets the eye. *Gerontology* (2011) 57(3):203–10. doi:10.1159/000314963

17. Lindholm B, Nilsson MH, Hansson O, Hagell P. The clinical significance of 10-m walk test standardizations in Parkinson's disease. *J Neurol* (2018) 265(8): 1829–35. doi:10.1007/s00415-018-8921-9

18. Crisafulli O, Trompetto C, Puce L, Marinelli L, Costi S, Abbruzzese G, et al. Dual task gait deteriorates gait performance in cervical dystonia patients: a pilot study. *J Neural Transm (Vienna)* (2021) 128(11):1677–85. doi:10.1007/s00702-021-02393-1

19. Crisafulli O, Ravizzotti E, Mezzarobba S, Cosentino C, Bonassi G, Botta A, et al. A gait-based paradigm to investigate central body representation in cervical dystonia patients. *Neurol Sci* (2022) 44:1311–8. doi:10.1007/s10072-022-06548-0

20. Rafee S, O'Riordan S, Reilly R, Hutchinson M. We must talk about sex and focal dystonia. *Mov Disord* (2021) 36(3):604–8. doi:10.1002/mds.28454

21. Defazio G, Gigante AF, Abbruzzese G, Bentivoglio AR, Colosimo C, Esposito M, et al. Tremor in primary adult-onset dystonia: prevalence and associated clinical features. *J Neurol Neurosurg Psychiatry* (2013) 84(4):404–8. doi:10.1136/jnnp-2012-303782

22. Shaikh AG, Beylergil SB, Scorr L, Kilic-Berkmen G, Freeman A, Klein C, et al. Dystonia and tremor: a cross-sectional study of the dystonia coalition cohort. *Neurology* (2020) 96:e563–e574. doi:10.1212/WNL.0000000000011049

23. Hvizdošová L, Nevrlý M, Otruba P, Hluštík P, Kaňovský P, Zapletalová J. The prevalence of dystonic tremor and tremor associated with dystonia in patients with cervical dystonia. *Sci Rep* (2020) 10(1):1436. doi:10.1038/s41598-020-58363-2

24. Hoffland BS, Veugen LC, Janssen MM, Pasman JW, Weerdesteyn V, van de Warrenburg BP. A gait paradigm reveals different patterns of abnormal cerebellar motor learning in primary focal dystonias. *Cerebellum* (2014) 13(6):760–6. doi:10.1007/s12311-014-0594-z

25. Remelius JG, Jones SL, House JD, Busa MA, Averill JL, Sugumaran K, et al. Gait impairments in persons with multiple sclerosis across preferred and fixed walking speeds. *Arch Phys Med Rehabil* (2012) 93(9):1637–42. doi:10.1016/j.apmr.2012.02.019

26. Baione V, Ferrazzano G, Celletti C, De Rosa M, Belvisi D, Fabbrini G, et al. Attention-demanding cognitive tasks worsen postural control in patients with cervical dystonia: A case-control study. *Front Neurol* (2021) 12:666438. doi:10.3389/fneur.2021.666438

27. Münchau A, Corna S, Gresty MA, Bhatia KP, Palmer JD, Dressler D, et al. Abnormal interaction between vestibular and voluntary head control in patients with spasmodic torticollis. *Brain* (2001) 124(1):47–59. doi:10.1093/brain/124.1.47

28. Martino D, Bonassi G, Lagravinese G, Pelosin E, Abbruzzese G, Avanzino L. Defective human motion perception in cervical dystonia correlates with coexisting tremor. *Mov Disord* (2020) 35(6):1067–71. doi:10.1002/mds.28017

29. Pelosin E, Bove M, Marinelli L, Abbruzzese G, Ghilardi MF. Cervical dystonia affects aimed movements of nondystonic segments. *Mov Disord* (2009) 24(13): 1955–61. doi:10.1002/mds.22693

30. Gresty M. Stability of the head: studies in normal subjects and in patients with labyrinthine disease, head tremor, and dystonia. *Mov Disord* (1987) 2(3):165–85. doi:10.1002/mds.870020304

31. Anastasopoulos D, Anastasopoulos L, Mergner T. Voluntary suppression of neck reflexes during passive head-on-trunk rotations: reflex gain control versus proprioceptive feedback. *J Neurophysiol* (2022) 127(1):161–72. doi:10.1152/jn.00297.2021

32. Jankovic J, Leder S, Warner D, Schwartz K. Cervical dystonia: clinical findings and associated movement disorders. *Neurology* (1991) 41(7):1088–91. doi:10.1212/wnl.41.7.1088

33. Adler CH, Zimmerman RS, Lyons MK, Simeone F, Brin MF. Perioperative use of botulinum toxin for movement disorder-induced cervical spine disease. *Mov Disord* (1996) 11(1):79–81. doi:10.1002/mds.870110114

34. Buckley E, Mazzà C, McNeill A. A systematic review of the gait characteristics associated with Cerebellar Ataxia. *Gait Posture* (2018/02/01/ 2018) 60:154–63. doi:10.1016/j.gaitpost.2017.11.024

35. Pattamon P, Hyun Joo C, Sang Wook L, Tianxia W, Mark H. The pathophysiology of dystonic tremors and comparison with essential tremor. *J Neurosci* (2020) 40:9317–26. doi:10.1523/JNEUROSCI.1181-20.2020

36. Wagle Shukla A. Reduction of neuronal hyperexcitability with modulation of T-type calcium channel or SK channel in essential tremor. *Int Rev Neurobiol* (2022) 163:335–55. doi:10.1016/bs.irn.2022.02.008

37. Pan MK, Li YS, Wong SB, Ni CL, Wang YM, Liu WC, et al. Cerebellar oscillations driven by synaptic pruning deficits of cerebellar climbing fibers contribute to tremor pathophysiology. *Sci translational Med* (2020) 12(526): eaay1769. doi:10.1126/scitranslmed.aay1769

38. Gallea C, Popa T, Garcia-Lorenzo D, Valabregue R, Legrand AP, Apartis E, et al. Orthostatic tremor: a cerebellar pathology? *Brain* (2016) 139(8):2182–97. doi:10.1093/brain/aww140

39. Benito-Leon J, Romero JP, Louis ED, Sánchez-Ferro A, Matarazzo M, Molina-Arjona JA, et al. Diffusion tensor imaging in orthostatic tremor: a tract-based spatial statistics study. *Ann Clin Transl Neurol* (2019) 6(11):2212–22. doi:10.1002/acn3.50916

40. Arkadir D, Louis ED. The balance and gait disorder of essential tremor: what does this mean for patients? *Ther Adv Neurol Disord* (2013) 6(4):229–36. doi:10.1177/1756285612471415

41. Louis ED, Rios E, Rao AK. Tandem gait performance in essential tremor: clinical correlates and association with midline tremors. *Mov Disord* (2010) 25(11): 1633–8. doi:10.1002/mds.23144

42. Bhatti D, Thompson R, Xia Y, Hellman A, Schmaderer L, Suing K, et al. Comprehensive, blinded assessment of balance in orthostatic tremor. *Parkinsonism Relat Disord* (2018) 47:22–5. doi:10.1016/j.parkreldis.2017.11.335

43. Feil K, Bottcher N, Guri F, Krafczyk S, Schöberl F, Zwergal A, et al. Long-term course of orthostatic tremor in serial posturographic measurement. *Parkinsonism Relat Disord* (2015) 21(8):905–10. doi:10.1016/j.parkreldis.2015.05.021

44. Wuehr M, Schlick C, Mohwald K, Schniepp R. Walking in orthostatic tremor modulates tremor features and is characterized by impaired gait stability. *Scientific Rep* (2018) 8(1):14152. doi:10.1038/s41598-018-32526-8

45. Croarkin E, Maring J, Pfalzer L, Harris-Love M, Siegel K, DiProspero N. Characterizing gait, locomotor status, and disease severity in children and adolescents with Friedreich ataxia. *J Neurol Phys Ther* (2009) 33(3):144–9. doi:10.1097/NPT.0b013e3181b5112e

46. Balasubramanian CK, Clark DJ, Gouelle A. Validity of the gait variability index in older adults: effect of aging and mobility impairments. *Gait Posture* (2015) 41(4):941–6. doi:10.1016/j.gaitpost.2015.03.349

DYSTONIA

TYPE Mini Review
PUBLISHED 07 November 2023
DOI 10.3389/dyst.2023.11347

OPEN ACCESS

EDITED BY
Aparna Wagle Shukla,
University of Florida, United States

*CORRESPONDENCE
Kai-Hsiang Stanley Chen,
stanleychen1230@gmail.com

RECEIVED 09 March 2023
ACCEPTED 24 October 2023
PUBLISHED 07 November 2023

CITATION
Kuo Y-CJ and Chen K-HS (2023), A mini-review of the pathophysiology of task-specific tremor: insights from electrophysiological and neuroimaging findings.
Dystonia 2:11347.
doi: 10.3389/dyst.2023.11347

A mini-review of the pathophysiology of task-specific tremor: insights from electrophysiological and neuroimaging findings

Yih-Chih Jacinta Kuo and Kai-Hsiang Stanley Chen*

Department of Neurology, National Taiwan University Hospital Hsin-Chu Branch, Hsinchu, Taiwan

Task-specific tremor (TST) is a specific type of tremor that occurs when performing or attempting to perform a specific task, such as writing or playing a musical instrument. The clinical entity of TST remains heterogeneous. Some TSTs can only be induced by conducting a specific task, while others can be elicited when adopting a particular position simulating a task. The pathophysiology of TST is controversial. Whether TST is an isolated tremor syndrome, a spectrum of dystonic tremor syndrome (DTS), or essential tremor (ET) is not yet clear. Evidence from electrophysiological studies suggests that TST patients have normal reciprocal inhibition responses but abnormal motor cortical excitability, especially relating to the maladaptive long-interval intracortical inhibitory circuitry. The blink recovery study and eyeblink classical conditioning studies demonstrated possible hyperexcitability of the brainstem circuits and cerebellar dysfunction in patients with TST. Functional MRI studies have further shown that patients with TST have reduced functional connectivity in the cerebellum, similar to patients with DTS and ET. Due to variable methodologies and the sparsity of functional MRI studies in TST, it remains uncertain if patients with TST share the connectivity abnormalities between the cortical or subcortical areas that have been demonstrated in patients with DTS. Comprehensive electrophysiological and functional neuroimaging studies may help to elucidate the pathophysiology of TST.

KEYWORDS

task-specific tremor, primary writing tremor, dystonic tremor syndrome, essential tremor, electrophysiology, transcranial magnetic stimulation, neuroimage, functional magnetic resonance imaging

Introduction

Task-specific tremor (TST) is a specific type of action tremor occurs only or predominantly when an affected individual is performing or attempting to perform a specific task. The clinical entity remains heterogeneous. TST can be induced by active movements or by adopting a specific position simulating the task, and is usually non-progressive [1]. TSTs mostly involve the upper limbs, especially dominant limbs, during

specific skilled tasks though sometimes the orolingual area (e.g., lip, chin) is affected [2]. TSTs have a mean frequency of 5–7 Hz (range 3–8 Hz), which may be accompanied by a jerky component in some cases [3]. To date, there are no known patients with TSTs involving the lower limbs.

The involved tasks are variable. For example, most commonly, TSTs are elicited while writing and referred to as "primary writing tremor" (PWT) [4]. TSTs in musicians (TSTM) occur mainly while playing an instrument, with cases reported in string instrumentalists [5–7] or flutists [8]. TSTs can also occur during other daily activities. For instance, finger tremors when playing carroms [9], lip tremors while drinking [10–13], chin tremors only while brushing teeth [14], finger tremors with the use of scissors [15], and wrist tremors during weightlifting [16–18]. Given its various clinical subtypes, limited case numbers, and diagnosis uncertainty, there are no accurate numbers for the prevalence and incidence of TST among general populations.

Despite limited reported cases, PWT and TSTM are the two most prevalent TST subtypes. Two case series with 21 and 56 patients with PWT, respectively [4, 19], reported the mean age of onset to be around 50 years of age (broad range: 16–72 years), with a male predominance (70%–95.2%), and up to 33%–44% of the patients reported a positive family history of PWT. These findings suggest that there may be a possible genetic susceptibility to PWT, in addition to environmental factors. However, no causative gene or mutation has been identified so far. In contrast to PWT cohorts, a case series of 23 musicians with TSTM reported the age of onset to be 44.6 ± 13.6 years, with equal gender distribution, and without a positive family history. Besides, TSTM was associated with a relatively long average duration of playing an instrument (35 years) prior to tremor onset [6]. The variable clinical features implied that different types of TST may not share an identical pathophysiology.

Some recent studies have alluded to the possibility that TST may be an early symptom before the onset of other parkinsonism features in patients with Parkinson's disease (PD) [14, 20, 21]. A case series reported that three of the fve patients with PWT (onset age between 46 and 76 years), later developed PD (within 1–5 years of PWT onset). All three patients had reduced uptake in DaTscan contralateral to the tremor-affected side, and were refractory to propranolol/primidone, but responded to carbidopa-levodopa treatment [20]. However, the interval between TST onset and a diagnosis of PD has been reported to be even longer (average: 13.66 years) in another case series [21]. Currently, the relationship between TST and PD is unclear.

The pathophysiology of TST has been debated in the past decade. The clinical presentation of being focally distributed and task-specific, sometimes with abnormal posturing [4, 22], the presence of coactivation and overflow of muscular activity to adjacent muscles in electromyography [23], a better response to botulinum toxin therapy, suggests a possible correlation between TST and dystonic tremor syndromes (DTS), which included both dystonic tremor and tremor associated with dystonia [24]. The alleviation of symptoms by gestes antagonistes has been described as a clinical hallmark characteristic of dystonia but was only reported in one patient with TST in the previous literature [25]. On the other hand, many studies have reported considerable symptomatic relief of TST by ethanol or propranolol [26–28], and identified a genetic susceptibility, with one case reported with bilateral involvements [26], which points to a possible relationship between TST with ET. Therefore, whether TST is an isolated tremor syndrome, a tremor associated with task-specific dystonia, or a variant of ET, remains uncertain [29, 30]. In this review, we explored the current electrophysiological and functional neuroimaging studies of TST and discussed the possible pathophysiology of TST.

Electrophysiological characteristics of TST

Electromyography (EMG) recording

Surface EMG is an important tool for recording muscular activity, especially in various movement disorders including tremor syndromes [31]. The EMG recording site depends on the subtype of TSTs. For example, in patients with PWT and TSTM, the commonly sampled muscles include the distal muscles of the upper limbs, such as the abductor pollicis brevis, abductor digiti minimi, wrist extensors, wrist flexors, and the more proximal muscles, such as the biceps, triceps, deltoid and pectoralis-major muscles [4, 6]. There are no specific hand muscles that are consistently involved in different kinds of TST patients.

Most of the EMG studies of TST were PWT patients. Alternating EMG bursts, with burst activity between the forearm agonist/antagonist muscles and phasic activity in the intrinsic hand muscles is a typical finding [4, 23, 28, 32]. However, a co-contraction pattern of the agonist/antagonist muscles, or solely extensor muscle activity, has also been documented [4, 28]. Usually, the tremor frequency ranges from 3 to 8 Hz, with a mean frequency of 6 Hz [4]. As a comparison, the usual frequency of the action tremor of the upper extremities in ET is 4–12 Hz, while the frequency being more variable with irregular amplitudes in dystonic tremor (mainly less than 7 Hz) [2]. While earlier studies in PWT did not provide definite evidence of excessive overflow of EMG activity into the proximal musculature [4], a recent study on TSTM demonstrated co-activation of the flexor and extensor muscles and excessive EMG activity in the adjacent muscles [33], implying a possible relationship with dystonia such as writer's cramp [34, 35].

Of note, EMG findings in TST are sometimes difficult to classify, as the muscle groups involved during a specific task, such

as holding a pen or playing an instrument may be subtly different for each patient. Moreover, some patients may use excessive force to control their movements, resulting in diverse and sometimes dystonic features when recording the EMG.

Reciprocal inhibition of Hoffmann's reflex

Hoffmann's reflex (H-reflex) refers to the reflex response of muscles after low-intensity electrical stimulation of Ia sensory afferents. Reciprocal inhibition of the H-reflex refers to the phenomenon in which the H-reflex response is reduced on a contraction of the antagonist muscle elicited by peripheral nerve stimulation at a certain period before the H-reflex. In forearm reciprocal inhibition, the H-reflex response arises from the flexor carpi radialis muscle when the median nerve is stimulated, while the radial nerve stimulation represents the conditioning stimulation [36, 37]. In healthy subjects, the time course of the forearm reciprocal inhibition has three distinct inhibitory phases, depending on the inter-stimulation interval (ISI) between the two stimulations. The first inhibitory phase is the ISI within 1 ms, which indicates Ia afferent disynaptic inhibition from the radial nerve to the flexor alpha motor neurons. The second phase is the ISI at 5–50 ms, which reflects presynaptic inhibition at the terminals of the flexor Ia afferent fibers. The third phase is the ISI at 50–100 ms, with an undetermined mechanism. There were no significant differences in the first (disynaptic) and second (presynaptic) phases of the forearm reciprocal inhibition between patients with PWT and healthy subjects [4, 38]. The third phase has not been comprehensively explored, but the inhibition has been shown to be normal at 75 ms as well [4]. For patients with ET, a significantly attenuated second phase of reciprocal inhibition (ISI at 10–30 ms) has been demonstrated in some studies [39, 40]. In contrast, Munchau et al. reported normal reciprocal inhibition in patients with ET [41]. For patients with writer's cramp, most studies have demonstrated attenuation of all three phases of the forearm reciprocal inhibition [42–44]. However, the 2nd phase of the RI was abnormal in patients who presented arm tremor in the beginning and later presented cervical dystonia [41]. These patients can be classified into ET plus syndrome or dystonia with tremor according to the new tremor classification. These findings suggest that patients with PWT may preserve their spinal inhibitory circuits, which distinguishes them from patients with dystonia or patients with ET.

Blink reflex

The R2 blink reflex recovery cycle (R2BRrc) is an electrophysiological measurement of brainstem excitability that measures the orbicularis oculi muscle responses during paired-pulse electrical stimulation of the supraorbital nerve. It is known to be abnormally enhanced in blepharospasm, PD, craniocervical dystonia, and dystonic tremor (DTS), indicating an alteration in brainstem interneuron excitability [44–47]. In contrast, R2BRrc tends to be normal in patients with ET [48].

The conditioning of the eyeblink reflex is a well-established paradigm in motor learning assessment. This is referred to as eyeblink classical conditioning (EBCC), with the neural circuitry involving the cerebellum, hippocampus, and prefrontal cortex [49]. The blink reflex is recorded as the responses of the orbicularis oculi muscle, with auditory condition stimulus (CS) from the ipsilateral ear, at a set frequency and amplitude (1,000 Hz, 70 dB, duration 540 ms) [50]. EBCC tends to be abnormal in patients with ET and DTS [51, 52], indicating underlying cerebellar dysfunction. This is consistent with the concept that a functional disturbance of the olivo-cerebellar circuit contributes to the expression of many types of tremors.

A recent study demonstrated a reduced R2BRrc in patients with PWT, which was similar to the patients with DTS, while those with ET experienced a normal R2BRrc [53]. Overall, in this study, a reduced conditioned response in EBCC was also found in all PWT, ET, and DTS patient groups, but normal in healthy subjects. According to these findings, though with limited large-scale studies, patients with TST tend to have increased brainstem excitability and impaired olivo-cerebellar circuitry, sharing a more common pathophysiology with DTS rather than ET.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a useful modality for exploring the electrophysiology of the brain. By generating induced currents, TMS can activate neurons and interneurons in the cortex. When paired stimulation is delivered, TMS can further assess the function of the intracortical facilitatory/inhibitory circuits at different ISI. Short-interval intracortical inhibition (SICI), a $GABA_A$-mediated inhibitory circuit, is the most frequently used paired-pulse TMS paradigm for evaluating motor cortex excitability. SICI is conducted via motor cortex stimulations with a sub-threshold conditioning stimulus, followed by a supra-threshold test stimulus, at the ISI of 1–6 ms. Likewise, long-interval intracortical inhibition (LICI), a $GABA_B$-mediated inhibitory circuit, is conducted via two supra-threshold stimuli at the ISI of 50–200 ms. Both SICI and LICI reduce the MEP amplitude compared to the MEP generated by a test stimulus alone. Another common TMS parameter used to evaluate the cortical inhibitory circuit is the cortical silent period (CSP). The CSP refers to a period of 50–300 ms of electrical silence in the active background EMG following a supra-threshold TMS pulse to the motor cortex. The duration of the CSP increases with stimulus intensity, but not with the size of the preceding MEP [54] or the contraction strength of the target muscle [55, 56].

A previous study demonstrated normal intracortical excitability at short and long ISIs in patients with PWT [38]. In contrast, some studies have shown a reduction of the SICI in patients with PWT [53, 57] and posterior displacement of the position of the cortical motor maps [57], suggesting possible dysfunction in the cortical inhibitory circuitry and disorganization of the corticomotor representation, similar to the studies in patients with writer's cramp [58–60]. The suppression ratio of SICI was approximately 40%–50% in patients with PWT and patients with DTS, but >60% in normal subjects [53]. The LICI was reduced by paired associative stimulation (PAS) in normal subjects but paradoxically enhanced in those patients with PWT or DTS, indicating maladaptive plasticity in the motor cortex [53, 61].

In individuals with and without PWT, the CSP duration is the same during writing or performing a voluntary contraction action of the hand of similar intensity on the affected side or between the sides [62]. Interestingly, a significantly shortened duration of the CSP during near-maximum voluntary contraction on both sides has been noted in patients with PWT. These findings indicate that patients with PWT may have impaired cortical inhibitory processes that are only apparent during strong voluntary activations, which are probably not directly linked to unilateral tremulous activity. In contrast, a shortened duration of the CSP was observed in patients with writer's cramp during dystonic contraction or voluntary contraction of a similar strength, but only on the affected side [63]. Meanwhile, most studies have demonstrated that the baseline cortical excitability including RMT, SICI, or CSP is not significantly different between patients with ET and healthy subjects [64–67].

In brief, TMS studies of patients with TST, or specifically primary PWT patients, suggest impairments in the central GABAergic pathways, and the impairments may be different from the patients with dystonia.

Neuroimaging insights of TST

Functional magnetic resonance image (fMRI) techniques provide a non-invasive assessment of the structural, functional, and metabolic alterations of neurological disorders. Numerous imaging studies have been performed in patients with ET and DTS, but the studies on TST are sparse.

In an early fMRI study involving three patients with PWT, PWT was shown to be associated with increased activity of the cerebellum bilaterally, with a more pronounced area of activation on the side ipsilateral to the affected hand, along with bilateral activation of the parietal lobule with a more pronounced activation on the side contralateral to the affected hand [68]. Conversely, recent studies have shown opposite findings in the cerebellum. For example, Hirdesh Sahni et al. showed overactivations of the primary and supplementary motor areas and reduced activity in the cingulate motor area and the cerebellum in six patients with PWT [69]. Another recent study using voxel-based morphometry and diffusion tensor imaging (DTI) found that there was predominantly gray matter atrophy in the frontal lobe and the cerebellum, along with white matter changes in the frontal lobe and the cingulum in patients with PWT when compared with healthy subjects [70]. Lenka et al. further applied graph theory-based neural network analysis to fMRI to explore connectivity during the resting state of the functional brain [71]. In this study, the brain was modeled as a complex functional network with two measurements including "clustering coefficient", which quantified the local connectivity as an index of network segregation; and "path length," which quantified the global connectivity as an index of network integration. The results of this analysis demonstrated that patients with PWT had a significantly lower clustering coefficient and a higher path length in the bilateral medial cerebellum, right dorsolateral prefrontal cortex, and left posterior parietal cortex, suggesting significant disruptions of the small-world brain architecture in these regions.

To our knowledge, to date, there are no studies that directly compared patients with TST to patients with ET or DTS. However, numerous studies have discussed the structural, functional, and metabolic presentations between patients with ET and patients with tremors associated with dystonia. Through understanding the difference between ET and DTS in the MRI images may shed lights on the pathophysiology of TST. Findings from DTI studies suggest an increased mean diffusivity and a decreased fractional anisotropy of the cerebellum in patients with ET, indicating possible microstructural tissue damage and a loss of cellular integrity [72–74]. fMRI studies in ET patients have further clearly demonstrated abnormal cerebellar function and altered connectivity in the cerebello-thalamico-cortical circuitry [75]. Another recent MRI study demonstrated grey matter hypertrophy of the thalamus and motor cortex in the cerebello-thalamo-cortical circuit among patients with DTS [76]. The author concluded that deficient input from the cerebellum towards the thalamo-cortical circuit with hypertrophy of the thalamus, may play a key role in the generation of DTS. To compare patients with ET and DTS, a functional MRI during a grip-force task as a proxy of tremor-related cerebral activity showed similar reduction of functional connectivity in the cerebellum in both patients with ET and DTS [77]. Nevertheless, when the region of interest was outside the cerebellum, compared to patients with ET, those with DTS have more widespread areas of reduced functional connectivity in the cortical regions when the seed regions were placed either in cortical regions, such as the sensorimotor cortex and inferior parietal lobule or subcortical areas, such as globus pallidus interna. Another study using multi-modal imaging combining resting-state functional MRI and DTI showed reduced functional connectivity between the cerebellum and dentate nucleus bilaterally for the ET group but not the DTS group, compared

TABLE 1 A summary of the differences between task-specific tremor (TST), dystonic tremor syndrome (DTS) and essential tremor (ET), from clinical, electrophysiological and neuroimage aspects.

	TST	ET	DTS
Clinical aspects			
Symptoms	Task-specific, focal, non-progressive (most induced by writing or playing specific instruments)	Posture-related, bilateral involved	During postural holding and reaching tasks, focal or segmental, gestes antagonistes
Electrophysiological studies			
Surface EMG	Alternating EMG bursts activity at 3–8 Hz (some reports with co-contraction, overflow activity) [4, 28, 33]	Rhythmic EMG burst at a 4–12 Hz bilaterally, without overflow or co-contractions [31]	Rhythmic EMG burst at 4–10 Hz, co-contractions, overflow, and mirror dystonia [34, 35, 81]
H reflex	Normal reciprocal inhibition of H reflex [4, 38]	Normal reciprocal inhibition [41] or attenuation of 2nd phase of reciprocal inhibition [39, 40]	Diminished reciprocal inhibition [42–44]
Blink reflex	Reduced blink recovery cycle, reduced EBCC [53]	Normal blink recovery cycle, reduced EBCC [46, 51, 53]	Reduced blink recovery cycle, reduced EBCC [52, 53]
TMS	Equivocal normal or slightly reduced SICI [38, 53, 57]	Normal SICI [64]	Reduced SICI [58, 59]
	Normal CSP [62]	Normal CSP [65]	Reduced CSP [63]
Neuroimaging studies			
Functional MRI	Decreased functional connectivity in cerebellum to other cortical areas [69–71]	Decreased connectivity in cerebello-thalamico-cortical circuitry [72–75]	Decreased connectivity in cortical-basal ganglia-cerebellar pathway [79–81]
			Reduced functional connectivity between cortical and subcortical regions [77]
Structural MRI	Gray matter atrophy in the cerebellum [69]	Loss of cerebellar integrity [72–74]	Thalamic hypertrophy [76]

CSP, cortical silent period; DTI, diffuse tensor image; EBCC, eyeblink classical conditioning; EMG, electromyography; MRI, magnetic resonance image; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation.

to healthy subjects [78]. From the treatment response viewpoint, both ET and DTS improved after deep brain stimulation were significantly correlated to the stimulation of the dentato-rubro-cortical tract, while only DTS, but not ET, presented a significant additional correlation to the pallidothalamic tract [79]. These findings point towards a second pathophysiological mechanism involving the basal ganglia in patients with DTS. Taken together, connectivity dysfunction of both the cerebello-thalamo-cortical and the basal ganglia-thalamo-cortical networks may both be involved in driving the pathophysiology of DTS [80, 81] which was different from ET who presented mainly cerebello-thalamo-cortical connectivity impairment.

Discussion and conclusion

There is an ongoing debate about whether TST is a distinct disease entity, a variant form of ET, or a focal task-specific dystonia with dystonic tremor. Based on current evidence, it is reasonable to classify TST as a subtype of DTS, rather than a subtype of ET. Clinically, TST occurs when the patient performs a specific task, similar to patients with writer's cramp who present with dystonic postures when they are writing. Moreover, TST usually affects the dominant hand only, unlike ET, which involves both sides bilaterally. On the contrary, the findings of electrophysiological studies suggest that TST showed normal spinal inhibitory circuits and motor cortical excitability, but a disinhibited brain stem inhibitory circuitry is evident from the reduced EBCC and R2BRrc. The loss of LICI modulation by PAS and reduced SICI are present in both TST and DTS patients. Nevertheless, patients with dystonia usually demonstrate other forms of hyperexcitability of the motor cortex, for example, a reduced CSP, or hyperexcitability of the spinal cord and a loss of reciprocal inhibition. Therefore, the overall electrophysiological characteristics of TST imply that the underlying pathophysiology is not entirely identical to dystonia.

Due to the variable methodologies used in fMRI studies and the sparsity of fMRI studies in patients with TST, it remains inconclusive whether TST is distinct from ET or DTS. Although cerebellar functional connectivity impairments were observed in PWT, it could also represent a fundamental abnormality for any tremor syndrome, since patients with ET and DTS also demonstrate a decreased connectivity in the cerebello-thalamo-cortical circuits. Whether the additional basal ganglion-thalamo-cortical circuits are involved, or whether a more widespread reduction in functional connectivity in the cortical regions occurs in the patients with TST is still uncertain. From the structural point of view, whether patients with TST presented thalamic hypertrophy, which implied dystonia characteristics, may be another clue to interpret the pathophysiology of TST in the future. All these aspects may be critical to distinguishing the underlying pathophysiology

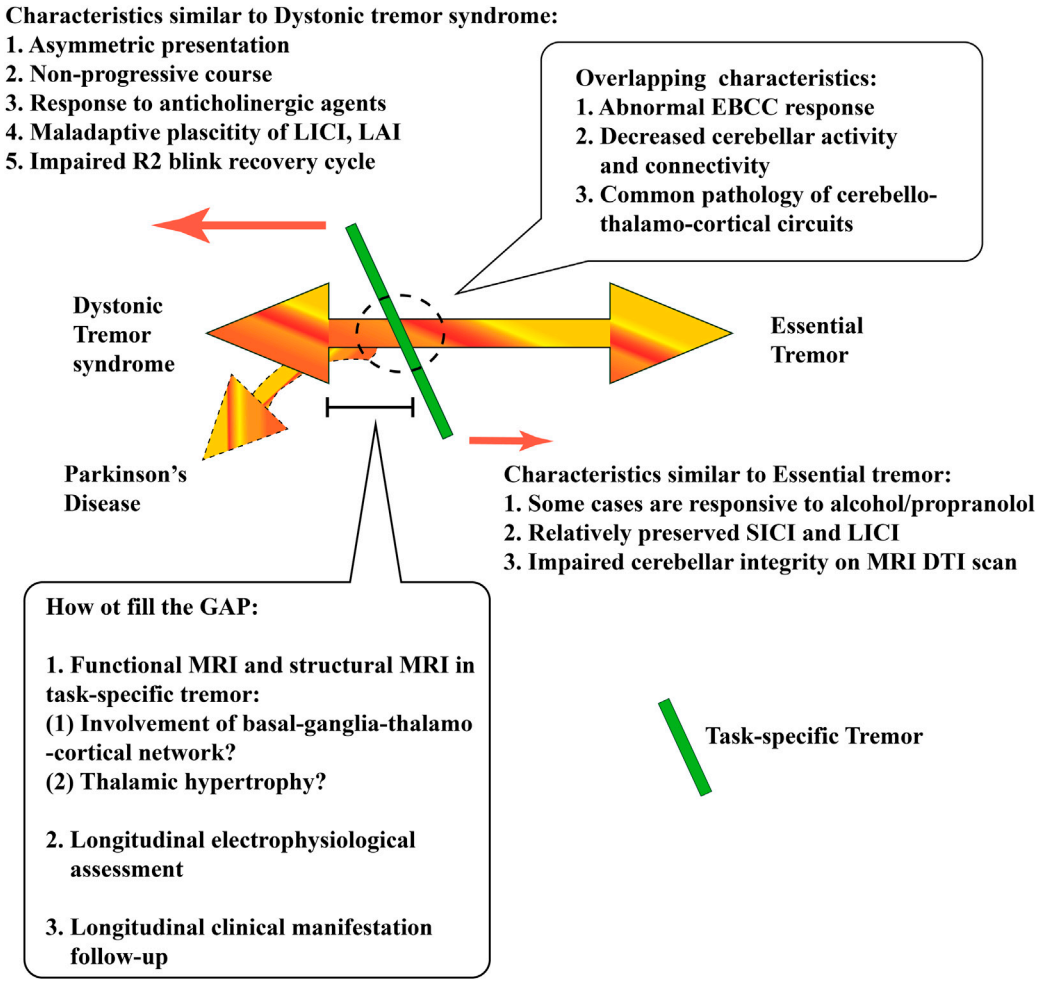

FIGURE 1
The current position of task-specific tremor (TST) in the tremor syndrome by integrating electrophysiological and fMRI findings, including the characteristics similar to or overlapped with dystonic tremor syndrome (DTS) and essential tremor (ET). There is still a knowledge gap, which might help clinicians understand the pathophysiology of TST in the future. DTI, diffuse tensor image; EBCC, eyeblink classical conditioning; LAI, long-latency afferent inhibition; LICI, long-Interval Intracortical Inhibition; MRI, magnetic resonance image; SICI, short-interval intracortical inhibition.

between TST, ET and DTS. Table 1 compares the different features, such as the clinical presentation, electrophysiological findings and fMRI results, between TST, ET, and DTS.

