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TITLE OF THE Ph.D. THESIS

THE DIAGNOSIS OF DYSTONIA, AN ISSUE YET TO BE SOLVED

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SUMMARY

According to the most recent consensus update, dystonia is defined as a condition characterized by *"sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation"*. Prevalence of dystonia in general population is probably underestimated, mainly due to the lack of validated diagnostic criteria for most type of dystonia, and the presence of a significant proportion of individuals with mild symptoms who are usually not referred to neurology clinics.

Due to the lack of validated diagnostic biomarkers, the diagnosis of dystonia is based on clinical examination and therefore may be challenging and open to bias. The factors contributing to misdiagnosis of dystonia can be summarized in two main points: i) the huge variability in the clinical phenomenology of dystonia; ii) the existence of a bunch of medical conditions (i.e., pseudodystonia) mimicking the abnormal postures/movements induced by dystonia. Within this context, the most common neurological and non-neurological imitators of dystonia are: functional dystonia; tics; head tilt; camptocormia/scoliosis; atlanto-axial and shoulder subluxation; Arnold-Chiari malformation; soft tissue neck mass; trigger digits; neuromuscular causes (such as myasthenia gravis etc.); spasms; orthopedic and rheumatological causes.

Functional dystonia is a clinical manifestation of functional motor disorder which is a common presentation of functional neurological disorder. Functional neurological disorder is a very common condition in clinical practice, and it is considered the second most frequent reason for a new outpatient neurological consultation. Indeed, functional motor disorder accounts for 2-10% of patients seen in movement disorder clinics. The diagnosis of functional motor disorder should not be considered a diagnosis of exclusion, and it should rely on positive clinical features for which laboratory findings may help. The two most important features that guide the clinical diagnosis of all FMDs are: i) inconsistency (i.e., clinical features may vary over time with susceptibility to

distraction); ii) incongruence (i.e., signs are incompatible with known determined patterns). The diagnosis of FMD, especially for some motor symptoms (such as functional distonia), may be very challenging.

This work is organized in two different part (Study 1 and Study 2) and the overall aim of the work is to help clinicians to better diagnosis idiopathic dystonia and functional dystonia.

The objective of Study 1 (*Sudden onset, fixed dystonia and acute peripheral trauma as diagnostic clues for functional dystonia)* is to identify clinical features suggestive of functional dystonia to guide physicians to distinguish functional dystonia from idiopathic dystonia. For this purpose, patient data were extracted from the Italian Registry of Functional Motor Disorders and the Italian Registry of Adult Dystonia. Patients with functional and idiopathic dystonia were followed up at the same clinical sites, and they were similar in age and sex. We identified 113 patients with functional dystonia and 125 with idiopathic dystonia. Sudden onset of dystonia, evidence of fixed dystonia, and acute peripheral trauma before dystonia onset were more frequent in the functional dystonia group. No study variable alone achieved satisfactory sensitivity and specificity, whereas a combination of variables yielded 85% sensitivity and 98% specificity. A diagnostic algorithm was developed to reduce the risk of misclassifying functional dystonia. The findings of Study 1 extend the current diagnostic approach to functional dystonia by showing that clinical information about symptom onset, fixed dystonia, and history of peripheral trauma may provide key clues in the diagnosis of functional dystonia.

Study 2 (*Validation of a guideline to reduce variability in diagnosing cervical dystonia*) was designed to provide practical guidance for clinicians in confirming or refuting suspected cervical dystonia, which is the most frequent type of dystonia. For this reason, participants of Study 2 were video-recorded according to a standardized protocol to assess 6 main clinical features possibly contributing to cervical dystonia diagnosis: presence of repetitive, patterned head/neck movements/postures inducing head/neck deviation from neutral position (item 1); sensory trick (item 2); and red flags related to conditions mimicking dystonia that should be absent in dystonia (items 3

to 6). Inter/intra-rater agreement among three independent raters was assessed by k statistics. To estimate sensitivity and specificity, the gold standard was cervical dystonia diagnosis reviewed at each site by independent senior neurologists. The validation sample included 43 idiopathic cervical dystonia patients and 21 control subjects (6 normal subjects, 2 patients with isolated head tremor, 2 with dyskinesia/chorea, 3 with tics, 2 with head ptosis, 4 with orthopedic/rheumatologic neck diseases, and 2 with ocular torticollis). The best combination of sensitivity and specificity was observed considering all the items except for an item related to capability to voluntarily suppress spasms (sensitivity: 96.1%; specificity: 81%). The findings of Study 2 show that an accurate diagnosis of cervical dystonia can be achieved if, in addition to the core motor features, we also consider some clinical features related to dystonia mimics that should be absent in dystonia.

In conclusion, this work sheds more light on the complex topic of the diagnosis of dystonia. Indeed, the algorithms proposed in Study 1 and Study 2 provide a helpful tool for clinicians in their practice. The findings of Study 1 may help in the differential diagnosis between functional dystonia and idiopathic dystonia; and the guideline proposed in Study 2 will reduce variability in diagnosing cervical dystonia, which was a crucial need in the field.

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ABBREVIATIONS

BoNT: Botulinum neurotoxin

BSP: Blepharospasm

CD: Cervical dystonia

FDYT: Functional dystonia

FMD: Functional motor disorder