Although the association between TST and Parkinson disease (PD) is less depicted in the previous literature, especially in the electrophysiological assessment, however, a recent study of eight patients with TST who later developed into PD showed an optimal response to apomorphine but was refractory to other dopaminergic agents [82]. Therefore, TST responses to the apomorphine test might provide an early hint to indicate that TST may be full-blown to PD in the future. Figure 1 delineated the current position of TST in the tremor syndrome by integrating electrophysiological and fMRI findings, and indicated the knowledge gap that might help clinicians to better understand the pathophysiology of TST in the future.

There is still a lack of comprehensive and consistent understanding of TST due to limitations in the currently available studies. First, most studies have a small sample size, with a large intra-subject variability. Second, the inclusion criteria in each study are varied, and some studies conducted even before the development of tremor classification and the definitions for the patient groups are ambiguous and non-standardized in some studies. For example, dystonic tremor or tremor with dystonia may not be necessarily shared the same pathophysiology, although they both can be sorted in the same disease population as "dystonic tremor syndromes" in most of the studies. A significant portion of the studies were conducted before the development of tremor classification criteria [83]. Third, the different methodologies and paradigm designs used in each study, including both electrophysiological and neuroimage aspects, have led to

inconclusive results. Fourth, most of the TST studies mentioned in this review focused on PWT patients, which might only represent a specific subtype of TST though still giving us an insight of the picture of the underlying pathophysiology. Moreover, most studies lack long-term follow-up. Thus, additional neurological signs that emerge over time may be left undetected (e.g., Parkinson's disease), which may have led to unreported but critical findings, misinterpretations, or incorrect inferences.

Findings from the available electrophysiological and fMRI studies on patients with PWT suggest that TST may be an isolated tremor entity or a spectrum of DTS, rather than an ET variant. This is consistent with the latest consensus statement on tremor classification from the task force on tremors of the International Parkinson and Movement Disorder Society [83], in which TST has been separately classified as a specific action-induced tremor, different from DTS or ET. Regular follow-ups and comprehensive symptoms documentation with longitudinal electrophysiological and neuroimaging assessment are the keys to fully understanding the underlying pathophysiology of each individual patient with TST.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bain PG. Chapter 50 - task-specific tremor. In: Weiner WJ, Tolosa E, editors. *Handbook of clinical neurology*. Amsterdam, Netherlands: Elsevier (2011). p. 711–8.

2. Lenka A, Jankovic J. Tremor syndromes: an updated review. *Front Neurol* (2021) 12:684835. doi:10.3389/fneur.2021.684835

3. Bhidayasiri R, Tarsy D. Primary writing tremor. In: Bhidayasiri R, Tarsy D, editors. *Movement disorders: a video atlas: a video atlas*. Totowa, NJ: Humana Press (2012). p. 62–3.

4. Bain PG, Findley LJ, Britton TC, Rothwell JC, Gresty MA, Thompson PD, et al. Primary writing tremor. *Brain* (1995) 118(6):1461–72. doi:10.1093/brain/118.6.1461

5. Lederman R. Primary bowing tremor a task-specific movement disorder of string instrumentalists. *Med Probl performing artists* (2012) 27:219–23. doi:10.21091/mppa.2012.4040

6. Lee A, Chadde M, Altenmüller E, Schoonderwaldt E. Characteristics of task-specific tremor in string instrument players. *Tremor and other hyperkinetic movements* (2014) 4:198. doi:10.7916/D86Q1V9W

7. Lee A, Furuya S, Altenmüller E. Epidemiology and treatment of 23 musicians with task specific tremor. *J Clin Mov Disord* (2014) 1(1):5. doi:10.1186/2054-7072-1-5

8. Lee J-E, Kim J-S. Task-specific hand tremor during embouchure in a flutist. *Neurol Sci* (2018) 39(8):1501–2. doi:10.1007/s10072-018-3317-2

9. Kahathuduwa CN, Weerasinghe VS, Dassanayake TL, Priyadarshana R, Dissanayake AL, Perera C. Task-specific kinetic finger tremor affects the performance of carrom players. *J Sports Sci* (2016) 34(10):923–8. doi:10.1080/02640414.2015.1078487

10. O'Gorman CM, Bower JH, Matsumoto JY, Kantarci OH, Kumar N. When drinking makes the tremor worse: a task-specific orolingual tremor. *Mov Disord Clin Pract* (2014) 1(3):237–9. doi:10.1002/mdc3.12041

11. Macerollo A, Meppelink AM, Teodoro T, Ricciardi L, Cordivari C, Edwards MJ. Isolated task-specific lip tremor. *Parkinsonism Relat Disord* (2016) 29:138–9. doi:10.1016/j.parkreldis.2016.04.019

12. Stampanoni Bassi M, Casciato S, Gilio L, Pavone L, Cafolla D, Sforza E, et al. Subclinical dysphagia in task-specific mouth tremor triggered by drinking. *Clin Neurophysiol* (2019) 130(8):1289–91. doi:10.1016/j.clinph.2019.05.009

13. Benedek K, Thomsen CE, Bakke M. Task-specific drinking tremor. *J Mov Disord* (2023) 16(1):98–100. doi:10.14802/jmd.22103

14. Yoo SW, Lee M, Ho SH, Lee KS, Kim JS. Task-specific focal chin tremor in idiopathic Parkinson's disease: is it an isolated phenomenon or a part of parkinsonism? *Neurol Sci* (2019) 40(3):649–51. doi:10.1007/s10072-018-3627-4

15. Oh YS, Ma HI, Kim YJ, Kim JS. Task-specific tremor with use of scissors. *Mov Disord* (2012) 27(7):921–2. doi:10.1002/mds.24984

16. Lang AE, Jog M, Ashby P. *"Weight-holding tremor": an unusual task-specific form of essential tremor? Mov Disord* (1995) 10(2):228–9. doi:10.1002/mds.870100220

17. Yong SW, Park DG, Yoon JH, Baik JS. Is an isolated weight-holding tremor a new subtype of isometric tremor? *Yonsei Med J* (2020) 61(7):644–6. doi:10.3349/ymj.2020.61.7.644

18. Villa-López M, Oh E, Chen R, Lang AE, Masellis M, Hopyan JJ. *Teaching video neuroImage: "weighing" in on an unusual tremor*. *Neurology* (2021) 97(9):e970–e971. doi:10.1212/WNL.0000000000012141

19. Ondo WG, Satija P. Task-specific writing tremor: clinical phenotypes, progression, treatment outcomes, and proposed nomenclature. *Int J Neurosci* (2012) 122(2):88–91. doi:10.3109/00207454.2011.630544

20. Smith K, Alawi A, Ramiro J, Chand P, et al. Pronounced task specific writing tremor in Parkinson's disease (P3.079). *Neurology* (2014) 82:P3.079.

21. Koneru V, Ondo WG. Task specific tremor subsequently developing into Parkinson's disease: case series. *Mov Disord Clin Pract* (2021) 8(1):111–3. doi:10.1002/mdc3.13109

22. Schreglmann SR, Baumann CR, Waldvogel D. Mirror writing tremor: dystonic clues. *Mov Disord Clin Pract* (2015) 2:316–7. doi:10.1002/mdc3.12182

23. Elble RJ, Moody C, Higgins C. Primary writing tremor. a form of focal dystonia? *Mov Disord* (1990) 5(2):118–26. doi:10.1002/mds.870050205

24. Papapetropoulos S, Singer C. Treatment of primary writing tremor with botulinum toxin type a snjections: report of a case series. *Clin Neuropharmacology* (2006) 29(6):364–7. doi:10.1097/01.WNF.0000236765.00785.9C

25. Bagella CF, Romito LM, Scaioli V, Elia AE. Sensory trick in task-specific tremor. *Neurol Sci* (2017) 38(7):1341–2. doi:10.1007/s10072-017-2913-x

26. Jiménez-Jiménez FJ, Cabrera-Valdivia F, Orti-Pareja M, Gasalla T, Tallon-Barranco A, Zurdo M. Bilateral primary writing tremor. *Eur J Neurol* (1998) 5(6):613–4. doi:10.1046/j.1468-1331.1998.560613.x

27. Koller WC, Martyn B. Writing tremor: its relationship to essential tremor. *J Neurol Neurosurg Psychiatry* (1986) 49:220. doi:10.1136/jnnp.49.2.220

28. Kachi T, Rothwell JC, Cowan JM, Marsden CD. Writing tremor: its relationship to benign essential tremor. *J Neurol Neurosurg & Psychiatry* (1985) 48:545–50. doi:10.1136/jnnp.48.6.545

29. Hai C, Yu-ping W, Hua W, Ying S. Advances in primary writing tremor. *Parkinsonism Relat Disord* (2010) 16(9):561–5. doi:10.1016/j.parkreldis.2010.06.013

30. Pita Lobo P, Quattrocchi G, Jutras MF, Sangla S, Apartis E, Vidailhet M, et al. Primary writing tremor and writer's cramp: two faces of a same coin? *Mov Disord* (2013) 28(9):1306–7. doi:10.1002/mds.25340

31. Vial F, Kassavetis P, Merchant S, Haubenberger D, Hallett M. How to do an electrophysiological study of tremor. *Clin Neurophysiol Pract* (2019) 4:134–42. doi:10.1016/j.cnp.2019.06.002

32. Ravits J, Hallett M, Baker M, Wilkins D. Primary writing tremor and myoclonic writer's cramp. *Neurology* (1985) 35(9):1387–91. doi:10.1212/wnl.35.9.1387

33. Lee A, Tominaga K, Furuya S, Miyazaki F, Altenmüller E. Electrophysiological characteristics of task-specific tremor in 22 instrumentalists. *J Neural Transm* (2015) 122(3):393–401. doi:10.1007/s00702-014-1275-2

34. Hughes M, McLellan DL. Increased co-activation of the upper limb muscles in writer's cramp. *J Neurol Neurosurg & Psychiatry* (1985) 48:782–7. doi:10.1136/jnnp.48.8.782

35. Cohen LG, Hallett M. Hand cramps: clinical features and electromyographic patterns in a focal dystonia. *Neurology* (1988) 38(7):1005–12. doi:10.1212/wnl.38.7.1005

36. Fuhr P, Hallett M. Reciprocal inhibition of the H-reflex in the forearm: methodological aspects. *Electroencephalography Clin Neurophysiology/Evoked Potentials Section* (1993) 89(5):319–27. doi:10.1016/0168-5597(93)90071-v

37. Knikou M. The H-reflex as a probe: pathways and pitfalls. *J Neurosci Methods* (2008) 171(1):1–12. doi:10.1016/j.jneumeth.2008.02.012

38. Modugno N, Nakamura Y, Bestmann S, Curra A, Berardelli A, Rothwell J. Neurophysiological investigations in patients with primary writing tremor. *Mov Disord* (2002) 17(6):1336–40. doi:10.1002/mds.10292

39. Mercuri B, Berardelli A, Modugno N, Vacca L, Ruggieri S, Manfredi M. Reciprocal inhibition in forearm muscles in patients with essential tremor. *Muscle & Nerve* (1998) 21(6):796–9. doi:10.1002/(sici)1097-4598(199806)21:6<796::aid-mus13>3.0.co;2-r

40. Modugno N, Priori A, Berardelli A, Vacca L, Mercuri B, Manfredi M. Botulinum toxin restores presynaptic inhibition of group Ia afferents in patients with essential tremor. *Muscle & Nerve* (1998) 21(12):1701–5. doi:10.1002/(sici)1097-4598(199812)21:12<1701::aid-mus12>3.0.co;2-k

41. Münchau A, Schrag A, Chuang C, MacKinnon CD, Bhatia KP, Quinn NP, et al. Arm tremor in cervical dystonia differs from essential tremor and can be classified by onset age and spread of symptoms. *Brain* (2001) 124(9):1765–76. doi:10.1093/brain/124.9.1765

42. Panizza ME, Hallett M, Nilsson J. Reciprocal inhibition in patients with hand cramps. *Neurology* (1989) 39(1):85–9. doi:10.1212/wnl.39.1.85

43. Nakashima K, Rothwell JC, Day BL, Thompson PD, Shannon K, Marsden CD. Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. *Brain* (1989) 112(3):681–97. doi:10.1093/brain/112.3.681

44. Chen RS, Tsai CH, Lu CS. Reciprocal inhibition in writer's cramp. *Mov Disord* (1995) 10(5):556–61. doi:10.1002/mds.870100505

45. Schwingenschuh P, Katschnig P, Edwards MJ, Teo JTH, Korlipara LVP, Rothwell JC, et al. The blink reflex recovery cycle differs between essential and presumed psychogenic blepharospasm. *Neurology* (2011) 76(7):610–4. doi:10.1212/WNL.0b013e31820c3074

46. Nisticò R, Salsone M, Vescio B, Morelli M, Trotta M, Barbagallo G, et al. Blink reflex recovery cycle distinguishes essential tremor with resting tremor from *de novo* Parkinson's disease: an exploratory study. *Parkinsonism Relat Disord* (2014) 20(2):153–6. doi:10.1016/j.parkreldis.2013.10.006

47. Nisticò R, Pirritano D, Salsone M, Valentino P, Novellino F, Condino F, et al. Blink reflex recovery cycle in patients with dystonic tremor: a cross-sectional study. *Neurology* (2012) 78(17):1363–5. doi:10.1212/WNL.0b013e3182518316

48. Nisticò R, Pirritano D, Novellino F, Salsone M, Morelli M, Valentino P, et al. Blink reflex recovery cycle in patients with essential tremor associated with resting tremor. *Neurology* (2012) 79(14):1490–5. doi:10.1212/WNL.0b013e31826d5f83

49. Yeo CH, Hesslow G. Cerebellum and conditioned reflexes. *Trends Cogn Sci* (1998) 2(9):322–30. doi:10.1016/s1364-6613(98)01219-4

50. Gerwig M, Dimitrova A, Maschke M, Kolb FP, Forsting M, Timmann D. Amplitude changes of unconditioned eyeblink responses in patients with cerebellar lesions. *Exp Brain Res* (2004) 155(3):341–51. doi:10.1007/s00221-003-1731-y

51. Kronenbuerger M, Gerwig M, Brol B, Block F, Timmann D. Eyeblink conditioning is impaired in subjects with essential tremor. *Brain* (2007) 130(6):1538–51. doi:10.1093/brain/awm081

52. Antelmi E, Di Stasio F, Rocchi L, Erro R, Liguori R, Ganos C, et al. Impaired eye blink classical conditioning distinguishes dystonic patients with and without tremor. *Parkinsonism Relat Disord* (2016) 31:23–7. doi:10.1016/j.parkreldis.2016.06.011

53. Latorre A, Rocchi L, Batla A, Berardelli A, Rothwell JC, Bhatia KP. The signature of primary writing tremor is dystonic. *Mov Disord* (2021) 36(7):1715–20. doi:10.1002/mds.28579

54. Triggs WJ, Cros D, Macdonell RA, Chiappa KH, Fang J, Day BJ. Cortical and spinal motor excitability during the transcranial magnetic stimulation silent period in humans. *Brain Res* (1993) 628(1):39–48. doi:10.1016/0006-8993(93)90935-g

55. Inghilleri M, Berardelli A, Cruccu G, Manfredi M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *J Physiol* (1993) 466(1):521–34. doi:10.1113/jphysiol.1993.sp019732

56. Kimiskidis VK, Papagiannopoulos S, Sotirakoglou K, Kazis DA, Kazis A, Mills KR. Silent period to transcranial magnetic stimulation: construction and properties of stimulus-response curves in healthy volunteers. *Exp Brain Res* (2005) 163(1):21–31. doi:10.1007/s00221-004-2134-4

57. Byrnes ML, Mastaglia FL, Walters SE, Archer SAR, Thickbroom GW. Primary writing tremor: motor cortex reorganisation and disinhibition. *J Clin Neurosci* (2005) 12(1):102–4. doi:10.1016/j.jocn.2004.08.004

58. Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *J Neurol Neurosurg Psychiatry* (1995) 59(5):493–8. doi:10.1136/jnnp.59.5.493

59. Stinear CM, Byblow WD. Elevated threshold for intracortical inhibition in focal hand dystonia. *Mov Disord* (2004) 19(11):1312–7. doi:10.1002/mds.20160

60. Byrnes ML, Thickbroom GW, Wilson SA, Sacco P, Shipman JM, Stell R, et al. The corticomotor representation of upper limb muscles in writer's cramp and changes following botulinum toxin injection. *Brain* (1998) 121(5):977–88. doi:10.1093/brain/121.5.977

61. Meunier S, Russmann H, Shamim E, Lamy JC, Hallett M. Plasticity of cortical inhibition in dystonia is impaired after motor learning and paired-associative stimulation. *Eur J Neurosci* (2012) 35(6):975–86. doi:10.1111/j.1460-9568.2012.08034.x

62. Ljubisavljevic M, Kacar A, Milanovic S, Svetel M, Kostic VS. Changes in cortical inhibition during task-specific contractions in primary writing tremor patients. *Mov Disord* (2006) 21(6):855–9. doi:10.1002/mds.20807

63. Filipović SR, Ljubisavljević M, Svetel M, Milanović S, Kacar A, Kostić VS. Impairment of cortical inhibition in writer's cramp as revealed by changes in electromyographic silent period after transcranial magnetic stimulation. *Neurosci Lett* (1997) 222(3):167–70. doi:10.1016/s0304-3940(97)13370-5

64. Romeo S, Berardelli A, Pedace F, Inghilleri M, Giovannelli M, Manfredi M. Cortical excitability in patients with essential tremor. *Muscle Nerve* (1998) 21(10):1304–8. doi:10.1002/(sici)1097-4598(199810)21:10<1304::aid-mus9>3.0.co;2-f

65. Khedr EM, El Fawal B, Abdelwarith A, Nasreldein A, Rothwell JC, Saber M. TMS excitability study in essential tremor: absence of gabaergic changes assessed by silent period recordings. *Neurophysiol Clin* (2019) 49(4):309–15. doi:10.1016/j.neucli.2019.05.065

66. Shukla G, Bhatia M, Pandey RM, Behari M. Cortical silent period in essential tremor. *Electromyogr Clin Neurophysiol* (2003) 43(6):329–33.

67. Chuang W-L, Huang YZ, Lu CS, Chen RS. Reduced cortical plasticity and GABAergic modulation in essential tremor. *Mov Disord* (2014) 29(4):501–7. doi:10.1002/mds.25809

68. Berg D, Preibisch C, Hofmann E, Naumann M. Cerebral activation pattern in primary writing tremor. *J Neurol Neurosurg Psychiatry* (2000) 69(6):780–6. doi:10.1136/jnnp.69.6.780

69. Sahni H, Jayakumar PN, Pal PK. Functional magnetic resonance imaging in primary writing tremor and writer's cramp: a pilot study. *Ann Indian Acad Neurol* (2010) 13(3):192–7. doi:10.4103/0972-2327.70884

70. Jhunjhunwala K, George L, Kotikalapudi R, Gupta PK, Lenka A, Stezin A, et al. A preliminary study of the neuroanatomical correlates of primary writing tremor: role of cerebellum. *Neuroradiology* (2016) 58(8):827–36. doi:10.1007/s00234-016-1700-3

71. Lenka A, Jhunjhunwala KR, Panda R, Saini J, Bharath RD, Yadav R, et al. Altered brain network measures in patients with primary writing tremor. *Neuroradiology* (2017) 59(10):1021–9. doi:10.1007/s00234-017-1895-y

72. Tikoo S, Pietracupa S, Tommasin S, Bologna M, Petsas N, Bharti K, et al. Functional disconnection of the dentate nucleus in essential tremor. *J Neurol* (2020) 267(5):1358–67. doi:10.1007/s00415-020-09711-9

73. Saini J, Bagepally BS, Bhatt MD, Chandran V, Bharath RD, Prasad C, et al. Diffusion tensor imaging: tract based spatial statistics study in essential tremor. *Parkinsonism Relat Disord* (2012) 18(5):477–82. doi:10.1016/j.parkreldis.2012.01.006

74. Shin DH, Han BS, Kim HS, Lee PH. Diffusion tensor imaging in patients with essential tremor. *Am J Neuroradiology* (2008) 29(1):151–3. doi:10.3174/ajnr.A0744

75. Holtbernd F, Shah NJ. Imaging the pathophysiology of essential tremor—a systematic review. *Front Neurol* (2021) 12:680254. doi:10.3389/fneur.2021.680254

76. Nieuwhof F, Toni I, Dirkx MF, Gallea C, Vidailhet M, Buijink AWG, et al. Cerebello-thalamic activity drives an abnormal motor network into dystonic tremor. *Neuroimage Clin* (2022) 33:102919. doi:10.1016/j.nicl.2021.102919

77. DeSimone JC, Archer DB, Vaillancourt DE, Wagle Shukla A. Network-level connectivity is a critical feature distinguishing dystonic tremor and essential tremor. *Brain* (2019) 142(6):1644–59. doi:10.1093/brain/awz085

78. Bédard P, Panyakaew P, Cho HJ, Hallett M, Horovitz SG. Multimodal imaging of essential tremor and dystonic tremor. *Neuroimage Clin* (2022) 36:103247. doi:10.1016/j.nicl.2022.103247

79. Tsuboi T, Wong JK, Eisinger RS, Okromelidze L, Burns MR, Ramirez-Zamora A, et al. Comparative connectivity correlates of dystonic and essential tremor deep brain stimulation. *Brain* (2021) 144(6):1774–86. doi:10.1093/brain/awab074

80. Rothkirch I, Granert O, Knutzen A, Wolff S, Gövert F, Pedersen A, et al. Dynamic causal modeling revealed dysfunctional effective connectivity in both, the cortico-basal-ganglia and the cerebello-cortical motor network in writers' cramp. *Neuroimage Clin* (2018) 18:149–59. doi:10.1016/j.nicl.2018.01.015

81. Panyakaew P, Jinnah HA, Shaikh AG. Clinical features, pathophysiology, treatment, and controversies of tremor in dystonia. *J Neurol Sci* (2022) 435:120199. doi:10.1016/j.jns.2022.120199

82. Ondo WG, Koneru V, Arif C. Task specific tremor in Parkinson's disease responds to apomorphine. *Tremor Other Hyperkinet Mov (N Y)* (2023) 13:20. doi:10.5334/tohm.764

83. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. from the task force on tremor of the international Parkinson and movement disorder society. *Mov Disord* (2018) 33(1):75–87. doi:10.1002/mds.27121

DYSTONIA

TYPE Original Research
PUBLISHED 09 February 2024
DOI 10.3389/dyst.2024.11468

OPEN ACCESS

EDITED BY
Aparna Wagle Shukla,
University of Florida, United States

*CORRESPONDENCE
Yiwen Wu,
wyw11380@rjh.com.cn

†These authors have contributed equally to this work

RECEIVED 12 April 2023
ACCEPTED 31 January 2024
PUBLISHED 09 February 2024

CITATION
Zhou Y, Wang L, Li H and Wu Y (2024), Non-motor symptoms in patients with isolated dystonia: comparison between the age of onset.
Dystonia 3:11468.
doi: 10.3389/dyst.2024.11468

Non-motor symptoms in patients with isolated dystonia: comparison between the age of onset

Yifan Zhou†, Lingbing Wang†, Hongxia Li and Yiwen Wu*

Department of Neurology and Institute of Neurology, Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China

Background: The etiology and motor presentation differs between pediatric- and adult-onset dystonia. Emerging evidence has demonstrated that non-motor symptoms are frequent in adult dystonia, which affect the quality of life. By contrast, little is known about the frequency and severity of such presentations in pediatric-onset individuals. Here, we investigated the motor and non-motor symptoms in a large cohort of Chinese patients with isolated dystonia and compared between pediatric-onset and adult-onset groups.

Methods: In this retrospective study, 34 pediatric-onset patients and 197 adult-onset patients with isolated dystonia were recruited. Motor impairment was assessed by the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Non-motor symptoms were evaluated through several validated scales, including fatigue (by Fatigue Severity Scale, FSS), excessive daytime sleepiness (by Epworth Sleepiness Scale, ESS), sleep disturbance (by Pittsburgh Sleep Quality Index, PSQI), anxiety (by Beck Anxiety Inventory, BAI) and depression (by Beck Depression Inventory 21, BDI-21).

Results: Generalized dystonia was more common in pediatric-onset patients and focal dystonia was more common in adult-onset patients ($p < 0.001$). Generally, the BFMDRS score in total pediatric-onset group was higher than adult-onset group ($p = 0.002$). No differences was found in BFMDRS score between pediatric-onset and adult-onset patients with cervical and multifocal subtype dystonia. Compared with adult-onset group, pediatric-onset group had a lower rate of sleep disturbance ($p < 0.0001$) and similar rates of fatigue, excessive daytime sleepiness, depression and anxiety. Logistic regression analysis on patients with cervical dystonia indicated that the adult-onset and motor severity were independently associated with increased odds of sleep disturbance ($p = 0.03$) and depression ($p = 0.01$), respectively.

Conclusion: Pediatric-onset dystonia patients were less likely to display focal dystonia. Most non-motor symptoms in pediatric-onset patients were

comparable to their adult-onset counterparts. Non-motor presentations may to some extent correlate with motor symptoms, but their underlying pathophysiology need to be investigated further.

KEYWORDS

dystonia, age, non-motor symptoms, motor severity, pediatric-onset

Introduction

Dystonia is the third most prevalent movement disorder characterized by involuntary muscle contractions that lead to abnormal movement (often twisting and repetitive), postures, or both. While the pathogenesis of dystonia still remains uncertain, for dystonia occurring at childhood and adolescence, here referred to as pediatric-onset dystonia, the cause is more detectable than adult-onset dystonia, which could be attributable to a list of known genetic and non-genetic factors [1].

Emerging evidence has demonstrated that it is of great importance in clinical practice to dissect the dystonia according to patients' onset age [1, 2]. In adult-onset patients, dystonia often remains focal, whereas in pediatric-onset patients, dystonia is more likely to progress from one body region to a generalized body involvement, which may pose burden on their development and daily life [2]. Apart from motor impairment, a sizable proportion of adult-onset dystonia patients have been shown to suffer from various non-motor symptoms, such as neuropsychiatric disturbance, sleep problems, sensory disorder and cognitive decline, some of them has been found to associate with the decreased quality of life [3–5].

Although non-motor symptoms have already been investigated among adult-onset dystonia patients by a number of studies, little is known about the frequency and severity of such presentations and their clinical relevance with motor impairment for pediatric-onset individuals. The largest retrospective study on 50 childhood dystonia patients has observed a higher incidence of anxiety and prosocial difficulties in young patients compared with their age-matched peers, suggesting that pediatric-onset dystonia patients also suffer from non-motor disorders [6]. To our knowledge, no study has compared the differences between pediatric-onset and adult-onset dystonia patients in terms of non-motor presentations so far.

Here, we report the motor and non-motor features in a large cohort of Chinese patients with isolated dystonia and compare the differences between pediatric-onset and adult-onset groups. The correlation between motor and non-motor impairment is also evaluated.

Methods

Patients

Isolated dystonia patients who were followed at the Movement Center of Ruijin Hospital (Shanghai Jiao Tong University School of Medicine, Shanghai) during July 2020 and June 2022 were enrolled in the present study. The diagnostic criterion of dystonia was based on the 2013 Consensus of Movement Disorder Society [1]. Clinical data was collected from hospital records. A series of standardized scales were used to evaluate the motor and non-motor symptoms at their latest visits. Exclusion criteria were: 1) had other movement disorders, such as parkinsonism. 2) had other neurological system diseases. 3) lack detailed demographic data. The flow chart of patient selection was presented in Figure 1. The study was approved by the Ethics Committee of Ruijin Hospital. Written informed consent was obtained from all participants.

Motor and non-motor symptoms assessment

The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was used to assess the severity of motor symptoms. Non-motor symptoms were determined by the following validated scales: Fatigue Severity Scale (FSS) was applied for fatigue; excessive daytime sleepiness was assessed

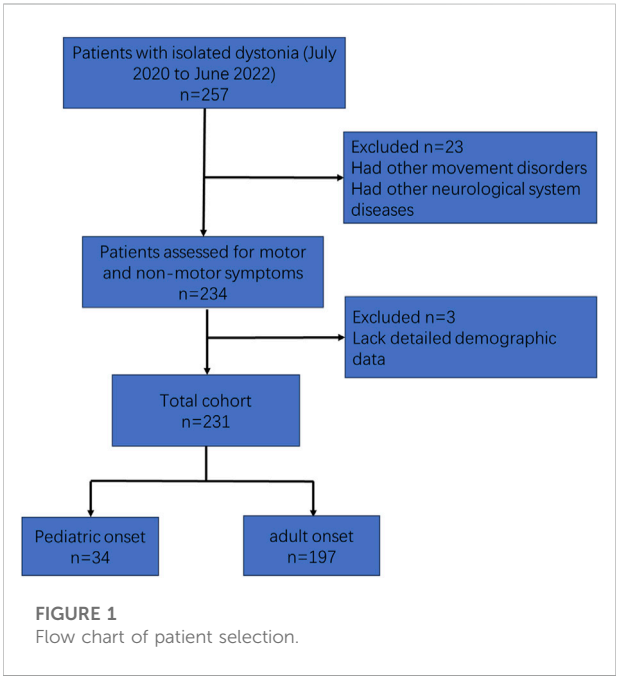

FIGURE 1
Flow chart of patient selection.

10.3389/dyst.2024.11468

TABLE 1 Demographic and clinical features of pediatric-onset and adult-onset patients with isolated dystonia.

	Pediatric (n = 34)	Adult (n = 197)	p-value
Gender ratio (F/M)	20/14 (1.4)	126/71 (1.8)	0.566
Age (y)	21 (16–29)	53 (40–64)	**<0.0001**
Age at onset (y)	15 (10–18)	48 (37–58)	**<0.0001**
Disease duration (y)	4.50 (0.92–13.75)	2.5 (0.75–7.00)	0.097
Body distribution, n (%)			
a. Focal	15/34 (44.12)	152/197 (77.16)	**<0.001**
b. Segmental	2/34 (5.88)	31/197 (15.74)	
c. Multifocal	6/34 (17.65)	9/197 (4.57)	
d. Generalized	10/34 (29.41)	4/197 (2.03)	
e. Hemidystonia	1/34 (2.94)	1/197 (0.51)	
Sensory trick, n (%)	20/34 (58.82)	85/187 (45.45)	0.191
BFMDRS, n (%)	31/34	180/197	
score	12.0 (6.0–33.0)	7.0 (4.6–11.0)	**0.002**
FSS, n (%)	32/34	180/197	
Score	29.5 (15.3–43.5)	37.5 (22.0–53.8)	0.088
≥36 (fatigue)	14/32 (43.75)	96/180 (53.33)	0.317
ESS, n (%)	32/34	176/197	
Score	4.0 (1.0–8.8)	6.0 (3.0–9.8)	0.242
0–10 (normal), n (%)	27/32 (84.38)	144/176 (81.82)	0.054
11–14 (mild excessive daytime sleepiness), n (%)	1/32 (3.13)	17/176 (9.66)	
15–17 (moderate excessive daytime sleepiness), n (%)	4/32 (12.50)	6/176 (3.41)	
18 or higher (severe excessive daytime sleepiness), n (%)	0/32 (0)	9/176 (5.11)	
PSQI, n (%)	33/34	176/197	
Sleep quality	1 (1–1)	1 (1–2)	**0.003**
Sleep latency	0 (0–1)	1 (0–3)	**0.001**
Sleep duration	0 (0–0)	0 (0–1)	**0.003**
Habitual sleep efficiency	0 (0–0)	0 (0–1)	**<0.0001**
Sleep disturbances	1 (1–1)	1 (1–1)	**0.027**
Use of sleeping medication	0 (0–0)	0 (0–2.25)	0.282
Daytime dysfunction	0 (0–1)	1 (0–1)	**0.017**
Total score	3.0 (2.0–6.5)	6.0 (4.0–10.0)	**<0.0001**
>5 (poor sleep), n (%)	10/33 (30.30)	105/176 (59.66)	**0.002**
BAI, n (%)	22/34	111/197	
Score	4.0 (0.0–8.3)	3.0 (1.0–8.0)	0.922
0–7 (minimal anxiety), n (%)	15/22 (68.18)	82/111 (73.87)	0.343
8–15 (mild anxiety), n (%)	6/22 (27.27)	16/111 (14.41)	

(Continued on following page)

TABLE 1 (*Continued*) Demographic and clinical features of pediatric-onset and adult-onset patients with isolated dystonia.

	Pediatric (n = 34)	Adult (n = 197)	p-value
16–25 (moderate anxiety), n (%)	1/22 (4.55)	6/111 (5.41)	
26–63 (severe anxiety), n (%)	0/22 (0)	7/111 (6.31)	
BDI-21, n (%)	32/34	181/197	
Score	6.5 (1.0–10.0)	6.0 (2.5–13.0)	0.258
0–13 (minimal depression), n (%)	28/32 (87.50)	140/181 (77.35)	0.331
14–19 (mild depression), n (%)	2/32 (6.25)	28/181 (15.47)	
20–28 (moderate depression), n (%)	2/32 (6.25)	7/181 (3.87)	
29–63 (severe depression), n (%)	0/32 (0)	6/181 (3.31)	

The bold values mean statistically significant.

by the Epworth Sleepiness Scale (ESS); the Pittsburgh Sleep Quality Index (PSQI) was used to measure individuals' sleep disturbance; the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory 21 (BDI-21) were implied to evaluate self-reported anxiety and depression, respectively.

Patients under 10 years old were not evaluated in this study.

Statistical analyses

Statistical analyses were performed on the SPSS version 26.0 (SPSS, Chicago, IL, United States). Continuous variables were presented as median (interquartile range [IQR]). Mann-Whitney U test, χ^2 test and the Fisher's exact test were used to compare the differences between pediatric-onset and adult-onset groups. The Pearson correlation analysis was use to explore the correlation between motor severity and the severity of non-motor symptoms. Logistic regression analysis was applied to assess the risk factors of non-motor symptoms, including fatigue (FSS ≥ 36), excessive daytime sleepiness (ESS > 10), sleep disturbance (PSQI > 5), anxiety (BAI > 7), and depression (BDI-21 > 13). Variables of clinical interests were included in univariable analysis, and variables with $p \leq 0.20$ were then entered into further multivariable analyses. A two-tail p-value < 0.05 was defined as statistically significant.

Results

Clinical characteristics of patients with pediatric-onset and adult-onset dystonia

A total of 34 pediatric-onset and 197 adult-onset patients were recruited in the present study. Table 1 showed the demographic and clinical features in patients with isolated dystonia. In the pediatric-onset group, the median age of onset was 15 years (range: 10–18 years) with a gender ratio (F/M) of 1.4:1. Median disease duration was 4.5 years (range: 0.92–13.75 years). The median age at the time of evaluation for the pediatric-onset onset group was 21 years (range: 16–29 years). One patient's age was less than 10 years old. The most prevalent phenotype of dystonia in pediatric-onset patients was focal dystonia (44.12%), which was followed by the generalized dystonia (29.41%), multi-focal dystonia (17.65%), segmental dystonia (5.88%) and hemi-dystonia (2.94%). Compared to their adult-onset counterparts, pediatric-onset patients were more likely to develop generalized dystonia and less likely to present with focal dystonia ($p < 0.001$). The median BFMDRS score in pediatric-onset patients was 12.0 (range: 6.0–33.0), which was markedly higher than that in adult-onset subjects (median: 7.0 (range: 4.6–11.0); $p < 0.001$).

In terms of non-motor symptoms, fatigue determined by the FSS score ≥ 36 was observed in nearly half of pediatric-onset cases (43.75%). The percentage of pediatric-onset patients with excessive daytime sleepiness (ESS > 10) was 15.63%. No difference was found in FSS and ESS between pediatric-onset and adult-onset groups. Approximately one-third of pediatric-onset cases had poor sleep (PSQI > 5), and its frequency was predominately lower compared with adult-onset patients (30.30% vs. 59.66%, $p = 0.002$). In addition, the level of PSQI global score ($p < 0.0001$) and the sub-components of PSQI, including sleep quality ($p = 0.003$), sleep latency ($p = 0.001$), sleep duration ($p = 0.0035$), habitual sleep efficiency ($p < 0.0001$), sleep disturbance ($p = 0.027$) and daytime dysfunction ($p = 0.0173$) in pediatric-onset group were all milder than those in adult-onset group. Anxiety (BAI > 7) and depression (BDI-21 > 13) was found in 31.82% and 12.5% of pediatric-onset patients, respectively. No difference was found in BAI and BDI-21 between two age groups.

Table 2 presented the motor and non-motor symptoms in pediatric-onset and adult-onset patients with different dystonia subtypes (n ≥ 5 in each group). The BFMDRS

TABLE 2 Motor and non-motor symptoms in pediatric-onset and adult-onset patients with different dystonia subtypes.

	Pediatric onset group		Adult onset group		P1	P2
	Cervical (n = 15)	Multifocal (n = 6)	Cervical (n = 139)	Multifocal (n = 9)		
BFMDRS	15/15	6/6	126/139	7/9		
Score	6.0 (4.0–11.0)	24.75 (13.38–54.13)	6.0 (4.0–8.625)	22.0 (14.0–34.0)	0.9669	0.5589
FSS	15/15	5/6	132/139	8/9		
Score	35.0 (15.0–58.0)	42.0 (32.0–47.0)	37.5 (21–53.75)	46.0 (32.0–56.5)	0.5862	0.5237
≥36	7/15 (46.67)	4/5 (80.0)	70/132 (53.03)	5/8 (62.5)	0.7864	>0.9999
ESS	15/15	5/6	130/139	8/9		
Score	4.0 (0–8.0)	7.0 (3.0–15.0)	6.0 (3.0–9.0)	5.0 (4.25–10.5)	0.6575	0.9207
0–10 (normal)	13/15 (86.67)	3/5 (60.0)	108/139 (77.70)	6/8 (75.0)	0.616	0.208
11–14 (mild excessive daytime sleepiness)	1/15 (6.67)	0/5 (0)	13/139 (9.35)	1/8 (12.5)		
15–17 (moderate excessive daytime sleepiness)	1/15 (6.67)	2/5 (40.0)	3/139 (2.16)	0/8 (0)		
18 or higher (severe excessive daytime sleepiness)	0/15 (0)	0/5 (0)	6/139 (4.32)	1/8 (12.5)		
PSQI	15/15	5/6	130/139	8/9		
Score	3.0 (2.0–6.0)	5.0 (4.0–7.0)	6.0 (4.0–10.0)	7.0 (3.25–12.5)	**0.0016**	0.5625
>5 (poor sleep)	4/15 (26.67)	4/5 (80.0)	76/130 (58.46)	5/8 (62.5)	**0.0269**	>0.9999
BAI	14/15	0/0	82/139	4/8		
Score	4.0 (0–7.25)	–	2.0 (0–7.0)	14.0 (1.0–33.0)	0.9357	—
0–7 (minimal anxiety)	11/14 (78.57)	–	63/82 (76.83)	2/4 (50.0)	0.861	–
8–15 (mild anxiety)	2/14 (14.29)	–	14/82 (17.07)	0/4 (0)		
16–25 (moderate anxiety)	1/14 (7.14)	–	3/82 (3.66)	0/4 (0)		
26–63 (severe anxiety)	0/14 (0)	–	2/82 (2.44)	2/4 (50.0)		
BDI-21	15/15	5/6	130/139	8/9		
Score	9.0 (2.0–12.0)	3.0 (2.0–10.0)	5.5 (2.0–13.0)	10.5 (5.25–15.0)	0.9166	0.1562
0–13 (minimal depression)	14/15 (93.33)	5/5 (100)	102/130 (78.46)	6/8 (75.0)	0.577	0.478
14–19 (mild depression)	1/15 (6.67)	0/5 (0)	21/130 (16.15)	1/8 (12.5)		
20–28 (moderate depression)	0/15 (0)	0/5 (0)	5/130 (3.85)	0/8 (0)		
29–63 (severe depression)	0/15 (0)	0/5 (0)	2/130 (1.54)	1/8 (12.5)		

The bold values mean statistically significant.

10.3389/dyst.2024.11468

10.3389/dyst.2024.11468

TABLE 3 Risk factors associated with non-motor symptoms in patients with cervical dystonia.

Risk factors of excessive daytime sleepiness	Univariable analysis			Multivariable analysis		
	p-value	OR	95% CI	*p*-value	OR	95% CI
Pediatric-onset	0.662	0.706	0.149–3.356			
Male	0.149	1.923	0.791–4.677			
Disease duration	0.654	0.984	0.918–1.055			
BFMDRS	**0.0001**	0.668	0.543–0.822	**0.0001**	0.661	0.535–0.816
FSS	0.093	2.264	0.872–5.876	0.071	2.601	0.922–7.339
PSQI	0.354	0.658	0.271–1.595			
BAI	0.634	0.718	0.184–2.798			
BDI	0.326	0.524	0.144–1.905			
Risk factors of sleep disturbance	**Univariable analysis**			**Multivariable analysis**		
	p-value	OR	95% CI	*p*-value	OR	95% CI
Pediatric-onset	**0.035**	0.275	0.083–0.913	0.079	0.311	0.084–1.144
Male	0.507	0.792	0.397–1.579			
Disease duration	0.431	0.98	0.933–1.03			
BFMDRS	0.311	1.052	0.953–1.162			
ESS	0.073	1.862	0.944–3.673	0.519	0.726	0.275–1.92
FSS	0.354	0.658	0.271–1.595			
BAI	0.867	0.919	0.341–2.479			
BDI	**0.001**	34.125	4.472–260.427	**0.001**	30.456	3.963–234.026
Risk factors of depression	**Univariable analysis**			**Multivariable analysis**		
	p-value	OR	95% CI	*p*-value	OR	95% CI
Pediatric-onset	0.215	0.269	0.034–2.143	0.685	0.627	0.066–5.983
Male	0.568	0.773	0.319–1.873			
Disease duration	0.703	0.987	0.924–1.054			
BFMDRS	**0.007**	1.181	1.046–1.333	**0.002**	1.255	1.084–1.453
FSS	0.626	1.236	0.527–2.903			
ESS	0.326	0.524	0.144–1.905			
PSQI	**0.001**	34.125	4.472–260.427	**0.001**	47.902	4.763–481.779
BAI	1					

The bold values mean statistically significant.

scores in pediatric-onset patients with cervical (focal) and multifocal dystonia were comparable to their adult-onset counterparts. The PSQI global score and the percentage of patients with poor sleep (PSQI > 5) were significantly higher in pediatric-onset cervical (focal) patients compared with adult-onset cervical (focal) patients (p = 0.0016 and p = 0.0269, respectively).

Correlation between motor and non-motor symptoms

To identify the association between motor and non-motor impairments, we analyzed the correlation between BFMDRS score and non-motor score measured by different validated scales. In pediatric-onset group, no correlation was found

between the BFMDRS score and any non-motor related score. However, in the adult-onset group, BFMDRS score had a positive correlation with the level of PSQI ($r = 0.278$, $p < 0.01$), BAI ($r = 0.384$, $p < 0.01$) and BDI-21 ($r = 0.354$, $p < 0.01$).

The risk factors of non-motor presentations

Finally, logistic regression models were performed to explore potential risk factors associated with different non-motor disorders (Table 3 and Supplementary Table S1). Since dystonia phenotype may exert an impact on motor as well as non-motor impairments, only patients with cervical (focal) dystonia (including 15 pediatric-onset and 139 adult-onset cases) were included in the analysis. Mono-variable model indicated that motor severity was associated with the decreased odds of excessive daytime sleepiness (ESS>10) ($p < 0.001$; OR: 0.668, 95% CI: 0.543–0.822). A pediatric-onset was associated with the decreased odds of poor sleep (PSQI > 5) ($p = 0.035$; OR: 0.275, 95% CI: 0.083–0.913), whereas depression (BDI-21 > 13) was associated with the increased odds of poor sleep (PSQI > 5) ($p = 0.001$; OR:34.125, 95% CI: 4.472–260.427). Moreover, there was a significantly positive correlation between motor severity and depression (BDI-21 > 13) ($p = 0.007$; OR: 1.181, 95% CI: 1.046–1.333).

Multi-variable analyses suggested that the motor severity was independently correlated with excessive daytime sleepiness (ESS > 10) ($p = 0.000$; OR: 0.661, 95% CI: 0.535–0.816) and depression (BDI-21 > 13) ($p = 0.002$; OR: 1.255, 95% CI: 1.084–1.453).

And the presence of poor sleep (PSQI > 5) was independently associated with depression (BDI-21 > 13) (0.001; OR: 30.456, 95% CI: 3.963–234.026).

Discussion

Our study highlighted three points: first, there was a high frequency of non-motor symptoms in Chinese pediatric-onset and adult-onset patients with isolated dystonia; second, compared to the adult-onset patients, pediatric-onset patients were less likely to suffer from sleep problems; third, although pediatric-onset patients was more likely to develop generalized dystonia, the frequency and severity of fatigue, anxiety and depression, were similar as compared to their adult-onset counterparts, suggesting that these non-motor presentations may to some extent be a primary deficit rather than a consequence of motor impairment.

As with other movement disorders, sleep problem is commonly seen in patients with dystonia. Recently, increased frequency of sleep disturbance has been reported in patients with cervical dystonia when compared with healthy subjects, and has been shown to be a risk factor of the quality of life [3, 7]. In the current study, sleep disturbance and excessive daytime sleepiness, as assessed by the PSQI and ESS scales, were observed in approximately 59% and 19% of adult-onset dystonia patients, respectively, which was in accordance with previous observation studies, which showed a high rate of sleep disturbance (~50%) in patients with focal dystonia whereas the frequency of excessive daytime sleepiness was relatively uncommon (6%–21%) [7–10]. Surprisingly, our study demonstrated that pediatric-onset dystonia patients exhibited a significantly lower rate of sleep disturbance than adult-onset dystonia patients (30% vs. 59%). Moreover, a pediatric-onset-onset was shown to be independently associated with decreased odds of poor sleep in patients with cervical dystonia. Since pediatric-onset dystonia patients usually suffered from greater dystonia severity, we then analyzed the association between sleep disturbance and motor impairment. No correlation was noted between the severity of sleep disturbance and the severity of motor impairment in pediatric-onset group. There was a correlation between the degrees of sleep disturbance and motor impairment in adult-onset patients, however, in the logistic regression analysis that only included cervical dystonia cases, we found that the sleep disturbance had no correlation with motor severity but a correlation with depression and age of onset. Therefore, it is reasonable to assume that sleep disorder might be different among various dystonia phenotypes. As sleep problem has been suggested to impair the quality of life, more clinical and basic investigations, including polysomnographic recording, neurotransmitter and neuronal circuit studies are warranted to explore the mechanism of sleep disturbance for both pediatric-onset and adult-onset dystonia patients.

Furthermore, our results reinforced previous observations that sleep disturbance was positively correlated with depression, which suggested that the sleep disturbance might be partly secondary to the depression [8, 11]. In addition to the depression, bruxism, restless legs syndrome (RLS) and female gender have been identified as risk factors of sleep problem in patients with focal dystonia [11]. Taken together, whether sleep disturbance is a primary or secondary abnormality in dystonia individuals need to be explored further.

Recently, an excess of neuropsychiatric presentations among adult-onset dystonia patients has been elucidated by many studies [12, 13]. By contrast, there is scarce data to analyses neuropsychiatric symptoms in pediatric-onset dystonia patients. In our pediatric-onset cohort, co-existence of anxiety and depression were found to be 31% and 13%, by the BAI and BDI-21 scales, respectively. The high frequency of anxiety was in accordance with the study by Rudebeck et al, in which 48% of childhood dystonia patients aged 7–17 years were found to experience anxiety [6]. Given that neuropsychiatric comorbidity has been shown to be a predictor of health-related quality of life, rather than the motor severity, in adult-onset patients with cervical dystonia, it would be of clinical importance to integrate mental health into the management of dystonia [14].

To date, the pathophysiology underlying neuropsychiatric symptoms remains to be poorly understood, but has been considered to be related to the disruption in cortical-limbic-striatal circuits [15]. Consistent with previous studies, which

found a correlation between neuropsychiatric and motor symptoms in adult-onset dystonia patients, our results observed a positive association between depression severity and motor severity in adult-onset group, and interestingly, not in pediatric-onset group [16, 17]. The discrepancies between two groups may be attributable to the differences in their dystonia phenotype and genetic susceptibility. This hypothesis could be supported by recent evidence which detected a higher frequency of depression and anxiety in patients with blepharospasm than in patients with cervical dystonia and writer's cramp [18]. Moreover, Berman et al. observed a higher rate of anxiety in cervical and laryngeal groups and lower rate of anxiety in upper cranial group among adult-onset dystonia subjects [17]. In addition, some dystonia related mutations also play a role in neuropsychiatric disorders. For instance, *DYT1* dystonia mutation carriers have been shown to confer an increased risk for recurrent major depression [19]. As genetically defined dystonia is more common for pediatric-onset cases, it would be more meaningful to investigate gene mutations and their relationship with non-motor presentations in our study in future. Notably, though the pediatric-onset patients displayed higher BFMDRS scores, the frequency and severity of depression and anxiety were comparable between pediatric-onset and adult-onset dystonia groups. This finding lent evidence that these neuropsychiatric disorders were unlikely to be a simple reaction to the disability induced by dystonia. Furthermore, previous studies have indicated that the occurrence of depression and anxiety could precede the onset of dystonia for many years in the majority of adult-onsets dystonia patients, suggesting that neuropsychiatric disorders may be part of the clinical spectrum of dystonia [20]. Taken together, our results uphold the notion that neuropsychiatric symptoms are primary endophenotypic deficits but can correlate with the motor symptoms in dystonia.

Our study had several limitations. Due to the retrospective design, sampling bias might restrict the interpretation of the results. The predominant recruitment of patients in the adult center may have led to the younger age dystonia individuals and children with mild symptoms being underrepresented. Some pediatric-onset and adult-onset patients were unwilling to complete all the scales, especially for BAI. Thus, we cannot exclude the possibility that these patients may lack corresponding symptoms to trigger screening, which would cause an overestimation of the prevalence of this symptom. No differences were found in the frequency and severity of most non-motor symptoms between the pediatric-onset and adult-onset groups. This may be due to a lack of statistical power because the number of pediatric-onset cases were relatively small. In addition, dystonia in children can be part of a metabolic disease with other neurological and psychiatric symptoms associated, which could influence the non-motor symptoms and should be considered. Further studies are required to take the causes and subtypes of dystonia into account for pediatric population. Finally, though the widely used scales for evaluating non-motor symptoms in our study have been applied for adult-onsets and adolescents in a number of studies [21–25], it would strengthen the ascertained conclusions if we could add age-matched controls because some features in people of different ages such as global cognitive and physical state may to some extent influence the score of scale.

In conclusion, most non-motor symptoms in pediatric-onset dystonia patients were comparable to that in adult-onsets in frequency and severity, with the exception of sleep disturbance. The pathophysiology of non-motor symptoms is complex and cannot be simply attributable to the motor impairment. Prospective and multicenter studies are needed to determine the prevalence and importance of non-motor presentations in pediatric-onset dystonia patients.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The study involving humans was approved by Ethics Committee of Ruijin Hospital. The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from all participants.

Author contributions

YW designed the study and recruited patients with dystonia. YZ and LW drafted the manuscript. HL assisted in survey. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/dyst.2024.11468/full#supplementary-material.

References

1. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* (2013) 28:863–73. doi:10.1002/mds.25475

2. van Egmond ME, Kuiper A, Eggink H, Sinke RJ, Brouwer OF, Verschuuren-Bemelmans CC, et al. Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm. *J Neurol Neurosurg Psychiatry* (2015) 86:774–81. doi:10.1136/jnnp-2014-309106

3. Han V, Skorvanek M, Smit M, Turcanova KM, Hoekstra T, van Dijk JP, et al. Prevalence of non-motor symptoms and their association with quality of life in cervical dystonia. *Acta Neurol Scand* (2020) 142:613–22. doi:10.1111/ane.13304

4. Junker J, Berman BD, Hall J, Wahba DW, Brandt V, Perlmutter JS, et al. Quality of life in isolated dystonia: non-motor manifestations matter. *J Neurol Neurosurg Psychiatry* (2021) 92:622–8. doi:10.1136/jnnp-2020-325193

5. Lee S, Chung SJ, Shin HW. Neuropsychiatric symptoms and quality of life in patients with adult-onset idiopathic focal dystonia and essential tremor. *Front Neurol* (2020) 11:1030. doi:10.3389/fneur.2020.01030

6. Bates L, Taylor M, Lin JP, Gimeno H, Kingston J, Rudebeck SR. Mental health and behaviour in children with dystonia: anxiety, challenging behaviour and the relationship to pain and self-esteem. *Eur J Paediatr Neurol* (2021) 35:40–8. doi:10.1016/j.ejpn.2021.09.002

7. Liang Y, Lin J, Hou Y, Zhang L, Ou R, Li C, et al. Health-related quality of life in cervical dystonia using EQ-5D-5L: a large cross-sectional study in China. *Front Neurol* (2022) 13:895272. doi:10.3389/fneur.2022.895272

8. Avanzino L, Martino D, Marchese R, Aniello MS, Minafra B, Superbo M, et al. Quality of sleep in primary focal dystonia: a case-control study. *Eur J Neurol* (2010) 17:576–81. doi:10.1111/j.1468-1331.2009.02884.x

9. Eichenseer SR, Stebbins GT, Comella CL. Beyond a motor disorder: a prospective evaluation of sleep quality in cervical dystonia. *Parkinsonism Relat Disord* (2014) 20:405–8. doi:10.1016/j.parkreldis.2014.01.004

10. Trotti LM, Esper CD, Feustel PJ, Bliwise DL, Factor SA. Excessive daytime sleepiness in cervical dystonia. *Parkinsonism Relat Disord* (2009) 15:784–6. doi:10.1016/j.parkreldis.2009.04.007

11. Paus S, Gross J, Moll-Muller M, Hentschel F, Spottke A, Wabbels B, et al. Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. *J Neurol* (2011) 258:1835–40. doi:10.1007/s00415-011-6029-6

12. Wadon ME, Fenner E, Kendall KM, Bailey GA, Sandor C, Rees E, et al. Clinical and genotypic analysis in determining dystonia non-motor phenotypic heterogeneity: a UK Biobank study. *J Neurol* (2022) 269:6436–51. doi:10.1007/s00415-022-11307-4

13. Lehn A, Mellick G, Boyle R. Psychiatric disorders in idiopathic-isolated focal dystonia. *J Neurol* (2014) 261:668–74. doi:10.1007/s00415-014-7244-8

14. Smit M, Kuiper A, Han V, Jiawan VC, Douma G, van Harten B, et al. Psychiatric comorbidity is highly prevalent in idiopathic cervical dystonia and significantly influences health-related quality of life: results of a controlled study. *Parkinsonism Relat Disord* (2016) 30:7–12. doi:10.1016/j.parkreldis.2016.06.004

15. Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. *Brain* (2012) 135:1668–81. doi:10.1093/brain/awr224

16. Gundel H, Busch R, Ceballos-Baumann A, Seifert E. Psychiatric comorbidity in patients with spasmodic dysphonia: a controlled study. *J Neurol Neurosurg Psychiatry* (2007) 78:1398–400. doi:10.1136/jnnp.2007.121699

17. Berman BD, Junker J, Shelton E, Sillau SH, Jinnah HA, Perlmutter JS, et al. Psychiatric associations of adult-onset focal dystonia phenotypes. *J Neurol Neurosurg Psychiatry* (2017) 88:595–602. doi:10.1136/jnnp-2016-315461

18. Novaretti N, Cunha A, Bezerra TC, Pena PM, de Oliveira DS, Macruz BM, et al. The prevalence and correlation of non-motor symptoms in adult patients with idiopathic focal or segmental dystonia. *Tremor Other Hyperkinet Mov (N Y)* (2019) 9:596. doi:10.7916/fhnv-v355

19. Heiman GA, Ottman R, Saunders-Pullman RJ, Ozelius LJ, Risch NJ, Bressman SB. Increased risk for recurrent major depression in DYT1 dystonia mutation carriers. *Neurology* (2004) 63:631–7. doi:10.1212/01.wnl.0000137113.39225.fa

20. Moraru E, Schnider P, Wimmer A, Wenzel T, Birner P, Griengl H, et al. Relation between depression and anxiety in dystonic patients: implications for clinical management. *Depress Anxiety* (2002) 16:100–3. doi:10.1002/da.10039

21. Loiacono B, Sunnquist M, Nicholson L, Jason LA. Activity measurement in pediatric chronic fatigue syndrome. *Chronic Illn* (2022) 18(2):268–76. doi:10.1177/1742395320949613

22. Gagua T, Tkeshelashvili B, Gagua D, McHedlishvili N. Assessment of anxiety and depression in adolescents with primary dysmenorrhea: a case-control study. *J Pediatr Adolesc Gynecol* (2013) 26(6):350–4. doi:10.1016/j.jpag.2013.06.018

23. Pike NA, Roy B, Gupta R, Singh S, Woo MA, Halnon NJ, et al. Brain abnormalities in cognition, anxiety, and depression regulatory regions in adolescents with single ventricle heart disease. *J Neurosci Res* (2018) 96(6):1104–18. doi:10.1002/jnr.24215

24. Zafar AB, Ness J, Dowdy S, Avis K, Bashir K. Examining sleep, fatigue, and daytime sleepiness in pediatric multiple sclerosis patients. *Mult Scler* (2012) 18(4):481–8. doi:10.1177/1352458511424307

25. Larche CL, Plante I, Roy M, Ingelmo PM, Ferland CE. The Pittsburgh sleep quality Index: reliability, factor structure, and related clinical factors among children, adolescents, and young adults with chronic pain. *Sleep Disord* (2021) 2021:5546484. doi:10.1155/2021/5546484

DYSTONIA

TYPE Original Research
PUBLISHED 06 March 2024
DOI 10.3389/dyst.2024.12347

OPEN ACCESS

EDITED BY
Aparna Wagle Shukla,
University of Florida, United States

*CORRESPONDENCE
Aasef G. Shaikh,
aasef.shaikh@case.edu

RECEIVED 31 October 2023
ACCEPTED 16 February 2024
PUBLISHED 06 March 2024

CITATION
Agharazi H, Jinnah HA, Zee DS and Shaikh AG (2024), Effects of botulinum neurotoxin on regularity of head oscillations in cervical dystonia. *Dystonia* 3:12347.
doi: 10.3389/dyst.2024.12347

Effects of botulinum neurotoxin on regularity of head oscillations in cervical dystonia

Hanieh Agharazi[1], H. A. Jinnah[2], David S. Zee[3] and Aasef G. Shaikh[1,4,5]*

[1]National VA Parkinson Consortium Center, Louis Stokes Cleveland VA Medical Center, Cleveland, OH, United States, [2]Department of Neurology, Emory University, Atlanta, GA, United States, [3]Department of Neurology, Johns Hopkins University, Baltimore, MD, United States, [4]Department of Neurology, University Hospitals, Case Western Reserve University, Cleveland, OH, United States, [5]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, United States

Introduction: This study explores the effects of botulinum neurotoxin (BoNT) on the relationship between dystonia and tremor, specifically focusing on cervical dystonia (CD) and its connection to head tremor.

Methods: Fourteen CD patients were recruited; eight (57%) with clinically observable head oscillations were included in further analysis. A high-resolution magnetic search coil system precisely measured head movements, addressing two questions: 1) BoNT's effects on head movement amplitude, frequency, and regularity, and 2) BoNT's influence on the relationship between head position and head oscillations. For the first question, temporal head position measurements of three patients were analyzed before and after BoNT injection. The second question examined the effects of BoNT injections on the dependence of the oscillations on the position of the head.

Results: Three distinct trends were observed: shifts from regular to irregular oscillations, transitions from irregular to regular oscillations, and an absence of change. Poincaré analysis revealed that BoNT induced changes in regularity, aligning oscillations closer to a consistent "set point" of regularity. BoNT injections reduced head oscillation amplitude, particularly in head orientations linked to high-intensity pre-injection oscillations. Oscillation frequency decreased in most cases, and overall variance in the amplitude of head position decreased post-injection.

Discussion: These findings illuminate the complexity of CD but also suggest therapeutic potential for BoNT. They show that co-existing mechanisms contribute to regular and irregular head oscillations in CD, which involve proprioception and central structures like the cerebellum and basal ganglia. These insights advocate for personalized treatment to optimize outcomes that is based on individual head oscillation characteristics.

KEYWORDS

dystonia, tremor, torticollis, botulinum neurotoxin, dystonic tremor

Introduction

The dystonias encompass a group of conditions marked by excessive muscle contractions leading to involuntary postures or movements characterized by repetitive or contorted postures [1–3]. As a collective entity, they stand as the third most prevalent movement disorder following tremors and Parkinson's disease, impacting over 3 million individuals across the globe. The clinical manifestations persist chronically without a cure, and only a limited number of treatments demonstrate broad efficacy.

Tremors are identified by rhythmic oscillations of a body region, typically featuring a sinusoidal pattern [4–6]. Among all movement disorders, tremor reign as the most prevalent, afflicting over 20 million individuals globally, constituting around 3% of the general population. Tremor is a progressive symptom, resulting in heightened disability with advanced age. Similar to dystonias, tremors are persistent, subjecting patients to prolonged and stigmatizing impairment.

While dystonia and tremor are distinct disorders, they have close relationship. A particularly contentious relationship exists between neck dystonia and head tremor. Cervical dystonia (CD), the most prevalent form of dystonia, exhibits tremor-like characteristics due to intermittent, repetitive, and rapid movements of the neck. These tremor-like movements display irregularity and jerkiness, they are not really "tremor" but a jerky form of dystonia [7]. Dystonia may coexist with typical forms of head tremors, which typically manifest as sinusoidal patterns owing to comparable movement speeds in opposing directions [8–16].

Treatments of CD and related head tremor are limited. Though it's well-established that botulinum neurotoxin (BoNT) significantly reduces muscle activity and head oscillations in up to 70% of cases, there are recognized limitations [17, 18]. BoNT injections are not effective in approximately 30% of patients. Higher doses of BoNT can markedly impact the quality of life by triggering difficulties in swallowing, speech, or breathing. Currently, the optimal selection of candidates for BoNT therapy hinges on trial and error, which can span months to years and is accompanied by high financial costs and the risk of severe side effects like dysphagia, dysarthria, and breathing problems. On the other hand, some types of CD are notoriously challenging to treat effectively. Some examples are predominant anterocollis with complex and varied movement patterns, and CD with prominent head tremor, a condition where oscillations are more prominent than abnormal postures [19–21] Our hypothesis centers on the idea that BoNT targets specific aspects of dystonia—abnormal turning versus irregular oscillations featuring jerky dystonia, or regular head tremor—with these aspects varying among patients. This inquiry revolves around which aspect of head oscillations BoNT modulates—whether amplitude, frequency, or irregularity. Does BoNT has different effects on various aspects of dystonia, and does this form the underlying reason why BoNT is highly effective in certain forms of dystonia, while it is ineffective in others, especially when head tremor is prominent. Elucidating the features of the complete dystonia phenotype and understanding how BoNT impacts these features will guide the selection of ideal candidates.

Methods

Participants

The study was approved by the Johns Hopkins University and Louis Stokes Cleveland VA Institutional Review Boards, and all participants gave informed consent before their involvement. Our goal was to examine effects of botulinum toxin injections on head tremor in CD. The head tremor is not always evident on clinical examination, often warranting objective measures [22–25]. Therefore we recruited 14 CD participants, whether or not they had head tremor during clinical examination. Head tremor was identified in 57% ($n = 8$ out of 14) of our cohort of CD patients when measured with search coils. These eight patients were further included the analysis reported in this current study. CD patients were excluded if they had known or presumed causes, broader involvement indicating segmental or generalized dystonia, and those who showed additional features suggestive of a more extensive neurodegenerative disorder. All participants had normal eye movements and

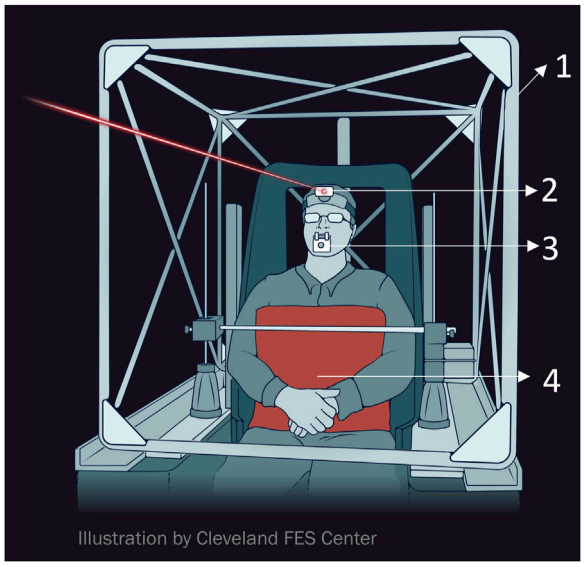

FIGURE 1
Schematic example of experiment setup (Images courtesy of The Cleveland FES Center). (1). search coil frame (2) head-fixed laser pointer (3) search coil affixed to the bitebar (4) body restraint system.

visual acuity, corrected with lenses if required. Head movements were evaluated when their CD was at its peak, within a week before the scheduled botulinum toxin injection. We also evaluated head movements about 4 weeks after the BoNT injection, at its therapeutic peak. None of the patients were taking other medications for CD at the time of testing.

Experiment setup

The evaluation involved recording horizontal, torsional, and vertical head movements through a dual (three-axis) search coil (Skalar, Delft, Netherlands) fixed onto a bite bar (Figure 1). Participants were positioned within the magnetic coil frame so that the midpoint between the angles of the mouth coincided with the frame's center (Figure 1). The trunk was stabilized by firm cushion mounted on a metal bar (Figure 1). Horizontal head movements were rotations around a vertical earth axis through the coil frame's center (i.e., turning the head to the right or left, also referred to as torticollis). Vertical head movements constituted rotations around a horizontal axis parallel to the inter-aural line and passing through the coil frame's center (i.e., head flexion and extension, also known as anterocollis or retrocollis). Torsional head movements occurred around a horizontal axis parallel to the naso-occipital axis of the head and through the coil frame's center (i.e., tilting the head so that one ear moves towards a shoulder, also termed laterocollis). The search coil's angular position with respect to magnetic fields was digitized at a rate of 1,000 Hz, and the data was processed to determine the head's three-dimensional position [26]. The recordings were conducted in a dimly lit room, with participants wearing a headband containing a laser pointer (Figure 1). They were instructed to turn their heads toward a light-emitting diode (LED) targets placed at 0°, and either 10°, 20°, or 30° to the right or left. After repositioning their heads, they were asked to align the head-fixed laser with each LED target for about 40 s. MATLAB® software (The Mathworks™, Natick, MA) was used to analyze the three-dimensional head positions. Angular head velocity was derived from mathematical calculations of angular head position. Signal noise inherent to mathematical differentiation was removed using low-pass filtering and three-point averaging. Statistical analysis was carried out using the MATLAB® statistics toolbox.

Analysis

Oscillatory head movements were analyzed after detrending the raw signal to remove the linear trend. Raw signal noise was eliminated through digital filtering, employing three-point averaging. Data from each axis underwent individual processing via a cycle-by-cycle analysis. A cycle was defined by initially eliminating bias from the detrended data (normalized amplitude = actual amplitude - mean amplitude). This rendered the cycle's peaks positive and troughs negative. The intersection of the data trace with the abscissa (positive zero-crossing) marked the X-coordinate at which this happened, denoting the start and end of the cycle. Cycle frequency was derived from the inverse of the period of the cycle while the difference between the peak and trough indicated the peak-to-peak amplitude of the cycle.

Variance

We assessed the irregularity of tremor by quantifying variance. Variance of a time series signifies the dispersion of time series values around their average. Variance measurements from instances of regular and irregular head position time series are illustrated (Figures 2A–C). Irregular oscillatory head movements exhibited higher variance. As shown in Figure 2C, variance was greater in irregular head position compared to regular ones.

Poincaré analysis

Poincaré analysis was applied to the time series data by capturing its non-linear features [27]. The core principle involves identifying the likeness between an oscillatory cycle and the subsequent cycle that follows it, then the cycle following that, and so forth. The conjecture is that close by cycles will resemble each other more, and this feature gives rise to Poincaré parameters. Regular and rhythmic waveforms tend to display more resemblance in contrast to irregular and arrhythmic signals. To measure resemblance, the Poincaré algorithm produces maps of data points in the time series in relation to their subsequent data points (Figure 2D). These maps illustrate the evolution of the time series data concerning its variability. An ellipse is fitted to the plot, and standard deviations along the minor and major semi-axes of the fitted ellipse are calculated. These parameters define short-term and long-term variability in the time series, and their ratio signifies the randomness within the time series. Examples of Poincaré plots, illustrating repetitive movements in regular and irregular head position time series, are shown in Figure 2D. In each case, a black ellipse is fitted, and SD1 represents the standard deviation of data points along the major semi-axis (green axis 1), indicating short-term variability. SD2 is the standard deviation of data points along the minor semi-axis (light blue axis 2), reflecting long-term variability. In a regular time series, most data points fall within the fitted ellipse, leading to a relatively small SD1 value and a relatively large SD2 value. The SD1/SD2 ratio denotes the randomness in the time series. A more regular time series is associated with a smaller ratio value. Poincaré ratio values that evolve over the cycles' proximity are depicted in Figure 2E, showing larger values for

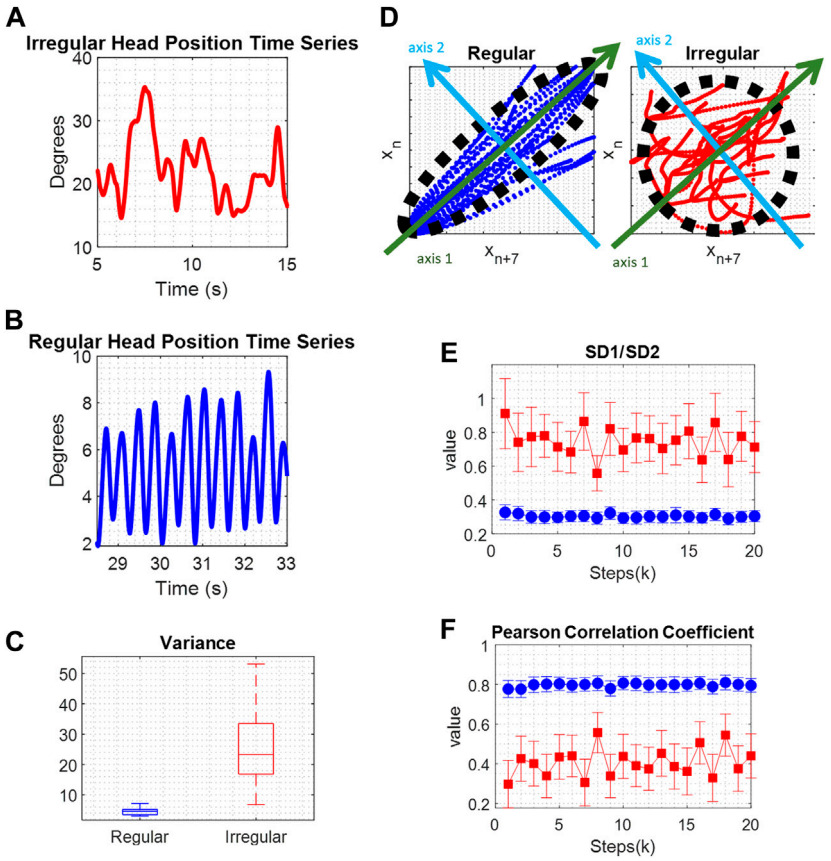

FIGURE 2
(A) Comparison of irregular movement, and **(B)** regular movement. **(C)** The boxplots of variance values show significantly larger values for irregular movement, red color, compared to regular movement, blue color. **(D)** Poincare maps depicting repetitive irregular, red color, and regular movements, blue color. A black ellipse is fitted and SD1, the standard deviations of the data points along the major semi-axis, green axis 1, and SD2, the standard deviations of the data points along the minor semi-axis, light blue axis 2, are calculated and compared. **(E)** The SD1/SD2 ratio represents the randomness in the time series. Lower values represent a more regular signal. **(F)** The Pearson Correlation Coefficient defines the linear correlation between a time series and its delayed version which means that regular time series data, has higher values compared to irregular time series data.

irregular time series (blue) and smaller values for regular time series (red). Another parameter examined in Poincaré analysis is the Pearson Correlation Coefficient, ρ. This value signifies the linear correlation between a time series and its delayed version, indicating that regular time series data exhibit higher ρ values compared to irregular time series data. Examples of ρ are shown in Figure 2F.

Results

This study aimed to investigate how BoNT affects oscillatory head movements in individuals with CD. Fourteen patients with CD were screened to find head tremor with dystonia; eight patients (57%) exhibited observable oscillatory head movements when assessed with instrumented measures using search coils. These eight patients were subsequently included in the experiment. The study's focus centered around addressing two specific questions:

1) To examine the effects of BoNT on amplitude, frequency, and regularity of oscillatory head movements in CD.
2) To examine the effects of BoNT on head-on-trunk position dependence of oscillatory head movements.

Question 1. To examine the effects of BoNT on amplitude, frequency, and regularity of oscillatory head movements.

In the upper panel of Figure 3, the measures of head positions in three exemplary patients are displayed as they look at targets positioned on their left (P7), right (P6), and center (P8). The measurements are presented in degrees, where positive values indicate rightward direction, negative values indicate leftward direction, and zero signifies the central direction. Within this

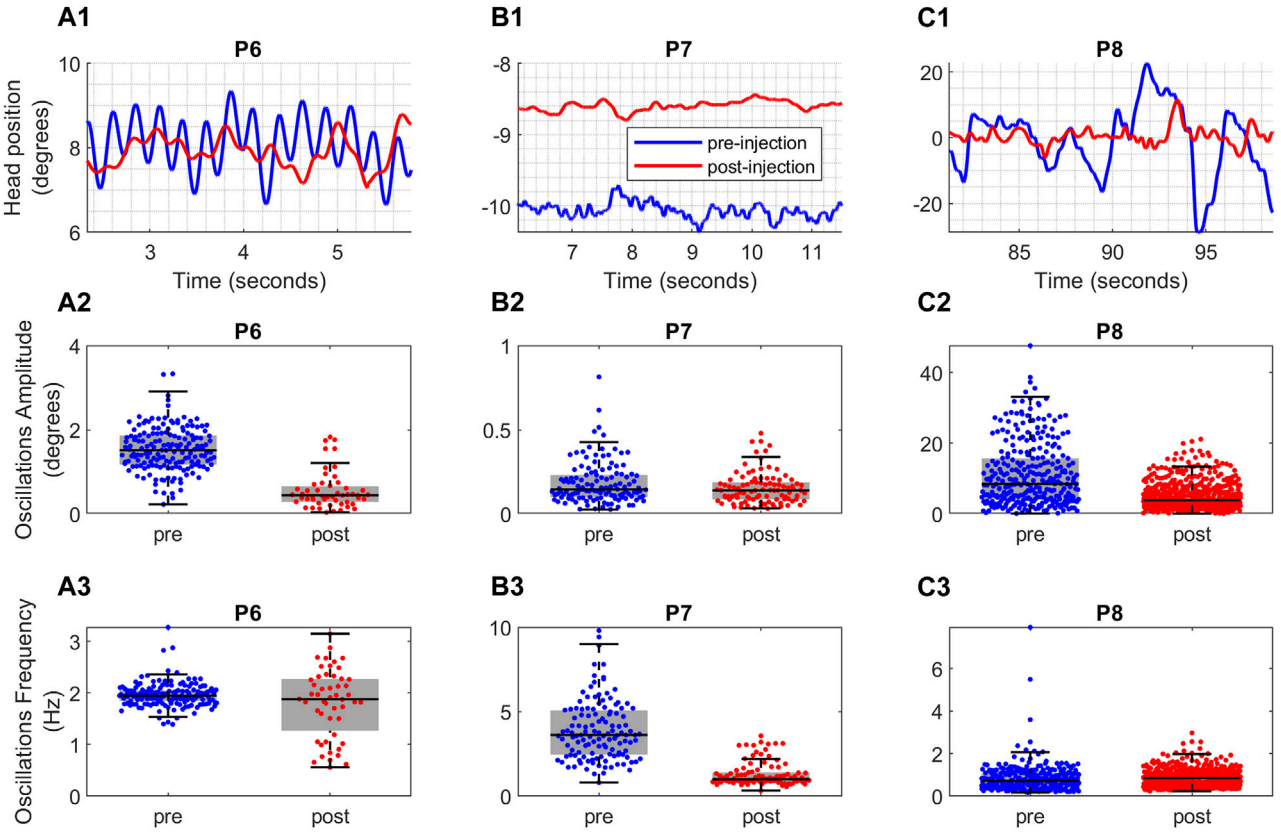

FIGURE 3
(A1,B1,C1) Raw data depicting the head position over time for three CD patients. The x-axis shows the time in seconds and the y-axis shows the head position in degrees. **(A2,B2,C2)** The effect of Botox injection on amplitude and **(A3,B3,C3)** frequency of oscillations for the patients. The blue color represents the head position measurements taken before Botox injection and red color represents the head position measurements taken after the Botox injection. The vertical axis shows the boxplots of the amplitude and frequency values. The horizontal black line in the middle of each box is the median of the data and the whiskers indicate the 25th and 75th percentiles. The horizontal axis provides the comparison between pre-injection (blue color) and post-injection (red color) values.

panel, the head position measurements before and after BoNT injection are shown for each patient with blue and red lines, respectively.

Three distinct trends in regularity change can be observed among these patients: prior to BoNT injection, patient P6's head oscillations in Figure 3A1 exhibited regular sinusoidal patterns with comparable frequencies and varying amplitudes. However, after the injection, these oscillations became irregular, featuring fluctuating frequencies and reduced amplitudes. Conversely, the oscillations of patient P7 in Figure 3B1 displayed minimal alterations in terms of regularity, with their amplitudes decreasing to some extent while higher frequencies were attenuated. Finally, patient P8's irregular oscillations in Figure 3C1 prior to BoNT injection became more regular with diminished amplitudes and consistent frequencies after the injection.

We assessed the amplitude and frequency of individual oscillations to look more closely into the effects of BoNT on the amplitude and frequency of head movements. The amplitude and frequency box plots for these single oscillations are provided in the middle and lower panels of Figure 3, respectively. Similarly, blue color signifies measurements taken before BoNT injection, while the red color represents the measurements taken after injection.

Upon close examination, three different post-injection effects were evident. The Patient P6 (Figure 3A2) had reduction in the amplitude of sinusoidal head oscillations, but there was no change in frequency (Figure 3A3; Supplementary Table S1). Prior to BoNT injection, P6's had regular and sinusoidal oscillations, which became less regular with varying amplitude and inconsistent frequency after injections (Figure 3A2). An example of patient P7 (Figure 3B1) had elimination of higher frequency oscillations following BoNT injection (Figure 3B3), while amplitudes remained unaffected (Figure 3B2; Supplementary Table S1). The irregular nature of oscillations persisted (Figure 3B1). Similarly, BoNT diminished head tremor amplitude in patient P8 (Figures 3C1, C2) but there was an increase in the frequency (Figure 3C3; Supplementary Table S1). There was improved regularity and less frequency variability in P8's head oscillations after BoNT injections.

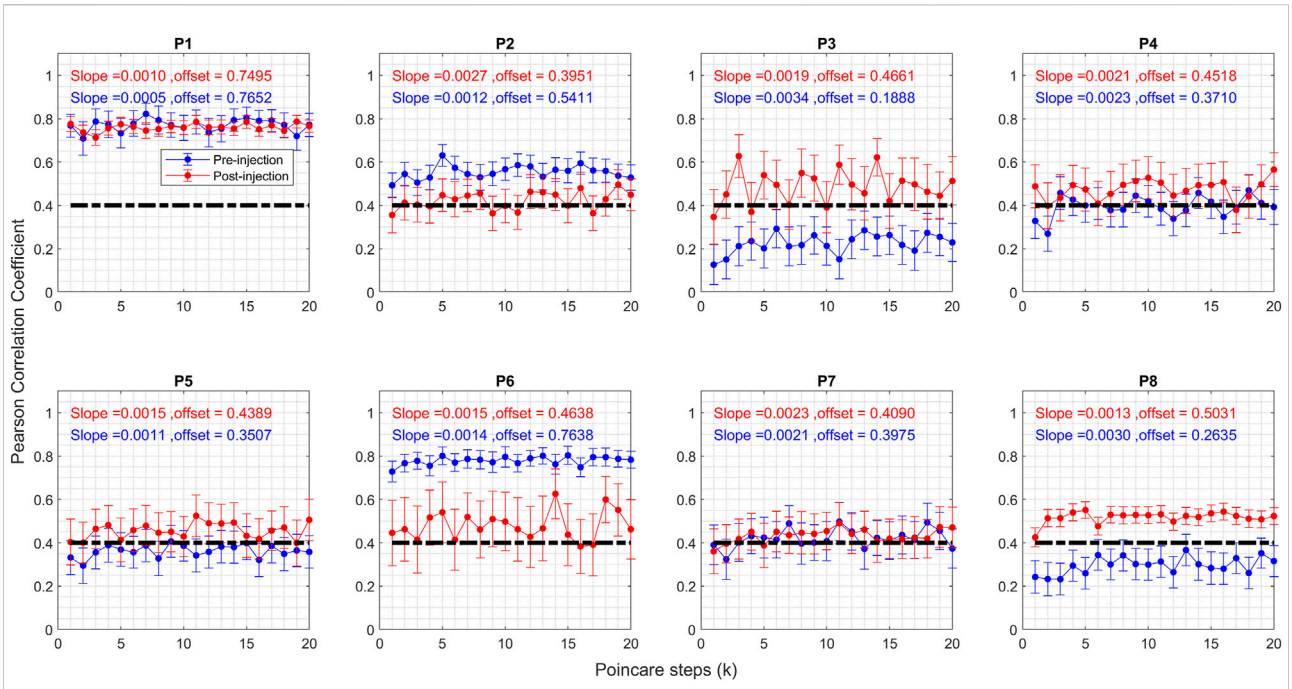

FIGURE 4
Graph of Pearson correlation coefficient of Poincare plot parameter for CD patients before and after the Botox injection. Blue circles represent pre-injection, and red circles represent post-injection. The vertical axis shows the Pearson correlation coefficient value, and the horizontal axis shows the steps. The vertical lines on the graphs represent 95% confidence interval at each step.

In summary, three trends emerge concerning the regularity of head tremor post BoNT injection: 1) a transition from irregular to regular, exemplified by P8 in Figure 3C; 2) a shift from regular to irregular, as observed in the case of P6 in Figure 3A; and 3) an absence of change, similar to what's seen in P7 in Figure 3B. To quantify these shifts, we used Poincaré analysis on the head position measurements and juxtapose Poincaré parameters before and after the BoNT injection. This involves segmenting the time series of head position measurements into distinct oscillations, followed by Poincaré analysis of these individual oscillations. Figure 4 displays the Pearson's correlation coefficient values for all patients based on the Poincaré steps. The horizontal axis signifies Poincaré steps denoted as "k," while the vertical axis depicts Pearson's correlation coefficient values before and after BoNT injection in blue and red colors, respectively. Each "k" represents the interval between single oscillations. For instance, at "k = 5," the first oscillation "x_1" is contrasted with the 6th oscillation "x_6," and the corresponding correlation coefficient value is computed. The filled circles denote mean values, and the whiskers represent error bars indicating a 95% confidence interval at each step.

The correlation coefficient serves as a marker for regularity within the time series, with higher values signifying a greater level of regularity. Several patterns appeared: 1) heightened regularity after botulinum toxin injection for P3, P4, P5, and P8; 2) diminished regularity post-injection for P2 and P6; and 3) sustained regularity for P1 and P7. Furthermore, it is evident that post-injection correlation coefficient values cluster around 0.4 for all patients, excluding P1, whereas these values showed a range of levels before BoNT injection. After excluding the outlier (P1), mean and standard deviation of offset values before injection was 0.41 ± 0.19. After injection the mean value of offset remained about the same, but the standard deviation significantly reduced (0.45 ± 0.04).

The SD1/SD2 ratio reflects the randomness of the head position measurements, with lower ratios indicating more regular head tremors. Figure 5 compares the ratios for all patients before and after injection. Like the correlation coefficient, post-injection values cluster around 0.6, whereas they were more dispersed prior to BoNT injection. Randomness in head tremor oscillations is diminished for P3, P4, P5, and P8, augmented for P2 and P6, and did not change for P1 and P7. This corroborates the findings derived from the correlation coefficient in Figure 4. As noted in Figure 4, for correlation coefficients, pre-injection values of offset had a higher spread (before: 0.83 ± 0.35); but the spread of the offset was significantly reduced after BoNT injection (after: 0.6830 ± 0.036).

Regarding the first question—the effect of BoNT injection on the regularity of the head oscillations -- the Poincaré

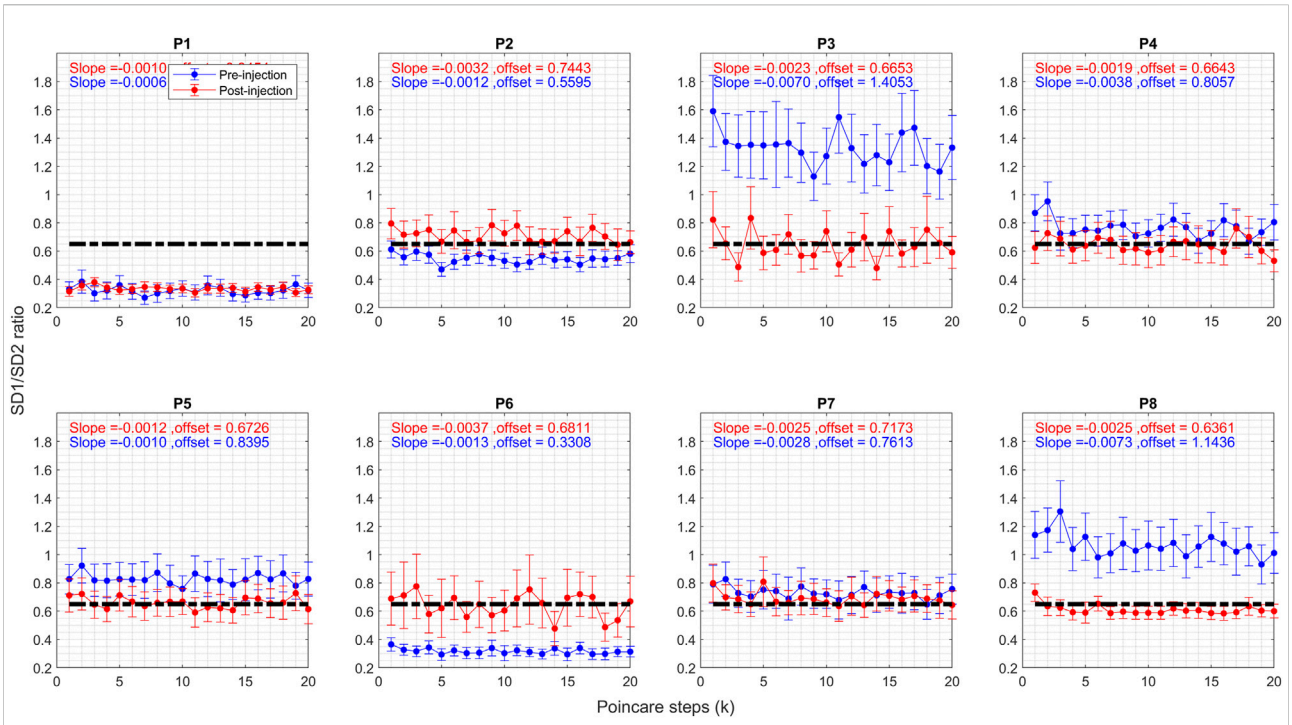

FIGURE 5
Graph of SD1/SD2 ratio of Poincare plot parameter for CD patients before and after the Botox injection. Blue circles represent pre-injection, and red circles represent post-injection. The vertical axis shows the Pearson correlation coefficient value, and the horizontal axis shows the steps. The vertical lines on the graphs represent 95% confidence interval at each step.

analysis indicates that BoNT injection did impact their regularity in some patients. The toxin imbues a certain regularity referred to as a "set point," which remains consistent across all patients. If pre-injection head oscillations are more irregular than this "set point," they tend to become more regular. Conversely, if pre-injection oscillations are more regular than the "set point," they shift towards increased irregularity.

The Poincaré analysis leads to an important insight into the nature of head oscillations in CD. It shows that these oscillations exhibit varying, random shapes, and the degree of randomness does not change although the time gap between two compared oscillations increases. In other words, the difference in shapes between the first (x_1) and sixth (x_6) oscillations is no different from the difference between the first (x_1) and twentieth (x_{20}) oscillation cycles. This observation was quantitatively assessed by analyzing the slope of a linear trend within the scatter plots in Figures 4, 5. This scatter plot compared the Pearson correlation coefficient and Poincaré steps, as well as the SD1/SD2 ratio and Poincaré steps. The slope of this trend would be greater if the disparity in shape between cycles increased with a greater time gap between them, but it would be zero if the randomness of the shapes remained constant. Specifically, before the administration of BoNT injections, the slopes comparing Pearson correlation coefficients and Poincaré steps were measured at 0.002 ± 0.0006, and after BoNT injections, they remained quite similar at 0.002 ± 0.0009. Likewise, the slopes comparing SD1/SD2 ratio and Poincaré steps were 0.002 ± 0.0009 before BoNT injection and about the same (0.003 ± 0.002) after BoNT injection. Furthermore, the variations between patients underscore an important observation—the effects of injection might hinge on the injection site and possibly the baseline disease phenomenology. The subsequent section explores the influence of these changes based on the head-on-trunk orientation.

To summarize, we find three distinct trends in the changes in the regularity of the head oscillations induced by BoNT among CD patients—head oscillations become irregular post-injection, oscillations remained relatively consistent in regularity, and the irregular oscillations transform into a more regular pattern. Poincaré analysis quantified these shifts in regularity, highlighting that BoNT brings regularity to a "set point." Moreover, the analysis reveals that head oscillations exhibit random shapes that remain consistent regardless of the time interval between cycles.

Question 2. To examine the effects of botulinum toxin on head-on-trunk position dependence of oscillatory head movements:

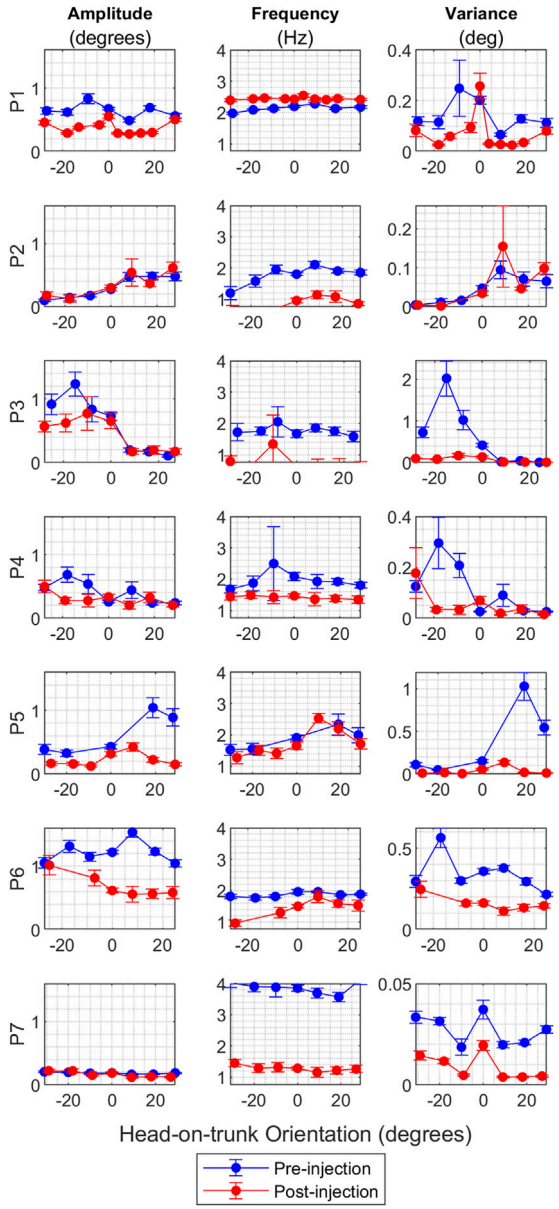

FIGURE 6
(A) The effect of BoNT injection on the amplitude of oscillations for all CD patients where multiple head on trunk orientations were measured. The vertical axis shows the oscillation amplitude value in degrees, and the horizontal axis shows the head orientation in degrees. Blue circles represent mean values for pre-injection, and red circles represent mean values for post-injection. The vertical lines on the graphs are 95% confidence interval at each head orientation. **(B)** The effect of BoNT injection on the frequency of oscillations for CD patients where head on trunk orientation dependence was measured. The vertical axis shows the oscillation frequency value in Hz, and the horizontal axis shows the head orientation in degrees. Blue circles represent mean values for pre-injection, and red circles represent mean values for post-injection. The vertical lines on the graphs are 95% confidence interval at each head orientation. **(C)** The effect of BoNT injection on the variance of oscillations amplitude for CD patients where head on trunk orientation dependence was measured. The vertical axis shows the variance, and the horizontal

(*Continued*)

FIGURE 6 (Continued)
axis shows the head orientation in degrees. Blue circles represent mean values for pre-injection, and red circles represent mean values for post-injection. The vertical lines on the graphs are 95% confidence interval at each head orientation.

The primary characteristic of CD is its dependence on the head's position relative to the trunk, particularly evident in head oscillations. Usually, the head oscillations are minimal in one specific head orientation, known as the null position, but increase in intensity as the head deviates further from this null orientation. In this section, we investigate how BoNT injections affect the relationship between head-on-trunk position and head oscillations. We begin by examining the amplitude and frequency of individual oscillations across various head orientations, as illustrated in Figures 6A, B, respectively. These figures display the mean values along with a 95% confidence interval for both amplitude and frequency at each head orientation. Figure 6A reveals a notable decrease in the amplitude of oscillations following BoNT injections for patients P1, P5, P6, and P8, across all measured head orientations. This reduction is most pronounced for head orientations previously associated with high-intensity pre-injection oscillations. This effect is most striking in the cases of P3, P4, and P7, where changes in head oscillations were only observed in head orientations that initially had high intensity oscillations pre-injection. Conversely, the effects were minimal in the cases of P2 and P7, where the intensity of head oscillations pre-injection was modest. Regarding the frequency of oscillations (Figure 6B), there was a decrease across all head orientations for all patients except for P1 and P5.

To further investigate the relationship between head-on-trunk position and BoNT injection effects, we analyzed the variance in head position amplitude, as shown in Figure 6C. There is a reduction in variance except in the case of P2, who consistently showed low-intensity head oscillations at baseline. In summary, the impact of BoNT on head oscillations is most pronounced in head orientations in which high intensity head oscillations were triggered before treatment.

To summarize, the results show a considerable reduction in head oscillation amplitude after BoNT injections, especially in head orientations associated with intense pre-injection oscillations. The frequency of oscillation decreased in all patients except two. The variance in head position amplitude decreased overall, except for one patient who had low-intensity head oscillations at baseline.

Discussion

The results of this study provide valuable insights into the effects of BoNT on oscillatory head movements in individuals

with CD. BoNT injections led to three types of changes: a transition from irregular to more regular oscillations, a shift from regular to more irregular oscillations, or unchanged regularity. The Poincaré analysis further supported these findings by quantifying regularity using correlation coefficient values. It indicated that BoNT injection affects head oscillations by altering their regularity. A "set point" of regularity is established by BoNT that tends to regularize irregular tremors, but it may also make regular tremors more irregular. The intriguing finding in this study is that across all patients, prior to BoNT treatment, head oscillations displayed a variable irregularity. In other words, one cycle of the oscillation could not predict the shape of subsequent cycles, suggesting that the oscillations were random in shape. Furthermore, the BoNT did not alter this trend of randomness. These results highlight that neck oscillations studied here do not satisfy the definition of tremor (although traditionally called dystonic "tremor") [3, 5–7]. The tremor by definition is regular, rhythmic, and back-and-forth oscillatory cycles that allow for predicting the shape of subsequent cycles based on the shape of one cycle [5, 6].

Another important observation was that BoNT affected the overall regularity of the oscillations. However, the effect of BoNT on the oscillations was variable among patients and it was independent of the baseline irregularity. In essence, if the oscillatory cycle was highly irregular before treatment, its irregularity decreased after BoNT administration, whereas if it was highly regular, its regularity decreased after BoNT injection. These results were measured using Poincaré analysis, which involved comparing the correlation Poincaré estimations of the oscillation shapes before and after BoNT treatment.

We speculate two co-existing phenomenology to explain these findings. One, there is a central oscillator that may be inherently similar in all CD patients but receives varied input from other feedback sources. These feedback sources can alter the oscillatory characteristics and introduce irregularity. The nature of the feedback influence could be determined by the type of connectivity pattern with the oscillator; some making it regular some making it irregular. In other words, CD in some patients involves neck muscles that influence oscillator to make it more regular while in other instances the oscillator may become irregular. Treatment of CD with BoNT may revert the oscillator at the "set point," returning the oscillations to an identical regularity. In addition, the neck oscillations in CD may be under cerebellar, basal ganglia, and neck proprioceptive influence. BoNT may directly affects proprioceptive modulation but it may not directly affect the cerebellum. Nevertheless, the cerebellum may still contribute to the oscillatory instability independent of the instability caused by proprioceptive feedback.

Our results are supports the idea of two separate pathophysiology contributing to head oscillations in CD, one originating from the cerebellum and basal ganglia and the other from proprioception. This concept is consistent with the notion that dystonia is a network disorder [28–30]. The results also support the idea that although dystonia and tremor often coexist, they may still represent distinct entities with different underlying pathophysiological mechanisms [31]. Recent physiological studies measuring single-neuron activity in CD participants have further emphasized these distinctions. For instance, individuals with irregular head oscillations combined with dystonia displayed distinct pallidal physiology compared to those with pure dystonia or jerky head oscillations [31].

Contemporary literature over the last one decade has increasingly supported the role of mesencephalic neural integrator for the control of the head position in CD [23, 25, 32–36]. According to the network model in CD, the impairment anywhere in the network, even outside of the integrator, may lead to deficits in the feedback dependent neural integration. There is increasing evidence for the involvement of cerebellum, proprioception, and basal ganglia, as three separate sources of the feedback in the network model for CD [28–32, 37–39]. The cerebellar role in dystonia is supported when the oscillations coexisting with dystonia have sinusoidal features as seen in tremor that is also thought to be related to cerebellar deficits. Our results support the role of proprioception as an independent source of feedback to the integrator, and effect of BoNT on the integrator function.

These findings also support the notion that head oscillations and CD may not effectively respond to a single treatment modality, and a combination of approaches may be necessary. Some types of head oscillations, particularly those more influenced by proprioception, could benefit from BoNT treatment, while others may require pharmacotherapy for tremor or even deep brain stimulation. The combination of deep brain stimulation and BoNT for the treatment of tremor and dystonia is a practice that aligns with these results and previous physiological experiments.

In conclusion, this study provides insights into the complex relationship between BoNT and head tremors in CD patients. It highlights the need for personalized treatment approaches, considering individual variations in tremor characteristics and head orientations. Understanding how BoNT influences the regularity and amplitude of head oscillations is a crucial step in optimizing its therapeutic benefits for CD patients.

Data availability statement

Deidentified data will be available to interested parties after completing all necessary documentation with Johns Hopkins University and U.S. Department of Veterans' Affairs. Requests to access the datasets should be directed to aasefshaikh@gmail.com.

Ethics statement

The studies involving humans were approved by Johns Hopkins University and Louis Stokes Cleveland VA Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HA: analyzed data, conceptualized analysis and interpretation, wrote and edited the paper. HJ and DZ: conceptualized analysis and interpretation, edited the paper. AS: collected data, analyzed data, conceptualized analysis and interpretation, wrote and edited the paper. All authors contributed to the article and approved the submitted version.

Funding

AS was supported by the Career Development Grant from the American Academy of Neurology, George C. Cotzias Memorial Fellowship, Network Models in Dystonia grant from the Dystonia Medical Research Foundation, Department of VA Merit Review (I01CX002086, I01RX003676), Department of VA SPiRE (I21RX003878) CareSource Ohio Community Partnership Grant, and philanthropic funds to the Department of Neurology at University Hospitals (Penni and Stephen Weinberg Chair in Brain Health and Allan Woll Fund).

Conflict of interest

AS serves on speaker bureau for Accorda Pharmaceuticals, and Abbott Neuroscience.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/dyst.2024.12347/full#supplementary-material.

References

1. Evatt ML, Freeman A, Factor S. Adult-onset dystonia. *Handb Clin Neurol* (2011) 100:481–511. doi:10.1016/B978-0-444-52014-2.00037-9

2. Jinnah HA, Berardelli A, Comella C, Defazio G, DeLong M, Factor S, et al. The focal dystonias: current views and challenges for future research. *Mov Disord* (2013) 7:926–43. doi:10.1002/mds.25567

3. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* (2013) 28(7):863–73. doi:10.1002/mds.25475

4. Elias WJ, Shah BB. Tremor. *JAMA* (2014) 311:948–54. doi:10.1001/jama.2014.1397

5. Deuschl G, Bain P, Brin M. Consensus statement of the movement disorder society on tremor. *ad hoc* scientific committee. *Mov Disord* (1998) 13(Suppl. 3): 2–23. doi:10.1002/mds.870131303

6. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From the task force on tremor of the international Parkinson and movement disorder society. *Mov Disord* (2018) 33(1): 75–87. doi:10.1002/mds.27121

7. Fahn S. The varied clinical expressions of dystonia. *Neurol Clin* (1984) 2: 541–54. doi:10.1016/s0733-8619(18)31090-9

8. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* (1991) 6:119–26. doi:10.1002/mds.870060206

9. Jankovic J, Leader S, Warner D, Schwartz K. Cervical dystonia: clinical findings and associated movement disorders. *Neurology* (1991) 41:1088–91. doi:10.1212/wnl.41.7.1088

10. Deuschl G, Heinen F, Guschlbauer B, Schneider S, Glocker FX, Lucking CH. Hand tremor in patients with spasmodic torticollis. *Mov Disord* (1997) 12:547–52. doi:10.1002/mds.870120411

11. Pal PK, Samii A, Schulzer M, Mak E, Tsui JK. Head tremor in cervical dystonia. *Can J Neurol Sci* (2000) 27:137–42. doi:10.1017/s0317167100052240

12. Schweinfurth JM, Billante M, Courey MS. Risk factors and demographics in patients with spasmodic dysphonia. *Laryngoscope* (2002) 112:220–3. doi:10.1097/00005537-200202000-00004

13. Shatunov A, Sambuughin N, Jankovic J, Elble R, Lee HS, Singleton AB, et al. Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23. *Brain* (2006) 129:2318–31. doi:10.1093/brain/awl120

14. Godeiro-Junior C, Felicio AC, Aguiar PC, Borges V, Silva SM, Ferraz HB. Head tremor in patients with cervical dystonia: different outcome? *Arq Neuropsiquiatr* (2008) 66:805–8. doi:10.1590/s0004-282x2008000600005

15. Hedera P, Phibbs FT, Fang JY, Cooper MK, Charles PD, Davis TL. Clustering of dystonia in some pedigrees with autosomal dominant essential tremor suggests the existence of a distinct subtype of essential tremor. *BMC Neurol* (2010) 10:66. doi:10.1186/1471-2377-10-66

16. Louis ED, Hernandez N, Alcalay RN, Tirri DJ, Ottman R, Clark LN. Prevalence and features of unreported dystonia in a family study of "pure" essential tremor. *Parkinsonism Relat Disord* (2013) 19:359–62. doi:10.1016/j.parkreldis.2012.09.015

17. Sethi KD, Rodriguez R, Olayinka B. Satisfaction with botulinum toxin treatment: a cross-sectional survey of patients with cervical dystonia. *J Med Econ* (2012) 15(3):419–23. doi:10.3111/13696998.2011.653726

18. Zoons E, Dijkgraaf MG, Dijk JM, van Schaik IN, Tijssen MA. Botulinum toxin as treatment for focal dystonia: a systematic review of the pharmaco-therapeutic and pharmaco-economic value. *J Neurol* (2012) 259:2519–26. doi:10.1007/s00415-012-6510-x

19. Jinnah HA. The dystonias. *Continuum (Minneap Minn)* (2019) 25(4): 976–1000. doi:10.1212/CON.0000000000000747

20. Jinnah HA, Comella CL, Perlmutter J, Lungu C, Hallett MDystonia Coalition Investigators. Longitudinal studies of botulinum toxin in cervical dystonia: why do patients discontinue therapy? *Toxicon* (2018) 147:89–95. doi:10.1016/j.toxicon.2017.09.004

21. Merola A, Dwivedi AK, Shaikh AG, Tareen TK, Da Prat GA, Kauffman MA, et al. Head tremor at disease onset: an ataxic phenotype of cervical dystonia. *J Neurol* (2019) 266(8):1844–51. doi:10.1007/s00415-019-09341-w

22. Beylergil SB, Singh AP, Zee DS, Jinnah HA, Shaikh AG. Relationship between jerky and sinusoidal oscillations in cervical dystonia. *Parkinsonism Relat Disord* (2019) 66:130–7. doi:10.1016/j.parkreldis.2019.07.024

23. Shaikh AG, Wong A, Zee DS, Jinnah HA. Why are voluntary head movements in cervical dystonia slow?. *Parkinsonism Relat Disord* (2015) 21(6):561–6. doi:10.1016/j.parkreldis.2015.03.005

24. Shaikh AG, Wong AL, Zee DS, Jinnah HA. Keeping your head on target. *J Neurosci* (2013) 33(27):11281–95. doi:10.1523/JNEUROSCI.3415-12.2013

25. Shaikh AG, Zee DS, Jinnah HA. Oscillatory head movements in cervical dystonia: dystonia, tremor, or both?. *Mov Disord* (2015) 30(6):834–42. doi:10.1002/mds.26231

26. Bergamin O, Zee DS, Roberts DC, Landau K, Lasker AG, Straumann D. Three-dimensional Hess screen test with binocular dual search coils in a three-field magnetic system. *Invest Ophthalmol Vis Sci* (2001) 42(3):660–7.

27. Woo MA, Stevenson WG, Moser DK, Trelease RB, Harper RM. Patterns of beat-to-beat heart rate variability in advanced heart failure. *Am Heart J* (1992) 123(3):704–10. doi:10.1016/0002-8703(92)90510-3

28. Prudente CN, Hess EJ, Jinnah HA. Dystonia as a network disorder: what is the role of the cerebellum?. *Neuroscience* (2014) 260:23–35. doi:10.1016/j.neuroscience.2013.11.062

29. Berman BD, Jinnah HA. Dystonia: five new things. *Neurol Clin Pract* (2015) 5:232–40. doi:10.1212/CPJ.0000000000000128

30. Neychev VK, Gross R, Lehericy S, Hess EJ, Jinnah HA. The functional neuroanatomy of dystonia. *Neurobiol Dis* (2011) 42:185–201. doi:10.1016/j.nbd.2011.01.026

31. Sedov A, Usova S, Semenova U, Gamaleya A, Tomskiy A, Beylergil SB, et al. Pallidal activity in cervical dystonia with and without head tremor. *Cerebellum* (2020) 19(3):409–18. doi:10.1007/s12311-020-01119-5

32. Sedov A, Semenova U, Usova S, Tomskiy A, Crawford JD, Jinnah HA, et al. Implications of asymmetric neural activity patterns in the basal ganglia outflow in the integrative neural network model for cervical dystonia. *Prog Brain Res* (2019) 249:261–8. doi:10.1016/bs.pbr.2019.03.030

33. Sedov A, Usova S, Semenova U, Gamaleya A, Tomskiy A, Crawford JD, et al. The role of pallidum in the neural integrator model of cervical dystonia. *Neurobiol Dis* (2019) 125:45–54. doi:10.1016/j.nbd.2019.01.011

34. Sedov A, Popov V, Shabalov V, Raeva S, Jinnah HA, Shaikh AG. Physiology of midbrain head movement neurons in cervical dystonia. *Mov Disord* (2017) 32(6):904–12. doi:10.1002/mds.26948

35. Shaikh AG, Zee DS, Crawford JD, Jinnah HA. Cervical dystonia: a neural integrator disorder. *Brain* (2016) 139:2590–9. doi:10.1093/brain/aww141

36. Shaikh AG, Wong AL, Zee DS, Jinnah HA. Keeping your head on target. *J Neurosci* (2013) 33:11281–95. doi:10.1523/JNEUROSCI.3415-12.2013

37. Pyatka N, Sedov A, Walter BL, Jinnah HA, Shaikh AG. Tremor in chronic inflammatory demyelinating polyneuropathy: proof of unifying network model for dystonia. *Prog Brain Res* (2019) 249:285–94. doi:10.1016/bs.pbr.2019.03.032

38. Neychev V, Fan X, Mitev VI, Hess EJ, Jinnah HA. The basal ganglia and cerebellum interact in the expression of dystonic movement. *Brain* (2008) 131:2499–509. doi:10.1093/brain/awn168

39. Pizoli CE, Jinnah HA, Billingsley ML, Hess EJ. Abnormal cerebellar signaling induces dystonia in mice. *J Neurosci* (2002) 22:7825–33. doi:10.1523/JNEUROSCI.22-17-07825.2002

DYSTONIA

TYPE Original Research
PUBLISHED 22 March 2024
DOI 10.3389/dyst.2024.11309

OPEN ACCESS

EDITED BY
Pattamon Panyakaew,
Chulalongkorn University, Thailand

*CORRESPONDENCE
Aasef G. Shaikh,
aasefshaikh@gmail.com

RECEIVED 26 February 2023
ACCEPTED 15 February 2024
PUBLISHED 22 March 2024

CITATION
Beylergil SB, Mukunda KN, Elkasaby M, Perlmutter JS, Factor S, Bäumer T, Feurestein J, Shelton E, Bellows S, Jankovic J, Mahajan A, Wamer-Rosen T, Reich SG, Wagle Shukla A, Malaty I, Espay A, Duque K, LeDoux MS, Saunders-Pullman R, Leaver K, Frank S, Pantelyat A, Fung V, Pirio Richardson S, Berman B, Stover N, Deik A, Ondo W, Groth C, Jinnah HA and Shaikh AG (2024), Tremor in cervical dystonia. *Dystonia* 3:11309.
doi: 10.3389/dyst.2024.11309

Tremor in cervical dystonia

Sinem Balta Beylergil[1], Krishna Nikhil Mukunda[1], Mohamed Elkasaby[1], Joel S. Perlmutter[2], Stewart Factor[3], Tobias Bäumer[4], Jeanne Feurestein[5], Erika Shelton[5], Steven Bellows[6], Joseph Jankovic[6], Abhimanyu Mahajan[7], Tila Wamer-Rosen[7], Stephen G. Reich[8], Aparna Wagle Shukla[9], Irene Malaty[9], Alberto Espay[10], Kevin Duque[10], Mark S. LeDoux[11], Rachel Saunders-Pullman[12], Katherine Leaver[12], Samuel Frank[13], Alexander Pantelyat[14], Victor Fung[15], Sarah Pirio Richardson[16], Brian Berman[17], Natividad Stover[18], Andres Deik[19], William Ondo[20], Christopher Groth[21], Hyder A. Jinnah[3] and Aasef G. Shaikh[1]*

[1]Department of Neurology, Case Western Reserve University, Cleveland, OH, United States, [2]Department of Neurology and Neurologic Surgery, Washington University School of Medicine, St. Louis, MO, United States, [3]Department of Neurology, Emory University School of Medicine, Atlanta, GA, United States, [4]Institute of Systems Motor Science, University of Lübeck, Lübeck, Germany, [5]Department of Neurology, University of Colorado School of Medicine, Aurora, CO, United States, [6]Department of Neurology, Baylor College of Medicine, Houston, TX, United States, [7]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, United States, [8]Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, Untied States, [9]Department of Neurology, University of Florida, Gainesville, FL, United States, [10]Deparment of Neurology, University of Cincinnati, Cincinnati, OH, United States, [11]Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, United States, [12]Department of Neurology, Mount Sinai Beth Israel, New York, NY, United States, [13]Department of Neurology, Harvard Medical School, Boston, MA, United States, [14]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [15]Sydney Medical School, University of Sydney, Sydney, NSW, Australia, [16]Department of Neurology, University of New Mexico, Albuquerque, NM, United States, [17]Department of Neurology, Virginia Commonwealth University, Richmond, VA, United States, [18]Department of Neurology, The University of Alabama, Tuscaloosa, AL, United States, [19]Department of Neurology, University of Pennsylvania, Philadelphia, PA, United States, [20]Houston Methodist Neurological Institute, Weill Cornell Medical School, Houston, TX, United States, [21]Department of Neurology, University of Iowa, Iowa City, IA, United States

Background: Cervical dystonia (CD) is the most common form of focal dystonia encountered in the clinic. Approximately one-third of CD patients have co-existing tremor in the head and hands. Assessment of tremor as regular or irregular in context of its oscillation trajectory, frequency, and amplitude is a major clinical challenge and can confound the diagnosis of CD. The misdiagnosis may lead to therapeutic failures, poor quality of life, and poor utilization of medical and financial resources.

Methods: We analyzed the largest cohort of CD patients (n = 3117) available to date, collected from 37 movement disorder centers in North America, Europe, and Asia. We used machine learning to determine what clinical features from clinician reports predicted the presence of tremor as well as its regular or irregular appearance.

Results: Out of 3,117 CD patients, 1,367 had neck tremor. The neck tremor was interpreted as irregular in 1,022, regular in 345, and mixed (both irregular and regular) in 442. A feature importance analysis determined that greater severity

of CD, longer disease duration, and older age, in descending order, predicted the presence of neck tremor. The probability of neck tremor was reduced if the dystonia affected other body parts in addition to the neck. We also found a significantly heightened risk for developing neck tremor in women. An additional feature importance analysis indicated that increased severity of dystonia affecting other body parts, severity of CD, and prolonged disease duration was associated with a lower likelihood of regular neck tremor while increased age predicted a higher likelihood.

Conclusion: Machine learning recognized the most relevant clinical features that can predict concurrent neck tremor and its irregularity in a large multi-center dystonia cohort. These results may facilitate a more accurate description of neck tremor and improved care path in CD.

KEYWORDS

dystonia, tremor, cervical dystonia, reularity, jerkiness

Introduction

Dystonia and tremor are two distinct neurological signs, which are often present in the same individual and are closely related. Despite this close relationship between the two conditions, previous studies showed highly variable prevalence of tremor in dystonia, ranging from 10% to 70% (Figure 1A). Such disparity in prevalence is also seen for dystonia in those who have tremor, ranging from 0% to 21% (Figure 1B). There have been several attempts to define "tremor-like" dystonic movements. Fahn (1984) called "dystonic tremor" based on its irregularity, jerky appearance of the waveform, dependence on the region of the body affected, and the presence of null point [1, 2]. However, "irregularity" is often viewed as variability in tremor frequency and amplitude, not just the "jerky" shape. On the contrary, the 1998 Movement Disorders Society (MDS) consensus statement on tremor classification [3], tremor is classified as dystonic tremor when it affects a body part that is also affected by dystonia. The 1998 MDS consensus added the definition "tremor associated with dystonia (TAWD)" to this statement to accommodate the cases where tremor occurs in body regions without overt dystonia.

There were a few caveats with the 1998 MDS committee's definition for dystonic tremor: the requirement of co-existing twisting movements, which can be subjective. For example, while slight tilting of the neck or minor spooning of the fingers are viewed as dystonia by some investigators, these are potentially normal variants of motor behavior according to others [4–12]. The other limitation of the 1998 MDS committee's definition was that its mutually exclusive diagnostic criteria inherently precluded the possibility that tremor and dystonia may be two distinct disorders that co-occur. The fundamental disagreement

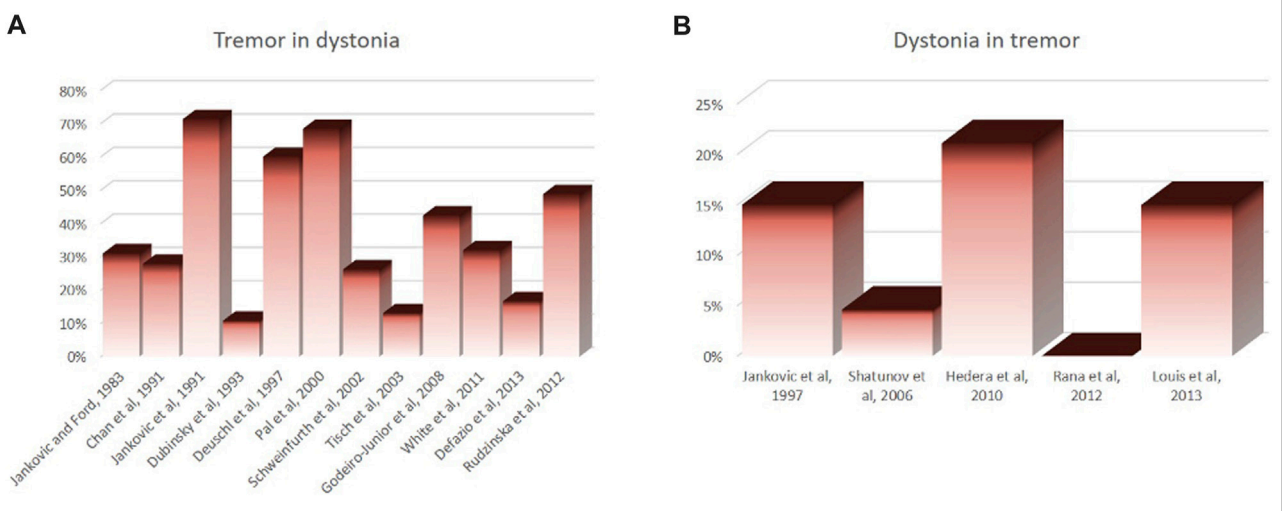

FIGURE 1
Disparity in reported prevalence rate of tremor in patients who have dystonia **(A)** and prevalence rate of dystonia in those who have tremor **(B)**.

on the definition of dystonic tremor called for more general re-evaluation of the operational definitions of how tremor relates to dystonia [4, 13–19]. The 2018 MDS Task Force on Tremor recently retained the definitions of dystonic tremor TAWD [20]. The 2018 taskforce divided essential tremor into essential tremor (i.e., pure tremor) and "essential tremor plus" (i.e., tremor that may be combined with questionable dystonic features) [20, 21].

It is particularly important to understand the relationship of neck tremor and CD because they are most common of all other types of tremor dystonia combinations. CD and jerky repetitive neck movements have different pathophysiological correlates compared to more sinusoidal neck oscillations that appear like tremor seen with essential tremor [22, 23]. To understand the relationships between neck tremor and CD, it is necessary to support the expert consensus-based opinions with empiric evidence. The need is critical from both clinical and research standpoints. A recent study examining a large number of CD cases from multiple centers provided useful guidance for understanding the nature and nosology of tremulous movements in different isolated dystonia syndromes (focal, segmental, multifocal and generalized) [24]. The study found an overall tremor prevalence of 53.3%, and factors predicting dystonic tremor varied according to the criteria (Fahn's vs. MDS 1998/2018) used to define them [1, 3, 20]. The study identified several important factors that significantly influenced the prevalence of tremor in dystonia. They included affected body regions, severity of dystonia, and differences in opinion among investigators. We set out to conceptualize a similar study with a comparable sample size, just focusing on CD. We studied the prevalence of neck tremor and manifestations of different types of tremor (irregular/jerky vs. regular/sinusoidal) in CD. The large number of cases and multi-center study design facilitated the identification of factors that influence the prevalence of neck tremor and importantly the ones that determine jerky versus regular tremor in CD. The results provide useful guidance for understanding the nature and nosology of tremulous neck movements in patients with CD.

Methods

Participants

Participants were recruited from 37 sites of the Dystonia Coalition, a part of the NIH Rare Diseases Clinical Research Network.[1] Most sites are in North America (United States and Canada), four in Europe (France, Germany, Italy, United Kingdom) and one in Australia.

We received institutional approval from an ethical standards committee on human experimentation for any protocol using human patients. All participants 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.

Inclusion criteria stated that participants had to have a minimum of 18 years of age and a diagnosis of CD [25]. Any region of the body could be affected, alone or in various combinations (focal, segmental, multifocal, and generalized). Most cases were idiopathic, but a small fraction had associated known genetic etiologies [26]. 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 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 was 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.

Clinical assessment of dystonia and tremor

Clinical assessment of dystonia and tremor has been explained in detail in our previous report [24]. In summary, a standardized form was used to collect data [27]. Experts of movement disorders evaluated the cases, following a standardized and structured neurologic examination [27]. The Global Dystonia Rating Scale (GDRS) [28] was used to assess severity and body distribution of dystonia. The Essential Tremor Rating Assessment Scale (TETRAS) [29] was employed for the assessment of tremors. Tremor was classified as irregular or regular based on Fahn's definition [30].

Characteristics of participants with dystonia

A total of 3,117 patients with non-zero GDRS neck scores were included in this report. The average age at evaluation was 60.1 ± 12.3 years (median 61, range 18–92). The average age at dystonia onset was 46.3 ± 14.7 years (median 48, range 0–82), with an average illness duration of 13.8 ± 12.47 years (median 10, range 0–81). Women (n = 2,257) outnumbered men (n = 860) by a ratio of 2.6 to 1. Most were white (n = 2,892) while others were black (n = 119), Asian (n = 27), American Indian or Alaska Native (n = 17) or of other or unknown/unreported race (n = 62).

1 rarediseasesnetwork.org/cms/dystonia

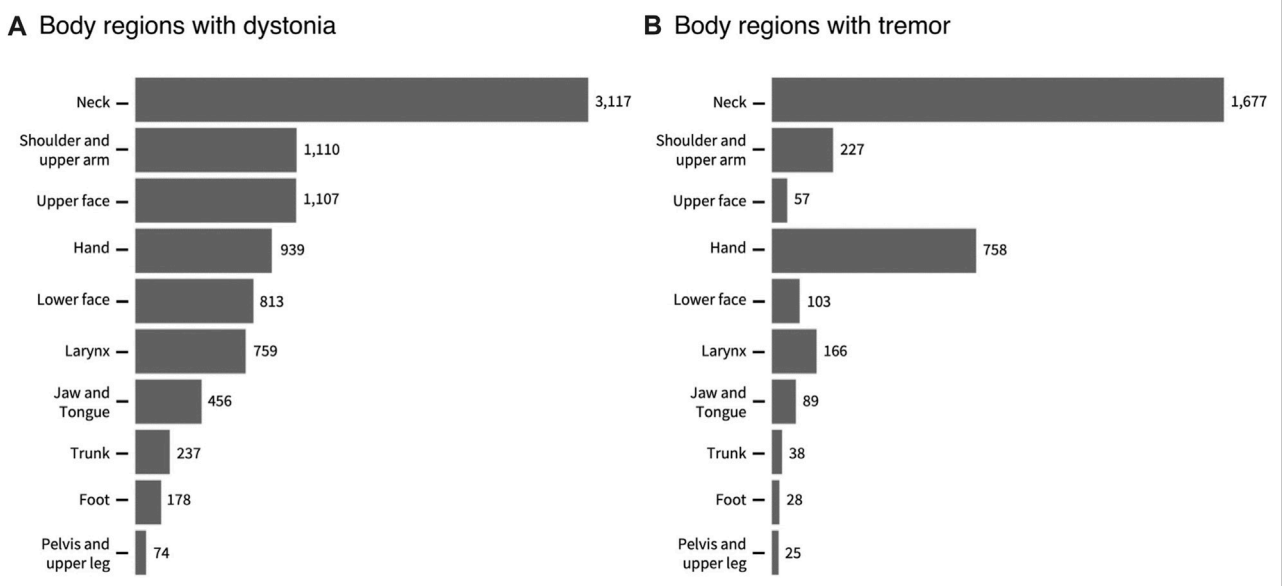

FIGURE 2
A The totals for individual body regions with dystonia **(A)** and tremor **(B)** in 3117 participants with cervical dystonia. The totals may sum up to more than the total number of participants because many participants had more than one body region affected. The numbers in the figures show the actual numbers of participants with each region affected.

In our cohort 2,696 patients were right-handed, 289 patients were left-handed, 95 patients were ambidextrous while handedness of 37 patients was unknown.

Among 3,117 patients with CD, the neck dystonia was isolated in 1,791 but some had segmental dystonia (n = 681), multifocal dystonia (n = 160), generalized dystonia (n = 96), or hemidystonia (n = 10). Average dystonia severity as assessed with GDRS total score was 9.18 ± 7.88 (median 7, range 1–113) with a mean GDRS neck score 4.55 ± 2.16 (median 4, range 1–10). The distribution of body regions with dystonia and tremor can be seen in Figures 2A, B.

In this cohort of 3117 individuals with CD, the overall prevalence of any type of tremor (regular or irregular or both) in any body region was 60%. At total of 37.8% of the cohort had focal CD. Based on the highest non-neck GDRS score, 31.4% of the cohort had additional limb dystonia (upper and lower extremities combined, including shoulder). 20.14% also had cranial dystonia affecting upper and lower face, tongue, or jaw. 8.24% had laryngeal dystonia, and 2.41% had pelvis/trunk dystonia.

Data analysis

Binomial logistic regression models with a logit link function were used to evaluate the clinical characteristics predictive of neck tremor and to determine the important features distinguishing neck tremor from no tremor. This analysis was also performed for female and male populations, separately, to test whether there are differences between men and women in the features related to neck tremor. Feature importance analyses were done using the Wald test (aka the Wald Chi-Squared Test) which was applied to each parameter of the model to test whether it has a significant contribution to the model. Clustering analyses were performed to identify cohort subgroups with common clinical features found significantly important in predicting the occurrence of neck tremor.

Binomial logistic regression models were also deployed to identify the important clinical characteristics associated with regular neck tremor in CD compared to the irregular type, as well as the ones related to regular neck tremor relative to no tremor. For a tremor case to be classified as "regular," the patient had to have either no other body part affected with tremor, or if they had other body parts affected with tremor, they had to be of regular type. Similarly, for a tremor case to be classified as "irregular," the patient had either no other body part with tremor, or other body parts affected with tremor also had irregular tremor type. The patients with mixed regular and irregular tremor were excluded from this analysis.

Results

Overall prevalence of neck tremor

To identify the important clinical characteristics associated with neck tremor in CD, we considered the patients with neck GDRS scores larger than zero. We aggregated the cases where dystonia was focal, multi-focal, segmental, or generalized (N =

TABLE 1 Summary of the results of the logistic regression models applied to the entire cohort (N = 2,999, top), to the female group (N = 2,115, middle) and to the male group (N = 712, bottom) formed by patients recruited by sites with equal or more than 20 patients. Significant factors are listed. Standardized coefficients are reported for continuous factors and odds ratios for categorical factors (with 95% confidence intervals).

Predictor	Std. Coefficient (95%)	Odds ratio (95% CI)	*p*-Value
Binomial multiple logistic regression analysis of Neck Tremor vs. No Neck Tremor—Entire Cohort			
GDRS neck	0.318 (0.236–0.401)		<0.001*
Dystonia duration	0.285 (0.201–0.371)		<0.001*
Age	0.218 (0.135–0.302)		<0.001*
GDRS other	−0.218 (−0.322–−0.118)		<0.001*
Dystonia location (Ref: non-focal CD)		1.183 (0.974–1.436)	0.090
Race (Ref: White)			
Black		0.661 (0.435–0.992)	0.048*
Other		0.705 (0.444–1.108)	0.133
Sex (Ref: Female)		0.736 (0.619–0.875)	<0.001*
Handedness (Ref: Right)			
Ambidextrous		0.922 (0.593–1.437)	0.718
Left		0.906 (0.695–1.182)	0.4665
Unknown		0.904 (0.441–1.862)	0.7827
Site (Ref: Median site with 52.06% prevalence rate)			
Site 18		2.601 (1.320–5.464)	0.008*
Site 30		0.032 (0.002–0.158)	<0.001*
Site 27		0.254 (0.083–0.645)	0.008*
Site 29		0.228 (0.083–0.567)	0.002*
Site 19		0.493 (0.243–0.971)	0.044*
Site 20		0.201 (0.076–0.469)	<0.001*
Binomial multiple logistic regression analysis of Neck Tremor vs. No Tremor—Female Patients			
GDRS neck score	0.274 (0.178–0.372)		<0.001*
Dystonia duration	0.267 (.169–0.367)		<0.001*
Age	0.244 (.148–0.341)		<0.001*
GDRS other	−0.260 (−.379–−0.146)		<0.001*
Dystonia location (Ref: non-focal CD)		1.227 (0.976–1.542)	0.080
Race (Ref: White)			
Black		0.593 (0.364–0.951)	0.032*
Other		0.672 (0.379–1.174)	0.1663
Handedness (Ref: Right)			
Ambidextrous		0.954 (0.553–1.657)	0.867
Left		0.822 (0.600–1.128)	0.2244
Unknown		0.447 (0.179–1.066)	0.0736
Site (Ref: Median site with 52.06% prevalence rate)			
Site 18		3.016 (1.439–6.842)	0.005*
Site 26		5.743 (1.590–36.852)	0.022*
Site 10		1.805 (1.038–3.203)	0.039*
Site 30		0.060 (0.003–0.329)	0.008*
Site 27		0.350 (0.112–0.919)	0.046*
Site 4		1.683 (1.115–2.552)	0.014*
Site 3		1.482 (1.018–2.166)	0.041*

(Continued on following page)

TABLE 1 (*Continued*) Summary of the results of the logistic regression models applied to the entire cohort (N = 2,999, top), to the female group (N = 2,115, middle) and to the male group (N = 712, bottom) formed by patients recruited by sites with equal or more than 20 patients. Significant factors are listed. Standardized coefficients are reported for continuous factors and odds ratios for categorical factors (with 95% confidence intervals).

Predictor	Std. Coefficient (95%)	Odds ratio (95% CI)	*p*-Value
Binomial multiple logistic regression analysis of Neck tremor vs. No Neck Tremor—Male Patients			
GDRS neck score	.480 (0.306–0.660)		<0.001*
Dystonia duration	.339 (0.159–0.525)		<0.001*
Age	.216 (0.039–0.396)		0.018*
GDRS other	−.229 (−0.468–−0.019)		0.044*
Dystonia location (Ref: non-focal CD)		1.115 (0.742–1.672)	0.598
Race (Ref: White)			
Black		1.135 (0.469–2.684)	0.775
Other		0.664 (0.279–1.490)	0.3338
Handedness (Ref: Right)			
Ambidextrous		1.032 (0.460–2.314)	0.9392
Left		1.139 (0.676–1.915)	0.6241
Site (Ref: Median site with 52.06% prevalence rate)			
Site 8		0.210 (0.089–0.469)	<0.001*
Site 7		0.418 (0.185–0.928)	0.033*
Site 9		0.281 (0.113–0.658)	0.004*
Site 6		0.305 (0.138–0.656)	0.003*
Site 17		0.332 (0.116–0.888)	0.032*
Site 5		0.390 (0.172–0.868)	0.022*
Site 19		0.179 (0.052–0.533)	0.003*

3117). 18 records with incomplete information (one age, two dystonia duration, and 15 GDRS scores) were discarded from the analysis. The remaining complete records (N = 2,999) were included into an GLM analysis to examine the relationship between neck tremor (two levels for presence and absence of neck tremor) and patient attributes including age, duration of dystonia, total neck GDRS score, total non-neck GDRS score, race (three levels for white, black, and other), sex (two levels for male and female), recruitment site (30 sites, each having minimum 20 patients), handedness (four levels for ambidextrous, left, right, and unknown) and dystonia location (two levels, one level for focal CD with zero GDRS score in body parts other than the neck, and another level for non-focal CD). Continuous attributes (age, duration, neck, and non-neck GDRS scores) were standardized by subtracting the mean and dividing by the standard deviation. The GLM was a binomial logistic regression with a logit link function:

$$\textit{Neck tremor}\,(Y/N) \sim \textit{Age} + \textit{Dystonia duration} + \textit{Neck GDRS} + \textit{Non-neck GDRS} + \textit{Dystonia type} + \textit{Race} + \textit{Sex} + \textit{Site} + \textit{Handedness}.$$

The logistic regression model with the listed predictors fitted significantly better than the null model (likelihood ratio test, Chi-squared = 350.32, $p < 0.001$). Analysis of variance for the model's individual terms is summarized in Table 1 (standardized regression coefficients are reported for numerical predictors and odds ratios for categorical variables). Figure 3A depicts the significantly important features that distinguish between neck tremor and no neck tremor conditions considering the entire cohort with CD. We found that severity of neck dystonia as assessed with neck GDRS score was the most important patient characteristic predicting neck tremor (standardized coefficient = 0.318 (0.236–0.401), $p < 0.001$). High CD severity was related to increased likelihood of neck tremor. The next most important predictors of neck tremor were dystonia duration and age, which were also associated with increased neck tremor prevalence (duration: 0.285 (0.201–0.371), age: 0.218 (0.135–0.302), $p < 0.001$). The negative coefficient of non-neck GDRS (total score minus neck score) indicated that severity of dystonia in other parts of the body was associated with decreased likelihood of neck tremor. Sex was also significant in predicting neck tremor. Compared to females, males were 0.736 times less likely to have neck tremor, suggesting a heightened risk of neck tremor for female patients. Site, i.e., the investigator bias, was a significant, but the least important predictor of neck tremor prevalence. The comparison was made with the reference site, revealing the

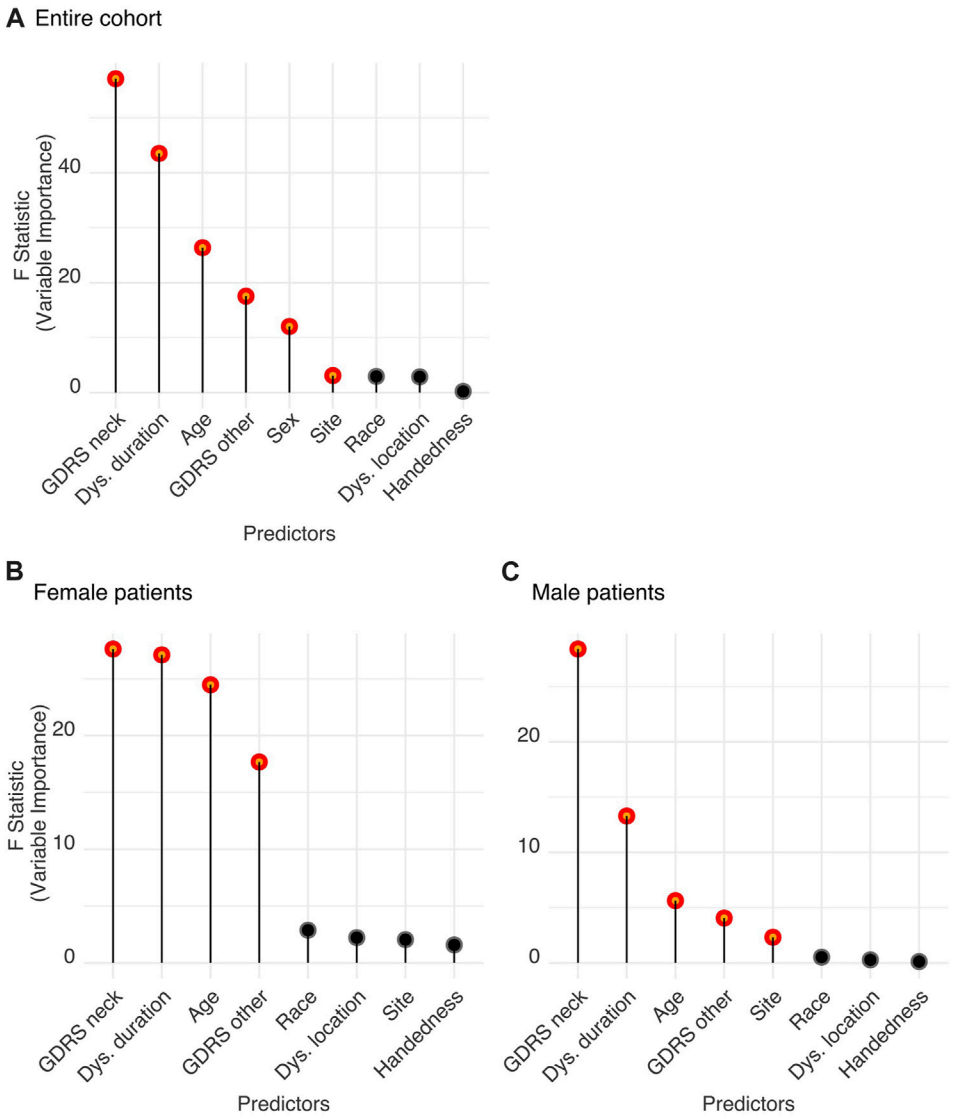

FIGURE 3
(A) Features relevant for neck tremor in the CD population. **(B,C)** Features relevant for neck tremor in **(B)** female and **(C)** male patients. Significant features predicting tremor were determined by Wald tests. Significant parameters (shown in red) are significantly different from zero and produce a statistically significant decline in the logistic regression model once removed. The impact of each parameter is estimated by the length of the line. Non-significant features are shown in black.

significant differences between six sites and the reference site with 52.06% neck tremor prevalence rate (see the odds ratios in Table 1). Race, dystonia location and handedness were not significant in predicting neck tremor ($p > 0.05$).

Additionally, we performed another logistic regression analysis to further examine the role of the second body part affected by dystonia in predicting the prevalence of neck tremor. We contrasted the following dystonia combinations to the isolated CD:

(1) neck + cranial region (including face, tongue, and jaw),
(2) neck + larynx,
(3) neck + limbs (including upper and lower extremities),
(4) neck + pelvis/trunk.

We found that CD with additional cranial symptoms significantly decreased the likelihood of neck tremor [OR (95% CI) = 0.632 (0.491–0.81), $p < 0.001$] while dystonia affecting the larynx in addition to the neck increased the likelihood of neck tremor [OR (95% CI) = 1.47 (1.056–2.058), $p = 0.024$]. Additional limb or pelvis/trunk dystonia did not have a significant influence on neck tremor ($p > 0.05$).

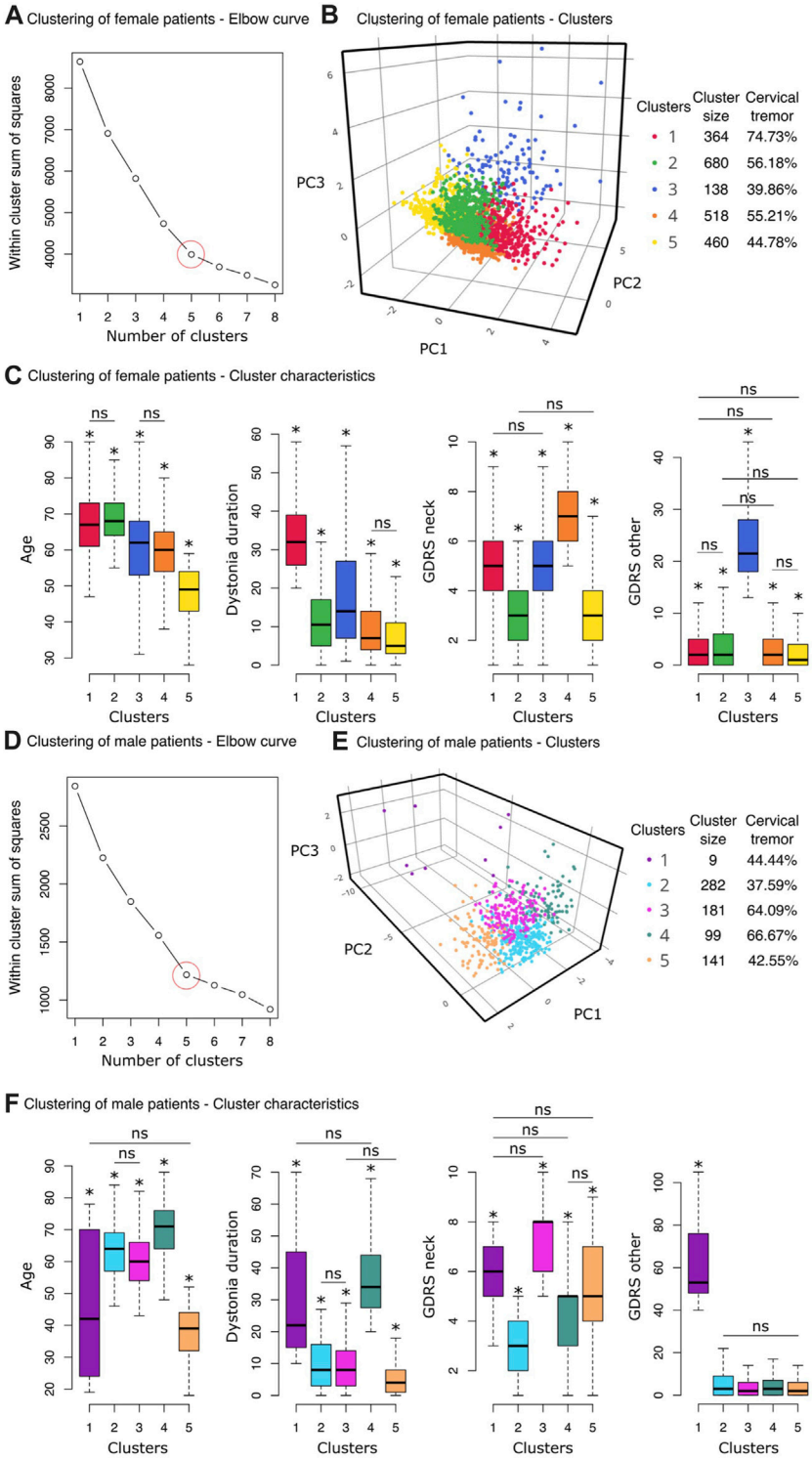

FIGURE 4
Clustering analyses results. **(A–C)** Clustering of female patients. **(A)** The Elbow method was used to find the optimum number of clusters, k. Within-cluster sum of squares (the sum of squared distance between each point and the centroid in a cluster) are plotted for a range of number of clusters (k = [1,8]). At k = 5, the slope of the graph changes, creating an elbow shape. This point was considered to be the optimal number of clusters for the female group. **(B)** The three-dimensional scatter plot displays the first three principal components of the five clusters detected by the k-means clustering algorithm (for interactive plot: https://chart-studio.plotly.com/~sinoscope/125). Cluster sizes and neck tremor prevalence rates of the clusters are shown in the legend. **(C)** Boxplots from left to right show age, dystonia duration, CD severity (GDRS neck) and non-CD severity

(*Continued*)

FIGURE 4 (Continued)
(GDRS other) distributions of the 5 clusters. An asterisk above a box indicates a statistically significant pair-wise difference between that box and all the others except for the pairs marked with "ns." **(D–F)** Clustering of male patients. **(D)** k = 5, where the graph makes an elbow shape, was considered to be the optimal number of clusters for the male cohort. **(E)** The three-dimensional scatter plot displays the first three principal components of the four clusters detected by the k-means clustering algorithm (for interactive plot: https://chart-studio.plotly.com/~sinoscope/131). Neck tremor prevalence rates of the clusters are shown in the legend. **(F)** Boxplots (from left to right) demonstrate age, dystonia duration, CD severity (GDRS neck) and non-CD severity (GDRS other) distributions of the 5 clusters. An asterisk above a box indicates a statistically significant pair-wise difference between that box and all the others except for the pairs marked with "ns."

TABLE 2 Summary of the characteristics of the clusters formed by a K-means clustering algorithm applied to female and male patients. There were five optimum clusters for each of these populations with meaningfully distinctive clinical features. Values represent the mean ± standard deviation. Sample sizes and neck tremor rates (within cluster, in percentages) are also noted for each cluster.

Cluster characteristics - female patients						
Clusters	**Size**	**Neck tremor prevalence (%)**	**Age**	**Dystonia duration**	**CD severity (GDRS neck)**	**Other dystonia severity (GDRS other)**
1	364	74.73	67.20 ± 9.10	34.16 ± 10.01	5.06 ± 3.67	2.97 ± 1.67
2	680	56.18	68.45 ± 6.39	11.40 ± 7.57	3.01 ± 3.83	3.41 ± 1.19
3	138	39.86	59.77 ± 13.10	17.92 ± 14.53	5.09 ± 10.86	24.79 ± 2.12
4	518	55.21	59.43 ± 8.74	9.16 ± 6.74	6.79 ± 3.73	2.95 ± 1.19
5	460	44.78	47.49 ± 8.64	7.64 ± 6.57	3.23 ± 3.93	2.72 ± 1.34
Cluster characteristics—Male Patients						
Clusters	**Size**	**Neck tremor prevalence (%)**	**Age**	**Dystonia duration**	**CD severity (GDRS neck)**	**Other dystonia severity (GDRS other)**
1	9	44.44	45.22 ± 23.93	32.22 ± 22.09	5.89 ± 1.76	62.89 ± 23.50
2	282	37.59	63.55 ± 8.63	9.75 ± 7.18	3.04 ± 1.31	5.60 ± 6.40
3	181	64.09	60.52 ± 8.18	9.43 ± 7.34	7.48 ± 1.25	3.39 ± 4.07
4	99	66.67	69.31 ± 9.90	36.58 ± 11.14	4.48 ± 1.76	5.09 ± 6.01
5	141	42.55	37.72 ± 7.81	5.99 ± 6.25	4.99 ± 2.02	4.10 ± 6.26

Clustering of the cohort based on the features predicting neck tremor

A K-means clustering analysis was applied using the statistically significant features of the logistic regression analysis reported in the previous section. Although recruitment site was found significant, it was excluded from the clustering analysis with which we aimed to consider only phenotypically relevant patient characteristics associated with dystonia. The clustering algorithms (K-means as well as other Gower-distance based methods) were found to be sensitive to the only categorical variable in the feature set: sex. All algorithms first grouped the cohort into two groups based on sex. Hence, we performed two independent clustering analyses: one for female and another for male sub-cohort, to be able to more accurately distinguish the subgroups based on the other important neck tremor-predicting features. The four significant predictors of neck tremor: CD severity (measured by GDRS of neck), dystonia duration, age, and non-CD severity (measured by GDRS non-neck) were included in the clustering analysis (as shown in Figure 3B for female and Figure 3C male patient data and detailed in Table 1).

The elbow method, which is an optimization method that finds the smallest number of clusters (k) accounting for the largest amount of variation in the data, was applied to the female subcohort. The optimum number of distinct groups appeared to be five (Figure 4A, circled in red). A three-dimensional scatterplot of the first three principal components (Figure 4B) illustrates the five clusters with prevalence of neck tremor varying from 39.86% (Cluster 3) to 74.73% (Cluster 1). The characteristics of the clusters are summarized in Table 2.

We carried out pairwise comparisons between the clusters for the four features used in the clustering of female patients (mean and standard deviations are in Table 2, pairwise comparison statistics in Supplemental Material). The difference was considered significant at $p < 0.001$ after correcting for multiple comparisons following Tukey's method. Asterisks in Figure 4C demonstrate the significant difference of the designated cluster from the other clusters except the pairs marked with "ns" for statistically non-significant difference. Cluster 1, which has the highest neck tremor prevalence (74.73%) among female patients, was distinguished with the longest dystonia duration (Mean ± SD: 34.16 ± 10.01 years) (Figure 4C). However, this cluster, which contained the oldest female patients along with Cluster 2, had only the second highest average CD severity (GDRS neck score: 5.06 ± 3.67). On the other hand, Cluster 4 with 55.21% neck tremor prevalence had significantly the highest CD severity among female patients (GDRS neck score: 6.79 ± 3.73). Cluster 5 was distinct from the other clusters by its highest non-CD severity (GDRS other: 24.79 ± 2.12). All other pairs were statistically similar in this feature. The youngest female patients (47.49 ± 8.64 years) were clustered into Cluster 5 which had 44.78% neck tremor prevalence (Figure 4C). The other characteristics of this cluster also took the lowest values among the other clusters. Cluster 2, with a slightly higher neck tremor rate of 56.18%, shared the lowest rank in CD severity with Cluster 5 (3.01 ± 3.83 and 3.23 ± 3.93) while having significantly higher average age than Cluster 5 (68.45 ± 6.39 vs. 47.49 ± 8.64).

For male patients, the elbow method also revealed five clusters as the optimum number of distinct subgroups (Figure 4D, circled in red). A three-dimensional scatterplot of the first three principal components (Figure 4E) illustrates the five clusters with prevalence of neck tremor varying from 37.59% (Cluster 2) to 66.67% (Cluster 4). The characteristics of the clusters are summarized in Table 2.

Pairwise comparisons were carried out between the clusters for the four features used in the clustering of male patients (mean and standard deviations are in Table 2, pairwise comparison statistics in Supplemental Material). The cluster with the minimum neck tremor prevalence rate of 37.59%, Cluster 2, contained the male patients with the minimum CD severity (3.04 ± 1.31) as well as the lowest dystonia duration (9.75 ± 7.18, together with Cluster 3) and lowest non-CD severity (5.60 ± 6.40, together with Clusters 3, 4, and 5) (Figure 4F). On the other hand, Cluster 4 had the highest neck tremor prevalence rate of 66.67% with the highest age (69.31 ± 9.90) and dystonia duration (36.58 ± 11.14 years) (together with Cluster 1) but not the highest cervical or non-CD severity (Figure 4F). Cluster 1, which has a neck tremor prevalence rate of 44.44% among male patients, was distinguished with the highest non-CD severity (62.89 ± 23.50) (Figure 4F). Cluster 3 with a neck tremor rate of 64.09% contained the male patients with the highest CD severity scores (7.48 ± 1.25, together with Cluster 1). Youngest patients (37.72 ± 7.81, together with Cluster 1) with lowest dystonia durations (5.99 ± 6.25, together with Cluster 3) were grouped into Cluster 5, which had a neck tremor rate 42.55% (Figure 4F).

Neck tremor regularity

Regular vs. irregular neck tremor

To identify the important clinical characteristics associated with regular neck tremor in CD compared to the irregular type, we included 1,367 patients from the cohort who have CD as well as neck tremor. These patients had a complete set of clinical features available and were recruited in sites with more than 20 patients. The percentages of patients with regular and irregular neck tremor were 25.24% and 74.76%, respectively.

The imbalance between the number of samples with regular and irregular neck tremor cases (1,022 irregular vs. 345 regular cases) may bias the logistic regression model towards the majority group. To overcome this imbalance, we drew a sample data set from the irregular neck tremor group with the size comparable to the size of the regular neck tremor group. This under-sampling process was carried out with stratification on the entire set of variables to make sure feature distributions were preserved (confirmed visually as well as by two-sample t-tests with $p > 0.05$). The resulting data set had a size of 539 patients (257 irregular vs. 282 regular cases). A GLM analysis was used to predict the relationship between regularity of neck tremor (compared to irregularity) and patient attributes including age, duration of dystonia, CD severity (GDRS neck), non-CD severity (GDRS other), race (three levels for white, black, and other), sex (two levels for male and female), recruitment site (11 sites), and dystonia location (two levels, one level for isolated CD and another level for non-isolated CD). Continuous attributes were standardized. The GLM was a binomial logistic regression with a logit link function:

$$\textit{Neck tremor type}\,(\textit{Regular}/\textit{Irregular}) \sim \textit{Age} + \textit{Dystonia duration} + \textit{GDRS neck} + \textit{GDRS other} + \textit{Dystonia location} + \textit{Race} + \textit{Sex} + \textit{Site}$$

The logistic regression model with the listed predictors fitted data significantly better than the null model (likelihood ratio test, $Chi^2 = 180.71$, $p < 0.001$). Analysis of variance for the model's individual terms is summarized in Table 3 (standardized regression coefficients are reported for numerical predictors and odds ratios for categorical variables). Important features are also displayed in Figure 5A with red. We found that non-CD severity was the most important patient characteristic predicting tremor regularity (standardized coefficient: 0.498 (−0.853 to −0.193), $p = 0.003$). High non-CD severity was related to decreased likelihood of regular neck tremor (i.e., increased likelihood of irregularity). The next most

TABLE 3 Summary of the results of the logistic regression models for factors differentiating regular from irregular tremor (top table) and regular from no tremor (bottom table). Significant factors are listed. Standardized coefficients are reported for continuous factors and odds ratios for categorical factors (with 95% confidence intervals).

Binomial multiple logistic regression analysis of regular vs. Irregular neck tremor			
Predictor	**Std. Coefficient (95%)**	**Odds ratio (95% CI)**	***p*-Value**
GDRS neck	−0.324 (−0.567–−0.088)		0.008*
Dystonia duration	−0.335 (−0.570–−0.108)		0.004*
Age	0.057 (−0.163–0.279)		0.612
GDRS other	−0.498 (−0.853–−0.193)		0.003*
Dystonia location (Ref: Non-isolated)		0.856 (0.496–1.458)	0.572
Race (Ref: White)			
Black		0.116 (0.005–0.972)	0.088
Other		0.728 (0.125–4.049)	0.715
Sex (Ref: Female)		1.109 (0.678–1.816)	0.681
Site (Ref: median site with 52.06% prevalence rate)			
Site 4		0.078 (0.012–0.293)	0.001*
Site 6		2.519 (1.065–6.078)	0.037
Site 2		15.782 (7.139–36.468)	<0.001*
Binomial multiple logistic regression analysis of Regular vs. No Neck tremor			
Predictor	Std. Coefficient (95%)	Odds Ratio (95% CI)	*p*-value
GDRS neck	0.141 (−0.064–0.347)		0.177
Dystonia duration	0.095 (−0.110–0.302)		0.366
Age	0.332 (0.123–0.547)		0.002*
GDRS other	−0.523 (−0.827–−0.248)		<0.001*
Dystonia location (Ref: Non-isolated)		0.831 (0.492–1.389)	0.483
Race (Ref: White)			
Black		0.215 (0.0319–0.853)	0.054
Other		0.824 (0.189–3.214)	0.784
Sex (Ref: Female)		0.881 (0.571–1.360)	0.566
Site (Ref: median site with 52.06% prevalence rate)			
Site 4		0.189 (0.028–0.730)	0.034*
Site 3		2.402 (1.192–4.920)	0.015*
Site 2		4.644 (2.412–9.108)	<0.001*

important predictor of neck tremor regularity was site. Out of 10 sites, two sites were associated with increased neck tremor regularity (one 2.519 (1.065–6.078) times and the other 15.782 (7.139–36.468) times) and one site with decreased neck tremor regularity (0.078 (0.012–0.293) times) compared the reference site with 52.06% tremor prevalence rate (the reference site used in the tremor vs. no tremor analysis) (Table 3). Dystonia duration [−0.335 (−0.570 to −0.108), $p = 0.004$] and CD severity [−0.324 (−0.567 to −0.088), $p = 0.008$] were the other features significantly distinguishing regular from irregular neck tremor. High values were associated with increased irregularity in neck tremor. Race, dystonia location, age, and sex were not found significant in differentiating regular from irregular neck tremor ($p > 0.05$).

Regular versus no neck tremor

We also investigated the important clinical characteristics associated with regular neck tremor in CD compared to the condition where no body part is affected with tremor. We included 1,531 patients from the cohort with either regular neck tremor ($n = 1,186$) or without *any* tremor ($n = 345$). These patients had a complete set of clinical features available

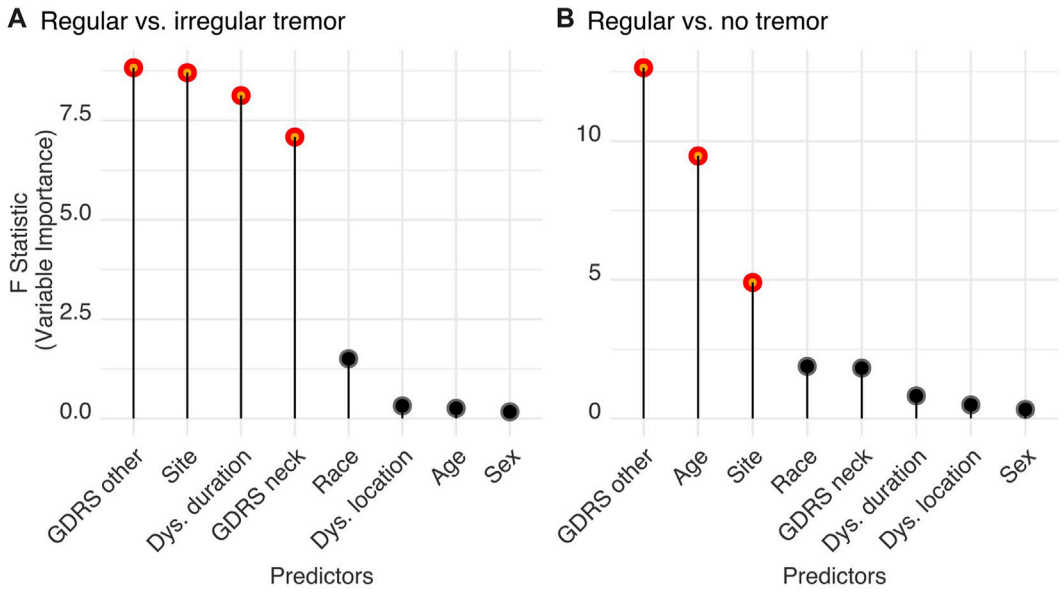

FIGURE 5
Features significantly distinguish **(A)** regular from irregular neck tremor, and **(B)** regular neck tremor from no tremor. Significant features (shown in red) are significantly different from zero as tested using Wald tests and produce a statistically significant decline in the logistic regression model once removed. The impact of each parameter is estimated by the length of the line. Non-significant features are shown in black.

and were recruited in sites with at least 20 patients. The percentage of patients with regular neck tremor and without tremor were 22.53% and 77.47% respectively.

Analogous to the previous analysis, we attempted to remove a potential bias that may emerge from the imbalance in the data by drawing a sample set from the no tremor group with the size comparable to the size of the regular neck tremor group. Sampling was done with stratification on the entire set of included variables to make sure feature distributions were protected (confirmed visually and by two-sample t-tests with $p > 0.05$). The resulting data set had 576 patients (284 no tremor vs. 292 regular cases). Age, duration of dystonia, CD severity (GDRS neck), non-CD severity (GDRS other), race (three levels for white, black, and other), sex (two levels for male and female), recruitment site (12 sites), and dystonia location (two levels, one level for isolated and another level for non-isolated CD) were included in a GLM model after the standardization of continuous attributes. The GLM was a binomial logistic regression with a logit link function:

$$\begin{aligned} &\textit{Neck tremor type}\ (\textit{Regular}/\textit{No Tremor}) \sim \textit{Age} \\ &+ \textit{Dystonia duration} + \textit{GDRS neck} + \textit{GDRS other} \\ &+ \textit{Dystonia location} + \textit{Race} + \textit{Sex} + \textit{Site} \end{aligned}$$

The logistic regression model with the listed predictors fitted significantly better than a null model (likelihood ratio test, Chisq = 148.67, $p < 0.001$). Results are summarized in Table 3; Figure 5B. Similar to the previous analysis, non-CD severity was again the most important patient characteristic distinguishing regular neck tremor from no tremor [−0.523 (−0.827 to −0.248), $p < 0.001$]. High non-CD severity was related to decreased likelihood of regular neck tremor (or increased likelihood of no neck tremor). The second most important feature predicting regular neck tremor with respect to no tremor condition was age—higher age predicted increased likelihood of regular neck tremor [0.332 (0.123–0.547), $p = 0.002$]. Site was also found significantly important for regular neck tremor. Out of 11 sites, two sites had significantly more patients with regular neck tremor than patients with no tremor compared to the reference site with 52.06% tremor prevalence rate [one site 2.402 (1.192–4.920) times and the other site 4.644 (2.412–9.108) times]. One site had significantly less regular neck tremor cases than no tremor in contrast to the reference site [0.189 (0.028–0.730) times]. Race, CD severity, dystonia duration, dystonia location, and sex were not found significant in differentiating regular irregular neck tremor from no tremor ($p > 0.05$).

Discussion

This is a prospective, multi-center investigation involving sites from North America, Europe, and Asia, examining the prevalence and semiology of clinically apparent neck tremors in patients with CD. Tremor is common in dystonia, and it is highly prevalent in focal forms such as CD [24]. There is a varying co-prevalence rate of tremor and dystonia and the rate depends on

factors such as the body regions affected with dystonia, age and duration of dystonia, severity of dystonia, and importantly how the tremor is defined and the investigators' threshold on labeling the given movement as "tremor" [24]. Our study found that severity of CD, increased dystonia duration and age, as well as female sex positively correlate with presence of neck tremor. Indeed neck tremor at disease onset represents a clinically distinguishable subtype of CD affecting predominantly older women, with worse ataxia and milder dystonia than the non-tremulous dystonic phenotype [31–33]. We also found that neck tremor is less likely to be present in CD if dystonia also exists elsewhere other than the neck. Increased severity of neck dystonia is not only associated with presence of neck tremor, but also with irregular tremor type. Here we address these findings and explain how they may facilitate the understanding of the dystonia-tremor relationship.

Clinical factors relevant to the prevalence of neck tremor in CD

The co-prevalence of tremor and dystonia have specific patterns and are influenced by several factors. For example, limb essential tremor is commonly associated with dystonia of head/neck and voice [34–37]. In line with prior studies [38, 39], we found that the prevalence of neck tremor depended on other factors such as age, as well as the duration and the severity of CD. We found robust variability in prevalence of tremor depending on how it was diagnosed. Such variability was also present in the very common CD [24]. It is also likely that threshold for diagnosing tremor varies across different investigators. The variation is even more robustly present for dystonic tremor, independent of the definition followed for diagnosis [40]. These between-investigator differences may explain the discrepancies among recent studies that included very similar cohorts of dystonia patients, using the same definitions for tremor [38, 39].

This study presents analytical results from the largest cohort of systematically evaluated CD patients available to date. The cohort is multi-center, involving multiple races, and ethnicities. The design of this study suggests that the conclusions are not influenced by issues related to small cohort size, non-representative subtypes of dystonia or tremor, or investigator bias for diagnosis and evaluations. Nevertheless, we also acknowledge some limitations of this study. The major limitation is the dependency of neck tremor detection threshold on clinical evaluation. There are more sensitive methods for detecting tremor including objective techniques such as kinematic tools [41–43] or electromyography [44–46]. These methods are much more sensitive than clinical examination alone [47]. Therefore, it is possible that the actual neck tremor prevalence is much higher than clinically estimated in this study.

Another limitation is related to the ongoing controversy over the definition of "dystonic tremor" and the lack of systematic and consistent evaluation for a "null point," which is characteristic feature of dystonic tremor [2]. Our design considered both commonly used definitions independently. It focused on the key differences in the diagnostic criteria such as regularity, jerkiness, and concurrence with dystonia. We found that despite the evidence-based approach, varying opinions among investigators influenced the impressions for labeling a tremor as "irregular" or "jerky." Varying opinions also influenced the diagnostic threshold for diagnosing a movement as "tremor" or labeling tremulous movements in body regions concordant with dystonia. In these situations, instrumented measures may better discriminate the characteristics of tremor [42, 43] and could be useful to determine the true prevalence of each type.

The third limitation was that the study relied on data recorded by the investigators at a recruitment site without the verification of an independent second evaluation. Although all investigators used the same protocol for evaluation, thresholds for diagnosing tremor clearly vary among investigators. Future studies may benefit from more objective and independent methods. Despite these weaknesses, the results provide the most comprehensive picture of tremor in subjects with CD currently available.

Biological factors relevant to neck tremor in CD

There is a high prevalence of tremor in CD, and increasing evidence suggests overlapping biological mechanisms. For instance, it is a common observation that an individual who has isolated tremor for many years can present with dystonia movements in same or another body part [48–50]. It is also possible that patients who have "pure" dystonia for a long time can present with emergence of tremor [49, 50]. There are studies showing common anatomical substrates for tremor and dystonia. Common tremor syndromes result from abnormal functioning of cerebellar circuits [51, 52]. The cerebellum has an important role in motor network causing dystonia [53–56], and particularly CD. A PET study using fluoro-deoxyglucose revealed multiple significant abnormalities when comparing patients with dystonia or essential tremor with normal controls [57]. These abnormalities overlap considerably among the dystonia and tremor groups. Patients with tremor [58] or dystonia [59, 60] have similar histopathological abnormalities affecting the cerebellum, such as loss of Purkinje neurons and torpedo inclusion bodies. A recent study identified physiological similarities in pallidal single unit responses in patients who have jerky, "dystonic tremor" and torsion neck dystonia [22].

Our study also found differences in predictors of tremor and dystonic tremor in male versus female patients. Such differences depict sex-specific distinctions in the pathophysiology of tremor and dystonia. Genetic and family studies provide further insights into shared biological mechanisms of dystonia and tremor [35, 61–64]. Although some such cases may represent misdiagnoses,

it seems more likely that the occurrence of tremor syndromes with "dystonia" genes represents the sometimes highly varied pleiomorphic clinical phenotypes associated with monogenic and oligogenic variants. Our study found differences in the predictors of tremor and dystonic tremor in male versus female patients. These findings point toward sex-specific differences in the pathophysiology of tremor and dystonia. In sum, we evaluated a large dystonia cohort and identified the most relevant clinical features that can predict concurrent tremor and its irregularity. Our results provide a more complete description of CD and may help improve care in CD and other forms of dystonia.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Emory University and Washington University IRB, Central IRB. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

The work was supported in part by grants to the Dystonia Coalition, a consortium of the Rare Diseases Clinical Research Network (RDCRN) that is supported by the Office of Rare Diseases Research (ORDR) at the National Center for Advancing Clinical and Translational Studies (NCATS; U54 TR001456) in collaboration with the National Institute for Neurological Diseases and Stroke (NINDS; U54 NS065701, U54 NS116025). Aasef Shaikh received a Dystonia Medical Research Foundation (DMRF) Research Grant. Shaikh is also supported by VA CSR&D Merit Review (I01 CX002086-01A2) and VA RR&D Merit Review (I01 RX00367-01A2).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Fahn S. The varied clinical expressions of dystonia. *Neurol Clin* (1984) 2(3): 541–54. doi:10.1016/s0733-8619(18)31090-9

2. Vu JP, Cisneros E, Zhao J, Lee HY, Jankovic J, Factor SA, et al. From null to midline: changes in head posture do not predictably change head tremor in cervical dystonia. *Dystonia* (2022) 1:10684. doi:10.3389/dyst.2022.10684

3. Deuschl G, Bain P, Brin M, Committee AHS. Consensus statement of the movement disorder society on tremor. *ad hoc* scientific committee. *Mov Disord* (1998) 13(S3):2–23. doi:10.1002/mds.870131303

4. Quinn NP, Schneider SA, Schwingenschuh P, Bhatia KP. Tremor—some controversial aspects. *Mov Disord* (2011) 26(1):18–23. doi:10.1002/mds.23289

5. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? *Arch Neurol* (2006) 63(8): 1100–4. doi:10.1001/archneur.63.8.1100

6. Schneider SA, Edwards MJ, Mir P, Cordivari C, Hooker J, Dickson J, et al. Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs). *Mov Disord* (2007) 22(15):2210–5. doi:10.1002/mds.21685

7. Albanese A, Lalli S. Is this dystonia? *Mov Disord* (2009) 24(12):1725–31. doi:10.1002/mds.22597

8. Lalli S, Albanese A. The diagnostic challenge of primary dystonia: evidence from misdiagnosis. *Mov Disord* (2010) 25(11):1619–26. doi:10.1002/mds.23137

9. Cardoso F. Difficult diagnoses in hyperkinetic disorders – a focused Review. *Front Neurol* (2012) 3:151. doi:10.3389/fneur.2012.00151

10. Macerollo A, Superbo M, Gigante AF, Livrea P, Defazio G. Diagnostic delay in adult-onset dystonia: data from an Italian movement disorder center. *J Clin Neurosci* (2015) 22(3):608–10. doi:10.1016/j.jocn.2014.09.014

11. Tiderington E, Goodman EM, Rosen AR, Hapner ER, Johns MM, Evatt ML, et al. How long does it take to diagnose cervical dystonia? *J Neurol Sci* (2013) 335(1): 72–4. doi:10.1016/j.jns.2013.08.028

12. Stamelou M, Charlesworth G, Cordivari C, Schneider SA, Kägi G, Sheerin UM, et al. The phenotypic spectrum of DYT24 due to ANO3 mutations. *Mov Disord* (2014) 29(7):928–34. doi:10.1002/mds.25802

13. Gövert F, Deuschl G. Tremor entities and their classification: an update. *Curr Opin Neurol* (2015) 28(4):393–9. doi:10.1097/WCO.0000000000000211

14. Elble RJ. What is essential tremor? *Curr Neurol Neurosci Rep* (2013) 13(6):353. doi:10.1007/s11910-013-0353-4

15. Elble RJ. Defining dystonic tremor. *Curr Neuropharmacology* (2013) 11(1): 48–52. doi:10.2174/157015913804999478

16. Albanese A, Sorbo FD. Dystonia and tremor: the clinical syndromes with isolated tremor. *Tremor Other Hyperkinet Mov (N Y)* (2016) 6:319. doi:10.7916/D8X34XBM

17. Hopfner F, Haubenberger D, Galpern WR, Gwinn K, Van't Veer A, White S, et al. Knowledge gaps and research recommendations for essential tremor. *Parkinsonism Relat Disord* (2016) 33:27–35. doi:10.1016/j.parkreldis.2016.10.002

18. Pandey S, Sarma N. Tremor in dystonia. *Parkinsonism Relat Disord* (2016) 29: 3–9. doi:10.1016/j.parkreldis.2016.03.024

19. Louis ED. The evolving definition of essential tremor: what are we dealing with? *Parkinsonism Relat Disord* (2018) 46:S87–91. doi:10.1016/j.parkreldis.2017.07.004

20. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From the task force on tremor of the international Parkinson and movement disorder society. *Mov Disord* (2018) 33(1): 75–87. doi:10.1002/mds.27121

21. Pandey S, Bhattad S, Hallett M. The problem of questionable dystonia in the diagnosis of 'essential tremor-plus.' *Tremor Other Hyperkinet Mov (N Y).* (2020) 10: 27. doi:10.5334/tohm.539

22. Sedov A, Usova S, Semenova U, Gamaleya A, Tomskiy A, Beylergil SB, et al. Pallidal activity in cervical dystonia with and without head tremor. *Cerebellum* (2020) 19(3):409–18. doi:10.1007/s12311-020-01119-5

23. Semenova U, Medvednik R, Popov V, Jinnah HA, Shaikh AG, Sedov A. Neuronal activity of pallidal versus cerebellar receiving thalamus in patients with cervical dystonia. *Cerebellum* (2021) 20(2):151–9. doi:10.1007/s12311-020-01194-8

24. Shaikh AG, Beylergil SB, Scorr L, Kilic-Berkmen G, Freeman A, Klein C, et al. Dystonia and tremor: a cross-sectional study of the dystonia coalition cohort. *Neurology* (2021) 96(4):e563–74. doi:10.1212/WNL.0000000000011049

25. Albanese A, Bhatia K, Bressman SB, DeLong MR, Fahn S, Fung VSC, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* (2013) 28(7):863–73. doi:10.1002/mds.25475

26. LeDoux MS, Vemula SR, Xiao J, Thompson MM, Perlmutter JS, Wright LJ, et al. Clinical and genetic features of cervical dystonia in a large multicenter cohort. *Neurol Genet* (2016) 2:e69. doi:10.1212/NXG.0000000000000069

27. Xiao J, Vemula SR, LeDoux MS. Recent advances in the genetics of dystonia. *Curr Neurol Neurosci Rep* (2014) 14(8):462. doi:10.1007/s11910-014-0462-8

28. LeDoux MS. The genetics of dystonias. *Adv Genet* (2012) 79:35–85. doi:10.1016/B978-0-12-394395-8.00002-5

29. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. *Nat Methods* (2010) 7(4):248–9. doi:10.1038/nmeth0410-248

30. Xiao J, Zhao Y, Bastian RW, Perlmutter JS, Racette BA, Tabbal SD, et al. The c.-237_236GA>TT THAP1 sequence variant does not increase risk for primary dystonia. *Mov Disord* (2011) 26(3):549–52. doi:10.1002/mds.23551

31. Merola A, Dwivedi AK, Shaikh AG, Tareen TK, Da Prat GA, Kauffman MA, et al. Head tremor at disease onset: an ataxic phenotype of cervical dystonia. *J Neurol* (2019) 266(8):1844–51. doi:10.1007/s00415-019-09341-w

32. Mahajan A, Schroder L, Rekhtman A, Dwivedi AK, Wang LL, Espay AJ. Tremor-Dominant cervical dystonia: a cerebellar syndrome. *Cerebellum* (2021) 20(2):300–5. doi:10.1007/s12311-020-01211-w

33. Mahajan A, Gupta P, Jacobs J, Marsili L, Sturchio A, Jinnah HA, et al. Impaired saccade adaptation in tremor-dominant cervical dystonia—evidence for maladaptive cerebellum. *Cerebellum* (2021) 20(5):678–86. doi:10.1007/s12311-020-01104-y

34. Lou JS, Jankovic J. Essential tremor: clinical correlates in 350 patients. *Neurology* (1991) 41(2 Part 1):234–8. doi:10.1212/wnl.41.2_part_1.234

35. Koller WC, Busenbark K, Miner K, Group TETS. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. *Ann Neurol* (1994) 35(6):717–23. doi:10.1002/ana.410350613

36. Whaley NR, Putzke JD, Baba Y, Wszolek ZK, Uitti RJ. Essential tremor: phenotypic expression in a clinical cohort. *Parkinsonism Relat Disord* (2007) 13(6):333–9. doi:10.1016/j.parkreldis.2006.12.004

37. Chen W, Hopfner F, Szymczak S, Granert O, Müller SH, Kuhlenbäumer G, et al. Topography of essential tremor. *Parkinsonism Relat Disord* (2017) 40:58–63. doi:10.1016/j.parkreldis.2017.04.012

38. Defazio G, Jankovic J, Giel JL, Papapetropoulos S. Descriptive epidemiology of cervical dystonia. *Tremor Other Hyperkinet Mov (N Y).* (2013) 3:03. doi:10.5334/tohm.170

39. Erro R, Rubio-Agusti I, Saifee TA, Cordivari C, Ganos C, Batla A, et al. Rest and other types of tremor in adult-onset primary dystonia. *J Neurol Neurosurg Psychiatry* (2014) 85(9):965–8. doi:10.1136/jnnp-2013-305876

40. Becktepe J, Govert F, Balint B, Schlenstedt C, Bhatia K, Elble R, et al. Exploring interrater disagreement on essential tremor using a standardized tremor elements assessment. *Mov Disord Clin Pract* (2021) 8(3):371–6. doi:10.1002/mdc3.13150

41. Rudzińska M, Krawczyk M, Wójcik-Pędziwiatr M, Szczudlik A, Wasielewska A. Tremor associated with focal and segmental dystonia. *Neurologia i Neurochirurgia Polska* (2013) 47(3):223–31. doi:10.5114/ninp.2013.35584

42. Shaikh AG, Wong AL, Zee DS, Jinnah HA. Keeping your head on target. *J Neurosci* (2013) 33(27):11281–95. doi:10.1523/JNEUROSCI.3415-12.2013

43. Shaikh AG, Zee DS, Jinnah HA. Oscillatory head movements in cervical dystonia: dystonia, tremor, or both? *Mov Disord* (2015) 30(6):834–42. doi:10.1002/mds.26231

44. Jedynak CP, Bonnet AM, Agid Y. Tremor and idiopathic dystonia. *Mov Disord* (1991) 6(3):230–6. doi:10.1002/mds.870060307

45. Grosse P, Edwards M, Tijssen Ma. j., Schrag A, Lees AJ, Bhatia Kp., et al. Patterns of EMG–EMG coherence in limb dystonia. *Mov Disord* (2004) 19(7):758–69. doi:10.1002/mds.20075

46. Yianni J, Wang SY, Liu X, Bain PG, Nandi D, Gregory R, et al. A dominant bursting electromyograph pattern in dystonic conditions predicts an early response to pallidal stimulation. *J Clin Neurosci* (2006) 13(7):738–46. doi:10.1016/j.jocn.2005.07.022

47. Haubenberger D, Abbruzzese G, Bain PG, Bajaj N, Benito-León J, Bhatia KP, et al. Transducer-based evaluation of tremor. *Mov Disord* (2016) 31(9):1327–36. doi:10.1002/mds.26671

48. Jankovic J, Leder S, Warner D, Schwartz K. Cervical dystonia: clinical findings and associated movement disorders. *Neurology* (1991) 41(7):1088–91. doi:10.1212/wnl.41.7.1088

49. Pal PK, Samii A, Schulzer M, Mak E, Tsui JKC. Head tremor in cervical dystonia. *Can J Neurol Sci* (2000) 27(2):137–42. doi:10.1017/s0317167100052240

50. Defazio G, Gigante AF, Abbruzzese G, Bentivoglio AR, Colosimo C, Esposito M, et al. Tremor in primary adult-onset dystonia: prevalence and associated clinical features. *J Neurol Neurosurg Psychiatry* (2013) 84(4):404–8. doi:10.1136/jnnp-2012-303782

51. Raethjen J, Deuschl G. The oscillating central network of Essential tremor. *Clin Neurophysiol* (2012) 123(1):61–4. doi:10.1016/j.clinph.2011.09.024

52. Louis ED. Essential tremor and the cerebellum. *Handb Clin Neurol* (2018) 155:245–58. doi:10.1016/B978-0-444-64189-2.00016-0

53. Neychev VK, Gross RE, Lehéricy S, Hess EJ, Jinnah HA. The functional neuroanatomy of dystonia. *Neurobiol Dis* (2011) 42(2):185–201. doi:10.1016/j.nbd.2011.01.026

54. Prudente CN, Hess EJ, Jinnah HA. Dystonia as a network disorder: what is the role of the cerebellum? *Neuroscience* (2014) 260:23–35. doi:10.1016/j.neuroscience.2013.11.062

55. Jinnah HA, Neychev V, Hess EJ. The anatomical basis for dystonia: the motor network model. *Tremor Other Hyperkinet Mov (N Y)* (2017) 7:506. doi:10.7916/D8V69X3S

56. Shakkottai VG, Batla A, Bhatia K, Dauer WT, Dresel C, Niethammer M, et al. Current opinions and areas of consensus on the role of the cerebellum in dystonia. *Cerebellum* (2017) 16(2):577–94. doi:10.1007/s12311-016-0825-6

57. Belenky V, Stanzhevsky A, Klicenko O, Skoromets A. Brain positron emission tomography with 2-18F-2-deoxi-D-glucose of patients with dystonia and essential tremor detects differences between these disorders. *Neuroradiol J* (2018) 31(1):60–8. doi:10.1177/1971400917719912

58. Louis ED. Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. *Lancet Neurol* (2010) 9(6):613–22. doi:10.1016/S1474-4422(10)70090-9

59. Ma K, Babij R, Cortés E, Vonsattel JG, Louis ED. Cerebellar pathology of a dual clinical diagnosis: patients with essential tremor and dystonia. *Tremor Other Hyperkinet Mov (N Y)* (2012) 2:12. doi:10.5334/tohm.94

60. Prudente CN, Pardo CA, Xiao J, Hanfelt J, Hess EJ, LeDoux MS, et al. Neuropathology of cervical dystonia. *Exp Neurol* (2013) 241:95–104. doi:10.1016/j.expneurol.2012.11.019

61. Jankovic J, Beach J, Pandolfo M, Patel PI. Familial essential tremor in 4 kindreds: prospects for genetic mapping. *Arch Neurol* (1997) 54(3):289–94. doi:10.1001/archneur.1997.00550150047015

62. Shatunov A, Sambuughin N, Jankovic J, Elble R, Lee HS, Singleton AB, et al. Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23. *Brain* (2006) 129(9):2318–31. doi:10.1093/brain/awl120

63. Hedera P, Phibbs FT, Fang JY, Cooper MK, Charles PD, Davis TL. Clustering of dystonia in some pedigrees with autosomal dominant essential tremor suggests the existence of a distinct subtype of essential tremor. *BMC Neurol* (2010) 10(1):66. doi:10.1186/1471-2377-10-66

64. Louis ED, Hernandez N, Alcalay RN, Tirri DJ, Ottman R, Clark LN. Prevalence and features of unreported dystonia in a family study of "pure" essential tremor. *Parkinsonism Relat Disord* (2013) 19(3):359–62. doi:10.1016/j.parkreldis.2012.09.015

DYSTONIA

TYPE Original Research
PUBLISHED 09 October 2024
DOI 10.3389/dyst.2024.12551

OPEN ACCESS

EDITED BY
Pattamon Panyakaew,
Chulalongkorn University, Thailand

*CORRESPONDENCE
Aparna Wagle Shukla,
aparna.shukla@neurology.ufl.edu

RECEIVED 11 December 2023
ACCEPTED 17 September 2024
PUBLISHED 09 October 2024

CITATION
Jabarkheel Z and Wagle Shukla A (2024) Clinical and physiological characteristics of tremor in a large cohort of focal and segmental dystonia. *Dystonia* 3:12551.
doi: 10.3389/dyst.2024.12551

Clinical and physiological characteristics of tremor in a large cohort of focal and segmental dystonia

Zakia Jabarkheel and Aparna Wagle Shukla*

Department of Neurology, University of Florida College of Medicine, Gainesville, FL, United States

Objective: Tremor is a frequent co-occurring feature in patients with dystonia, especially in focal and segmental dystonia. Clinical studies have shown that tremor is more commonly observed when dystonia spreads to contiguous body regions. However, there is insufficient characterization of tremor physiology in focal and segmental forms of dystonia. We aimed to ascertain the characteristics of tremor presenting in these specific subtypes.

Methods: We enrolled dystonia patients with head and arm tremors presenting to our center. We categorized these participants as focal and segmental dystonia following the Movement Disorders Society guidelines. We recorded the frequency, amplitude, rhythmicity, burst duration, and discharge pattern on accelerometer and electromyography recordings. We compared the physiology of tremors in focal vs. segmental dystonia. We determined whether the physiology was affected by clinical features such as demographics, age at onset, dystonia duration, alcohol responsiveness, family history, and botulinum toxin responsiveness.

Results: 72 patients, mainly focal cervical dystonia and focal cervical + arm or cranial dystonia (segmental) were enrolled. In the analysis of the head tremor recordings (n = 66; frequency range 3–6.5 Hz), we found that focal vs. segmental dystonia comparisons revealed a significantly lower frequency (mean $\pm$ standard deviation; 4.0 $\pm$ 0.9 Hz vs. 4.7 $\pm$ 1.0 Hz; p = 0.02), lower amplitude (0.004 $\pm$ 0.008 g^2/Hz vs. 0.006 $\pm$ 0.008 g^2/Hz; p = 0.03) and longer muscle burst durations (111.1 $\pm$ 40.4 ms vs. 91.5 $\pm$ 24 ms; p = 0.04). In the analysis of arm tremor recordings (n = 31; frequency range 3.5–7 Hz), we found focal vs. segmental dystonia comparison revealed a lower amplitude (0.04 $\pm$ 0.07 g^2/Hz vs. 0.06 $\pm$ 0.06 g^2/Hz; p = 0.045). In the stepwise regression analysis, the age at evaluation (β - 0.44; p = 0.006) and age at onset (β - 0.61; p = 0.005) significantly predicted the head tremor frequency whereas the alcohol responsiveness tended to predict the amplitude of the head tremor (β - 0.5; p = 0.04) and the arm tremor (β - 0.6; p = 0.02).

Conclusion: Our study found that the physiological characteristics of tremor in focal and segmental dystonia are somewhat distinct, suggesting that the spread of dystonia symptoms from one body region to another may have a bearing on the physiology of co-occurring tremor. The frequency of head tremors in

younger participants was observed to be higher compared to older participants. The head and arm tremor tended be less severe in patients reporting alcohol responsiveness.

KEYWORDS

dystonic tremor, physiology, head tremor, arm tremor, focal dystonia, cervical dystonia, segmental dystonia

Introduction

According to many recent clinical studies, tremor is frequently observed to affect patients with dystonia [1–4]. Tremor manifests more commonly in females and is mostly observed during posture maintenance and kinetic tasks, but in some can present even when the body part is at rest [5, 6]. The Movement Disorders Society (MDS) provides guidelines to classify dystonia [7] and tremor according to the clinical and etiological characteristics (clinical and etiological axis). An important classification feature for dystonia is body distribution and the tremor are more common in focal and segmental dystonia compared to generalized or multifocal dystonia. Tremor is even more prevalent when there is a spread of dystonia symptoms [3]. While the optimal definition (or term) for tremor in dystonia requires further refinement, the MDS consensus statement from 2018 describes dystonic tremor as tremor and dystonia affecting the same body part, and tremor associated with dystonia as the tremor and dystonia affecting different body parts [8]. Although a number of studies have reported data on the prevalence of tremors in dystonia, a detailed clinical phenomenological and physiological characterization is lacking. In this study we describe the clinical and physiological characteristics of head and arm tremor observed in a large cohort of dystonia. These patients were categorized into focal and segmental dystonia groups and physiological characteristics were compared. We then examined whether the tremor physiology was influenced by clinical features such as demographics, age at onset for dystonia, duration of dystonia, family history, alcohol responsiveness, and botulinum toxin responsiveness for clinical symptoms.

Methods

We used an IRB approved protocol to prospectively enroll dystonia patients with a co-occurring tremor presenting at the University of Florida. The diagnosis of dystonia was confirmed by a movement disorder neurologist following the MDS criteria. We assessed the characteristics of head and arm tremor in patients categorized as focal dystonia (symptoms in a single body region) and segmental dystonia (symptoms in two contiguous body regions). The participants were diagnosed with focal cervical dystonia, focal arm dystonia and segmental dystonia comprising of cervical + arm or cervical + cranial dystonia (involving face, jaw, eyes). Head and arm tremors were noted to involve the same or different body regions affected by dystonia. Tremor and dystonia were considered to involve the same body region when there was evident abnormal neck posturing, restricted range of movements and a null point was observed during physical examination in the case of head tremor and features such as arm posturing (splaying and spooning of fingers, thumb hyperextension), shoulder elevation, tremor with a directional character, and a null point was observed in the case of an arm tremor [9–11]. When tremor presented in the contiguous body segment but without the above mentioned dystonic features, we considered the patients to be in the focal dystonia category [12, 13]. For example, focal cervical dystonia patients with arm tremor that was non-dystonic or focal arm dystonia with head tremor that was non-dystonic were categorized as focal dystonia.

Participants were required to withhold their oral medications (at least 8 h) prescribed for treating dystonia and/or tremor and those recruited from botulinum toxin clinic were examined at three or more months after the last round of botulinum toxin injections. We ensured participants did not have comorbidities such as hyperthyroidism, diabetes, and active psychiatric diseases that contribute to enhanced physiological tremor. The clinical characteristics of tremor were recorded during rest, maintenance of posture, and kinetic tasks. Rest tremor was assessed while the participants were lying supine with the head and arms resting. The kinetic head component was assessed when participants were instructed to turn their heads to the extreme right or left, and the kinetic arm component was assessed with participants holding a pen and approximating a dot marked on a sheet placed in front of them. For the postural head component participants were sitting on a chair and instructed to look straight ahead in a neutral position, keeping the head off the wall and trunk of the backrest. The postural arm component was assessed with arms, and hands outstretched at 90° from vertical, keeping parallel to the ground with the palms facing down and the fingers spreading slightly apart. Using the Fahn-Tolosa-Marin standardized rating scale (head and arm tremor items) the tremor amplitude was determined to be mild (score 1), moderate (score 2), and severe (score 3 or 4). Further characteristics such as whether the tremor was fine or coarse, or rhythmic or jerky were determined based on clinical visual assessment.

Electrophysiology setup and data acquisition

We used the Trigno™ Wireless system (Delsys, Inc., Massachusetts) consisting of triaxial orthogonal accelerometers for tremor frequency, amplitude, rhythmicity, and sensors for computing electromyography (EMG) burst duration and the discharge pattern. Participants were seated comfortably in an upright chair with a backrest and an armrest. We recorded the physiology of the head and the arm tremor when maintaining a steady posture for 30–60 s (postural component of the tremor). Sensors were mounted over the glabella and on the dorsum of the most affected hand at 1 cm distance proximal to the third metacarpophalangeal joint to capture the accelerometer data. Sensors were also mounted over the agonist and antagonist muscles of the neck (sternocleidomastoid and splenius capitis muscles) and over muscles of the most affected arm (flexor carpi ulnaris, flexor carpi radialis, and extensor carpi ulnaris and extensor carpi radialis) to capture the surface EMG signals. The location for sensor placement was guided by bony landmarks and muscle palpation during active flexion, extension and rotation of cervical joints and flexion and extension of the elbow joints. The placement was further confirmed with inspection of EMG output recorded with Delsys, EMG works software. We ensured there was a consistent sensor placement across individuals. Data for head and arm tremor physiology recorded over three trials was individually analyzed. In a subset of patients with dystonic arm tremor (n = 8), weights (500 g and 1,000 g) were strapped to the dorsum of the hand for examining the effects of inertial loading on the tremor frequency.

Electrophysiology analysis

The EMG data from the sensor was sampled at 1926 Hz, amplified, digitized, and filtered at 20–450 Hz. The raw accelerometer signal was sampled at 148 Hz, digitized and filtered (0–50 Hz), and analyzed to calculate frequency peak, spectral power for amplitude, and half-peak bandwidth of the frequency peak for quantification of rhythmicity. EMG data recorded during three trials was visually inspected, and data contaminated with noise signals was excluded from the final segment selected for offline analysis. We assigned onset and offset markers manually to the EMG bursts for calculation of muscle burst duration. We averaged the EMG burst duration across all muscles for the head tremor and the arm tremor at the participant level and the group level. We coded the pattern of agonist and antagonist EMG discharges as a co-contraction pattern, alternating pattern, or mixed pattern (neither co-contraction nor alternating).

A commercial software (EMG Works analysis) performed Fast Fourier transform (FFT) analysis with the Welch method to generate the frequency peak (auto spectra), also known as power spectral density (PSD). A select data series (10-second epochs) was first divided into overlapping sections of a specified window length and window overlap. Then the squared magnitude of the FFT computed for each section was averaged and zero-padded to identify the dominant frequency peak. A baseline shift sometimes observed in raw accelerometer signals due to a limb sway relative to the gravity (de trending and re-zeroing) was calculated with a PSD script [14]. A peak spectral power for the tremor was derived off-line by squaring and summating the peaks of frequency power in x, y, and z-axes and calculating the square root of the summated power [15]. A cycle-to-cycle variability in the frequency was achieved by calculating half-peak bandwidth; width of the spectral peak at one-half the peak amplitude in the power spectrum (wider bandwidth of frequency peak indicating a more irregular tremor) [16]. The analysis of tremor physiology was performed by investigators blinded to the clinical findings.

Statistical analysis for the physiological data was performed using SPSS version 28 with significance set to a threshold of $p < 0.05$. The mean, standard deviation (SD), and range for each physiological measure was calculated at the individual and group level. Based on normality distribution assessed with the Shapiro-Wilkes test, we used non-parametric tests such as Mann-Whitney test for the focal vs. segmental dystonia and tremor and dystonia affecting same or different body region comparisons. We used stepwise linear regression analysis with bootstrapping (to account for skewed distribution) to determine the effects of demographics and dystonia characteristics (age at onset and evaluation, dystonia duration, alcohol responsiveness, family history, and botulinum toxin responsiveness) on the tremor physiology (frequency, amplitude, half-peak bandwidth, and EMG burst duration). The type I error rates for multiple comparisons were also corrected with Holm-Bonferroni method, which adjusts p values for each hypothesis with a range of significance thresholds (0.01–0.008).

Results

Patient characteristics

72 patients (8 males, 64 females) participated. There were 28 patients with head tremor alone, 38 patients with head + arm tremor and six patients with arm tremor alone (66 patients or 91% with head tremor and 31 patients or 36% with arm tremor). Based on the body distribution of dystonia, these patients were classified into focal and segmental dystonia categories (Figure 1; Table 1). While the majority of patients would be classified as having dystonic tremor, only a few fit the category of tremor associated with dystonia. These patients had nondystonic arm tremor associated with cervical dystonia and dystonic head tremor (n = 6) or nondystonic head tremor associated with arm dystonia and dystonic arm tremor (n = 3).

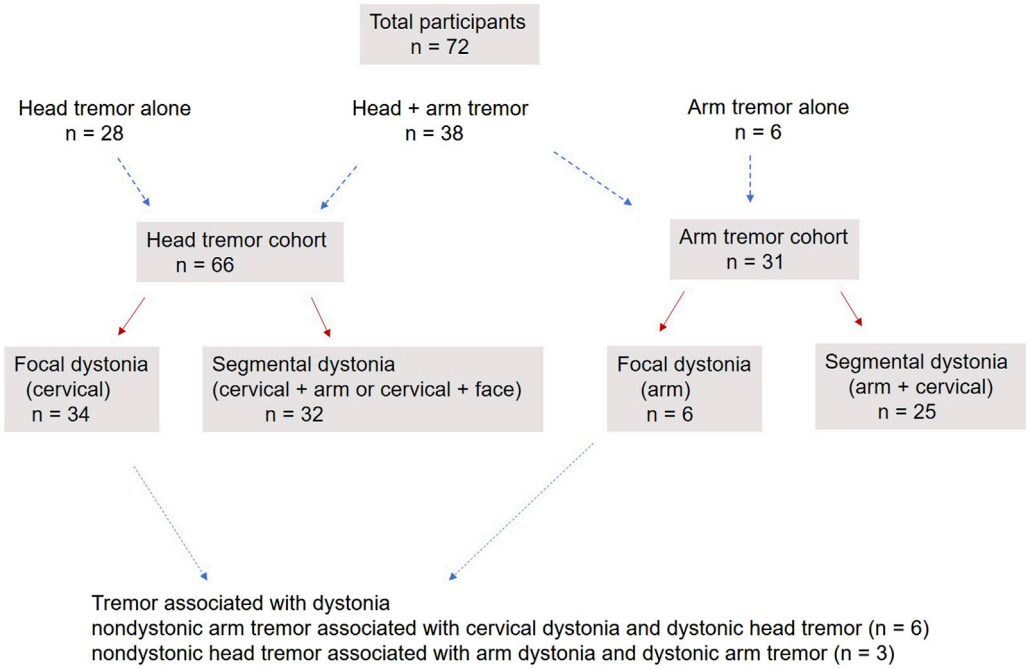

FIGURE 1
The figure illustrates the participants enrolled in the cohort with head tremors, arm tremors, or both. It shows the distribution of participants into focal and segmental dystonia categories. The figure also shows the number of patients meeting the criterion for tremor associated with dystonia.

The mean (±SD) age for the cohort was 67.1 ± 9.2 years, the mean age at onset for dystonia symptoms was 49.5 ± 16.1 years, and the mean duration of symptoms was 17.6 ± 12.4 years. Most participants (n = 68) reported that tremors presented around the same time as dystonia symptoms. Dystonia manifested before tremor for three patients and tremor manifested before dystonia for two patients; however, the time interval between the two clinical features was less than a decade. 60 out of 72 patients were recruited from our botulinum toxin clinic and 90% of patients endorsed improvements with botulinum treatments. Nearly 50% of the cohort reported a positive family history for dystonia, 25% reported their tremor improved with alcohol (subjective self-report) and 75% reported improvement with botulinum toxin injections. The clinical profile for the participants categorized as focal and segmental dystonia (mostly similar) is presented in Table 1.

In the clinical assessment of head tremor, there were 34 patients with focal cervical dystonia (6 patients had nondystonic arm tremor) and 32 patients with segmental dystonia (cervical + arm or cervical + face). A postural component was observed in all 66 patients (80%), kinetic component in 57 (80%) patients, whereas the resting component was seen in 25 (37%) patients. Head tremor was mostly mild (54%) or moderate (28%) in intensity and had a fine and rhythmic character in nearly 2/3rd (68%) of the cohort. Head tremor manifested before arm tremor in more than 75% of patients.

In the clinical assessment of arm tremor, there were six patients with focal arm dystonia (3 patients had non-dystonic head tremor) and 25 patients with segmental dystonia (arm + cervical) Arm tremor was distal in distribution in more than 90% of patients. The postural component was seen in all 100% of participants, the kinetic component in 80%, and the resting component seen in only 36% of the patients. More than 30% of patients presenting with arm tremor had a unilateral tremor. In patients with bilateral tremors, more than 90% of patients had a remarkably asymmetric tremor (amplitude difference between the two arms greater than two points). More patients had a fine, rhythmic or sinusoidal tremor compared to coarse, irregular or jerky arm tremor.

Physiological characteristics of head and arm tremor

The physiological characteristics of head and arm tremors are charted in Table 2. The mean ± SD frequency for the head tremor was 4.4 Hz ± 1.0 (range 3–6.5 Hz). While the study aims did not involve direct comparisons between head and arm tremor, the accelerometer-based frequency of head tremor (4.4 ± 1.0 Hz; range 3.3–5 Hz) was slightly lower than the arm tremor (5.3 ± 0.9 Hz; range 3.5–7 Hz), the accelerometer amplitude for the head tremor (0.005 ±

TABLE 1 Demographics and clinical profile and clinical characteristics of tremor.

Demographics and clinical profile	n = 72		
Age in years, mean ± SD	67.1 ± 9.2		
Sex, male/female	8/64		
Age at onset in years, mean ± SD	49.5 ± 16.1		
Disease duration in years, mean ± SD	17.6 ± 12.4		
Alcohol responsiveness, n (%)	19 (26)		
Family history of dystonia, n (%)	33 (46)		
Botulinum toxin responsiveness, n (%)	56 (78)		
	Total	**Focal dystonia**	**Segmental dystonia**
Head tremor characteristics	n = 66	n = 34	n = 32
Rest/Posture/Kinetic (n)	25/66/57	12/34/32	13/32/29
Mild/Moderate/Severe (n)	39/20/7	14/6/4	20/11/1
Fine/Coarse (n)	43/23	21/13	22/10
Rhythmic/Jerky (n)	45/21	25/9	20/12
Arm tremor characteristics	n = 31	n = 6	n = 25
Rest/Posture/Kinetic (n)	13/31/25	5/6/6	6/25/20
Mild/Moderate/Severe (n)	5/22/4	2/3/1	8/15/2
Fine/Coarse (n)	17/14	3/3	14/11
Rhythmic/Jerky (n)	14/12	7/3	8/8
Unilateral/Bilateral (n)	11/20	3/3	8/17
Symmetric/Asymmetric (when bilateral) (n)	5/15	1/2	5/12

0.009 g^2/Hz) was lower than the arm tremor (0.05 ± 0.7 g^2/Hz) and the average duration for EMG bursts was shorter for the neck muscles (101.5 ± 31.5 ms) compared to the arm muscles (128.5 ± 39.3 ms). However, the head tremor and the arm tremor had similar half peak bandwidth (0.55 ± 0.09 Hz). In the EMG recordings, three patterns of contractions were observed in the agonist-antagonist pair: synchronous or co-contraction pattern, alternating contraction, and a mixed discharge pattern (a combination of co-contraction and alternating pattern). In more than 80% of the patients, mixed pattern was the dominant pattern for both head and arm tremor recordings. Inertial loading at the wrist did not change the arm tremor frequency but lowered the amplitude measured with the accelerometer and EMG. Figure 2 illustrates the power spectrum analysis of head tremor and arm tremors and EMG tracings recorded from one of the participants.

Comparisons of focal vs. segmental dystonia

Focal dystonia vs. segmental dystonia comparisons revealed that the head tremor frequency (4.0 ± 0.9 Hz vs. 4.7 ± 1.0 Hz; p = 0.01) and amplitude (0.004 ± 0.008 vs. 0.006 ± 0.008; p = 0.015) was lower and the EMG burst duration longer (111.1 ± 40.4 ms vs. 91.5 ± 24 ms; p = 0.04). Furthermore, comparisons for the arm tremor data revealed a lower amplitude (p = 0.045) in focal dystonia (0.04 ± 0.07) compared to segmental dystonia (0.06 ± 0.06). The remaining data comparisons for tremors did not reach statistical significance.

Comparisons when tremor and dystonia involving same or different body regions

We had six patients with focal cervical dystonia and non-dystonic arm tremor, all of whom also exhibited head tremor. Similarly, we had three patients with focal arm dystonia and non-dystonic head tremor, and these patients also experienced arm tremor. When comparing patients with tremor physiology affecting the same or different body regions impacted by dystonia, our analyses did not produce significant findings, except for a notable finding regarding the head tremor frequency (4.0 ± 0.9 vs. 5.0 ± 0.3; p = 0.01) (Table 3). However, considering the highly uneven sample sizes in the two comparison groups, the reliability and validity of the results will need to be interpreted with caution.

Factors impacting physiology of head and arm tremors

In the stepwise regression analysis, the age at evaluation (β - 0.44; p = 0.006) and age at onset (β - 0.61; p = 0.005) significantly predicted the head tremor frequency whereas the alcohol responsiveness tended to predict the amplitude of the head tremor (β - 0.5; p = 0.04) and the arm tremor (β - 0.6; p = 0.02). Figure 3. The other physiological features were not observed to have significant predictors.

Discussion

Our cohort mainly comprised of cervical dystonia, there was a preponderance of middle-aged females, 25% of patients reported alcohol sensitivity, and most patients reported

TABLE 2 Electrophysiological characterization of head and arm tremors.

	Participants	Focal dystonia	Segmental dystonia	p-value *indicates significance
Head tremor	n = 66	n = 34	n = 32	
Frequency in Hz, mean ± SD	4.4 ± 1.0	4.0 ± 0.9	4.7 ± 1.0	0.01*
Amplitude in g^2/Hz, mean ± SD	0.005 ± 0.009	0.004 ± 0.008	0.006 ± 0.008	0.015*
Half peak bandwidth/irregularity in Hz, mean ± SD	0.6 ± 0.41	0.5 ± 0.24	0.6 ± 0.42	0.37
EMG burst duration in ms, mean ± SD	101.5 ± 31.5	111.1 ± 40.4	91.5 ± 24.1	0.04*
EMG pattern, synchronous/mixed/alternating	7/50/9	3/25/6	3/23/6	
Arm tremor	n = 31	n = 6	n = 25	
Frequency in Hz, mean ± SD	5.3 ± 0.9	5.2 ± 0.9	5.3 ± 1.1	0.35
Amplitude in g^2/Hz, mean ± SD	0.05 ± 0.7	0.04 ± 0.07	0.06 ± 0.06	0.045*
Half peak bandwidth/irregularity in Hz, mean ± SD	0.5 ± 0.49	0.5 ± 0.44	0.5 ± 0.32	0.61
EMG burst duration in ms, mean ± SD	128.5 ± 39.3	127.2 ± 40.2	130.3 ± 38.1	0.21
EMG pattern, synchronous/mixed/alternating	3/21/7	1/4/1	2/17/6	

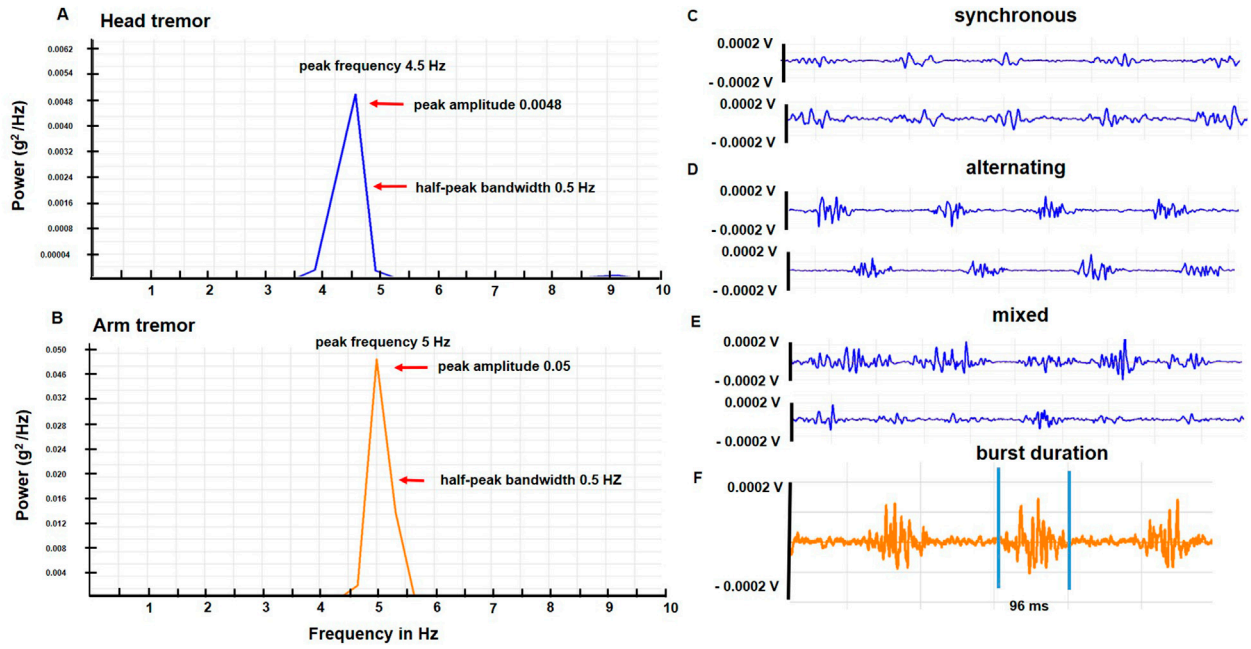

FIGURE 2
(A, B) illustrate power spectrum analysis for the head and arm tremor accelerometer recordings, respectively conducted in one of the participants. The arrows point to the peak frequency, amplitude, and half-peak bandwidth. **(C–E)** are sample EMG tracings from a patient with a dystonic head tremor that illustrates the three discharge patterns (synchronous, alternating, and mixed) **(F)** Reveals the burst duration of EMG discharge from a sample arm tracing.

simultaneous onset around 50 years of age for tremor and dystonia symptoms. These findings are consistent with those reported in the past [5]. While patients consistently presented with a postural and kinetic component, the resting component for tremor was seen for patients presenting with a head and/or an arm tremor in nearly 40% of patients as reported in previous studies [6, 15]. The head tremor manifested before the arm tremor in the majority of patients, and the arm tremor was

TABLE 3 Electrophysiology with tremor and dystonia involving same or different body regions.

	Tremor & dystonia in same body region	Tremor & dystonia in different body regions	p-value * indicates significance
Head tremor			
	n = 66	n = 3	
Frequency in Hz, mean ± SD	4.0 ± 0.9	5.0 ± 0.3	0.01*
Amplitude in g^2/Hz, mean ± SD	0.005 ± 0.009	0.006 ± 0.006	0.11
Half peak bandwidth/irregularity in Hz, mean ± SD	0.5 ± 0.8	0.5 ± 0.6	0.75
EMG burst duration in ms, mean ± SD	101.3 ± 35.3	99.5 ± 14.2	0.054
Arm tremor			
	n = 31	n = 6	
Frequency in Hz, mean ± SD	5.0 ± 0.1	5.7 ± 0.8	0.06
Amplitude in g^2/Hz, mean ± SD	0.06 ± 0.1	0.04 ± 0.1	0.051
Half peak bandwidth/irregularity in Hz, mean ± SD	0.5 ± 0.3	0.5 ± 0.4	0.81
EMG burst duration in ms, mean ± SD	132.4 ± 40.3	127.2 ± 31.8	0.21

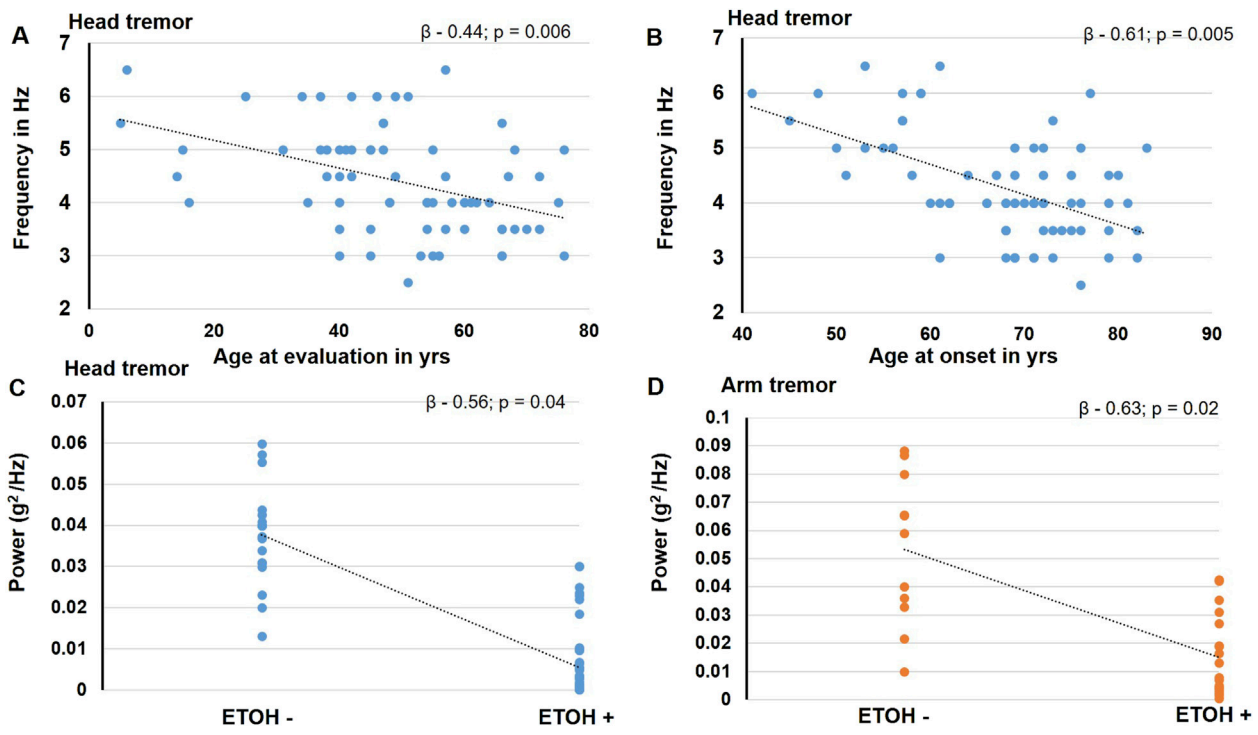

FIGURE 3
The figure illustrates the findings noted to be significant in the stepwise regression analysis. The blue circles represent data for head tremor findings, and the orange circles represent data for the arm tremor findings. The age at evaluation **(A)** and age at onset **(B)** is found to predict the head tremor frequency significantly. Alcohol responsiveness is found to significantly predict the amplitude of the head tremor **(C)** and the arm tremor **(D)**.

distinctly unilateral in a third of patients. Patients in our cohort were relatively younger, had tremor onset at an earlier age, and had a longer duration of symptoms than earlier reports [3].

Our data analysis confirms that tremor manifesting in dystonia tends to have a low to medium range frequency (4–5 Hz), which is in keeping with the MDS consensus statement [17]. We also found that

tremor arises from medium duration (~100 ms) muscle bursts and a mixed pattern of muscle discharges as the dominant pattern. We also found that the frequency of head tremor was notably higher in younger individuals when compared to their older counterparts. Additionally, individuals reporting alcohol responsiveness tended to experience less severe head and arm tremors.

Tremor in focal dystonia vs. segmental dystonia

Natural history studies have ascertained that dystonia patients with focal onset symptoms can experience a spread of symptoms into contiguous body regions during the course of their disease [18] The spread of dystonia symptoms occurs in greater than 20% of patients, and the risk of spread is higher in patients who have a tremor [12, 19, 20]. An important goal of the study was to probe whether the clinical nosologic classification into focal and segmental dystonia categories also reflected a distinct physiological segregation, as this would facilitate development of more specific treatments in future [10]. Our study found that many physiological aspects of tremor in focal dystonia such as the frequency, amplitude and muscle burst duration of the head tremor and the amplitude of the arm tremor was distinguishable from segmental dystonia. Future imaging studies are necessary to elucidate the brain networks specific to focal and segmental dystonia. Although the brain networks for dystonia and tremor are likely distinct, they probably interact to some extent, considering they share anatomical structures such as the cerebellum and motor cortex. Thus, alterations in the function of the dystonia network could potentially influence the underlying pathophysiology of tremor. For example, functions of the cerebello-thalamo-cortical pathway might be more involved in segmental dystonia and these may explain our findings of differing tremor physiology in focal dystonia compared to segmental dystonia. Future studies could shed light on the networks that correspond to specific forms of dystonia. In our study, we examined if the physiology was impacted whether tremor and dystonia involved the same or different body parts. Some researchers are concerned that categorizing patients as dystonic tremor or tremor associated with dystonia may not necessarily identify distinct pathophysiological differences [5, 8]. Similarly, in our study, we did not observe significant differences when tremor and dystonia affected the same or different body regions. However, as noted in the results, the uneven distribution of samples limits the strength of these conclusions.

Factors influencing the tremor physiology

We found an inverse relationship between the age at evaluation and the frequency of head tremor, which is similar to essential tremor literature that found the frequency of the tremor decreases with increasing age [21]. We also found that the presence of alcohol (or ethanol) sensitivity tended to be associated with a lower amplitude of the head and arm tremor. In a recent large study involving over 1,000 patients with dystonia, the presence of alcohol responsiveness was seen in nearly 30% of patients with cervical dystonia and was particularly noted in patients with a co-occurring tremor [22]. While the mechanisms underlying the effects of ethanol in dystonia are not known, these have been studied in essential tremor and have been attributed to increased firing of Purkinje cell neurons of the cerebellum through presynaptic effects and decreased firing of the dentate neurons through postsynaptic effects [23–25]. These potential mechanisms could be extended to the dystonia population as there is evidence to support an underlying dysfunction in cerebellum [26–28]. In our recent functional MRI study, the blood oxygen level-dependent activity in the cerebellum and connectivity between the cerebellum and other brain regions was significantly reduced in patients with dystonia and tremor [29]. Thus, the relationship between alcohol responsiveness and the tremor amplitude seen in our study is likely related to the modulation of dentate nucleus pathway of the cerebellum.

Our study examined the effects of inertial loading to determine whether the tremor had a mechanical-reflex component. Previous inertial loading studies found that the mechanical-reflex component could be separated from the 8–12 Hz central component (synchronous modulation of motor unit discharges that are central in origin) in patients with a physiological tremor. In the power spectral analysis, there was an emergence of the mechanical-reflex peak separate from the 8–12 Hz central peak. However, such a separation of two frequency peaks was not seen in essential tremor and Parkinson's disease tremor, lending credence to a central origin for these tremors [30–32]. McAuley et al. found a lowering of the arm tremor amplitude with inertial loading which was also seen in our cohort. However they found the separation of mechanical and central frequencies in two of the six patients studied [33], which was not seen in our patients. These discrepancies could be related to differences in the comorbidity burden; we specifically excluded conditions that could lead to a co-occurring enhanced physiological tremor.

Our study has many strengths, given that the data was collected from one of the largest and well-characterized cohort of patients. Our study advances the physiological understanding of tremor manifesting in dystonia, which can potentially lead to more effective treatments. For example, in patients treated with deep brain stimulation of the ventral intermedius nucleus of the thalamus [34], the selection of stimulation frequency could be adapted and optimized based on the frequency of tremors in keeping with closed-loop neuromodulation principles [35, 36]. Then, differences in tremor physiology between individuals could be leveraged in understanding

variation in the treatment response to neuromodulation. As new drugs are being investigated for treatment, treatments based on neurophysiological characteristics might emerge instead of clinical characteristics. Indeed, a third pathophysiology-based axis of classification has been proposed to guide the effective management of patients [37].

We acknowledge that our study has several limitations, including the lack of longitudinal recordings and the purely clinical assessment of certain characteristics, such as jerky or rhythmic tremors. Additionally, the study lacks physiological assessment of the resting and kinetic components of tremor and does not include tremors in other body parts, such as the jaw and legs. As recommended by the MDS, a sub-classification based on the age of onset for dystonia or temporal pattern of dystonia was not given due consideration. While the recordings were performed off medications, we have not assessed the response of physiological characteristics to medications. Finally, regarding the analysis, we have yet to determine the coherence between signals recorded from homologous muscles of the two sides, as most recordings were for the head tremor and the arm tremor recordings were unilateral in many patients.

In summary, our research identified a significant prevalence of tremors in both focal and segmental dystonia. These tremors were predominantly postural/kinetic, featuring some rest component, and exhibited a tendency towards fine and rhythmic characteristics rather than coarse and jerky movements. The observed distinctions in tremor physiology between focal and segmental dystonia categories indicate that the distribution and spread of dystonia symptoms play a role in shaping tremor features. Our findings also suggest that an earlier age of symptom onset is linked to a higher frequency of head tremor, and alcohol-responsive head and arm tremors tend to be milder. It is important to note that these hypotheses require further examination in larger cohorts. Nevertheless, the intriguing connection between tremor and dystonia networks, along with the impact of disease progression, warrants further research. Tracking these aspects could be achieved through future longitudinal natural history studies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by University of Florida Institutional Review Boards. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZJ and AWS fulfilled the authorship criteria by substantial contributions to the conception of the work, providing data for the work, revisiting it critically for important intellectual content, approving the final version, and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to acknowledge the Tyler's Hope Foundation for dystonia cure.

Conflict of interest

AW reports grant support from the NIH R01NS122943 as PI and Ro1NS121120-01 as a Co-I. She reports past funding from Benign Essential Blepharospasm Research foundation, Dystonia coalition, Dystonia Medical Research foundation, National Organization for Rare Disorders. AW has received consultant fees from Merz, Jazz and Acadia. She is the current Vice President for the Tremor Research Group and recent advisor for Supernus, Encora therapeutics, Fasikl and Biogen-Sage.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Pal PK, Samii A, Schulzer M, Mak E, Tsui JK. Head tremor in cervical dystonia. *The Can J Neurol Sci Le J canadien des Sci neurologiques* (2000) 27:137–42. doi:10.1017/s0317167100052240

2. Rudzińska M, Krawczyk M, Wójcik-Pędziwiatr M, Szczudlik A, Wasielewska A. Tremor associated with focal and segmental dystonia. *Neurologia i neurochirurgia polska* (2013) 47:223–31. doi:10.5114/ninp.2013.35584

3. Defazio G, Gigante AF, Abbruzzese G, Bentivoglio AR, Colosimo C, Esposito M, et al. Tremor in primary adult-onset dystonia: prevalence and associated clinical features. *J Neurol Neurosurg Psychiatry* (2013) 84:404–8. doi:10.1136/jnnp-2012-303782

4. Shaikh AG, Beylergil SB, Scorr L, Kilic-Berkmen G, Freeman A, Klein C, et al. Dystonia and tremor: a cross-sectional study of the dystonia coalition cohort. *Neurology* (2020) 96:e563–e574. doi:10.1212/WNL.0000000000011049

5. Defazio G, Conte A, Gigante AF, Fabbrini G, Berardelli A. Is tremor in dystonia a phenotypic feature of dystonia? *Neurology* (2015) 84:1053–9. doi:10.1212/WNL.0000000000001341

6. Erro R, Rubio-Agusti I, Saifee TA, Cordivari C, Ganos C, Batla A, et al. Rest and other types of tremor in adult-onset primary dystonia. *J Neurol Neurosurg Psychiatry* (2014) 85:965–8. doi:10.1136/jnnp-2013-305876

7. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VSC, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* (2013) 28:863–73. doi:10.1002/mds.25475

8. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From the task force on tremor of the international Parkinson and movement disorder society. *Mov Disord : official J Mov Disord Soc* (2018) 33:75–87. doi:10.1002/mds.27121

9. Rivest J, Marsden CD. Trunk and head tremor as isolated manifestations of dystonia. *Mov Disord : official J Mov Disord Soc* (1990) 5:60–5. doi:10.1002/mds.870050115

10. Quinn NP, Schneider SA, Schwingenschuh P, Bhatia KP. Tremor--some controversial aspects. *Mov Disord : official J Mov Disord Soc* (2011) 26:18–23. doi:10.1002/mds.23289

11. Deuschl G, Heinen F, Guschlbauer B, Schneider S, Glocker FX, Lücking CH. Hand tremor in patients with spasmodic torticollis. *Mov Disord : official J Mov Disord Soc* (1997) 12:547–52. doi:10.1002/mds.870120411

12. Norris SA, Jinnah HA, Espay AJ, Klein C, Brüggemann N, Barbano RL, et al. Clinical and demographic characteristics related to onset site and spread of cervical dystonia. *Mov Disord : official J Mov Disord Soc* (2016) 31:1874–82. doi:10.1002/mds.26817

13. Kilic-Berkmen G, Pirio Richardson S, Perlmutter JS, Hallett M, Klein C, Wagle-Shukla A, et al. Current guidelines for classifying and diagnosing cervical dystonia: empirical evidence and recommendations. *Mov Disord Clin Pract* (2022) 9:183–90. doi:10.1002/mdc3.13376

14. Wagle Shukla A, Lunny C, Hisham I, Cagle J, Malea J, Santos A, et al. Phenomenology and physiology of tacrolimus induced tremor. *Tremor Other Hyperkinet Mov (N Y)* (2023) 13:2. doi:10.5334/tohm.725

15. Shaikh AG, Jinnah HA, Tripp RM, Optican LM, Ramat S, Lenz FA, et al. Irregularity distinguishes limb tremor in cervical dystonia from essential tremor. *J Neurol Neurosurg Psychiatry* (2008) 79:187–9. doi:10.1136/jnnp.2007.131110

16. Elble RJ, McNames J. Using portable transducers to measure tremor severity. *Tremor and other hyperkinetic movements (New York, NY)* (2016) 6:375. doi:10.7916/D8DR2VCC

17. Deuschl G, Bain P, Brin M. Consensus statement of the movement disorder society on tremor. *ad hoc* scientific committee. *Mov Disord : official J Mov Disord Soc* (1998) 13(Suppl. 3):2–23. doi:10.1002/mds.870131303

18. Berman BD, Groth CL, Sillau SH, Pirio Richardson S, Norris SA, Junker J, et al. Risk of spread in adult-onset isolated focal dystonia: a prospective international cohort study. *J Neurol Neurosurg Psychiatry* (2020) 91:314–20. doi:10.1136/jnnp-2019-321794

19. Abbruzzese G, Berardelli A, Girlanda P, Marchese R, Martino D, Morgante F, et al. Long-term assessment of the risk of spread in primary late-onset focal dystonia. *J Neurol Neurosurg Psychiatry* (2008) 79:392–6. doi:10.1136/jnnp.2007.124594

20. Martino D, Berardelli A, Abbruzzese G, Bentivoglio AR, Esposito M, Fabbrini G, et al. Age at onset and symptom spread in primary adult-onset blepharospasm and cervical dystonia. *Mov Disord : official J Mov Disord Soc* (2012) 27:1447–50. doi:10.1002/mds.25088

21. Elble RJ. Essential tremor frequency decreases with time. *Neurology* (2000) 55:1547–51. doi:10.1212/wnl.55.10.1547

22. Junker J, Brandt V, Berman BD, Vidailhet M, Roze E, Weissbach A, et al. Predictors of alcohol responsiveness in dystonia. *Neurology* (2018) 91:e2020–6. doi:10.1212/WNL.0000000000006551

23. Wu J, Tang H, Chen S, Cao L. Mechanisms and pharmacotherapy for ethanol-responsive movement disorders. *Front Neurol* (2020) 11:892. doi:10.3389/fneur.2020.00892

24. Paris-Robidas S, Brochu E, Sintes M, Emond V, Bousquet M, Vandal M, et al. Defective dentate nucleus GABA receptors in essential tremor. *Brain* (2012) 135:105–16. doi:10.1093/brain/awr301

25. Boecker H, Weindl A, Brooks DJ, Ceballos-Baumann AO, Liedtke C, Miederer M, et al. GABAergic dysfunction in essential tremor: an 11C-flumazenil PET study. *J Nucl Med : official Publ Soc Nucl Med* (2010) 51:1030–5. doi:10.2967/jnumed.109.074120

26. Prudente CN, Hess EJ, Jinnah HA. Dystonia as a network disorder: what is the role of the cerebellum? *Neuroscience* (2014) 260:23–35. doi:10.1016/j.neuroscience.2013.11.062

27. Hess CW, Gatto B, Chung JW, Ho RLM, Wang WE, Wagle Shukla A, et al. Cortical oscillations in cervical dystonia and dystonic tremor. *Cereb Cortex Commun* (2020) 1:tgaa048. doi:10.1093/texcom/tgaa048

28. Wagle SA. Basis of movement control in dystonia and why botulinum toxin should influence it? *Toxicon* (2023):107251. doi:10.1016/j.toxicon.2023.107251

29. Dba JCDS, Vaillancourt DE, Shukla AW. Network-level connectivity is a critical feature distinguishing dystonic tremor and essential tremor. *Brain* (2019) 142:1644–59. doi:10.1093/brain/awz085

30. Elble RJ. Central mechanisms of tremor. *J Clin Neurophysiol : official Publ Am Electroencephalographic Soc* (1996) 13:133–44. doi:10.1097/00004691-199603000-00004

31. Wagle SA. Diagnosis and treatment of essential tremor. *Continuum (Minneap Minn)* (2022) 28:1333–49. doi:10.1212/CON.0000000000001181

32. Wagle SA. Reduction of neuronal hyperexcitability with modulation of T-type calcium channel or SK channel in essential tremor. *Int Rev Neurobiol* (2022) 163:335–55. doi:10.1016/bs.irn.2022.02.008

33. McAuley J, Rothwell J. Identification of psychogenic, dystonic, and other organic tremors by a coherence entrainment test. *Mov Disord : official J Mov Disord Soc* (2004) 19:253–67. doi:10.1002/mds.10707

34. Tsuboi T, Jabarkheel Z, Zeilman PR, Barabas MJ, Foote KD, Okun MS, et al. Longitudinal follow-up with VIM thalamic deep brain stimulation for dystonic or essential tremor. *Neurology* (2020) 94:e1073–84. doi:10.1212/WNL.0000000000008875

35. Yamamoto T, Katayama Y, Ushiba J, Yoshino H, Obuchi T, Kobayashi K, et al. On-demand control system for deep brain stimulation for treatment of intention tremor. *Neuromodulation : J Int Neuromodulation Soc* (2013) 16:230–5. discussion 235. doi:10.1111/j.1525-1403.2012.00521.x

36. Tan H, Debarros J, He S, Pogosyan A, Aziz TZ, Huang Y, et al. Decoding voluntary movements and postural tremor based on thalamic LFPs as a basis for closed-loop stimulation for essential tremor. *Brain stimulation* (2019) 12:858–67. doi:10.1016/j.brs.2019.02.011

37. Buijink AWG, van Rootselaar AF, Helmich RC. Connecting tremors - a circuits perspective. *Curr Opin Neurol* (2022) 35:518–24. doi:10.1097/WCO.0000000000001071

DYSTONIA

Dystonia is the official journal of
the Dystonia Medical Research Foundation

The mission of the DMRF is to advance research for more treatments and ultimately a cure, to promote awareness and education, and to support the needs and well being of affected individuals and families.

Discover more of our Special Issues

See more →

fro.ntiers.in/special-issue
frontierspartnerships.org

Contact
+41 (0) 21 510 17 40
dystonia@frontierspartnerships.org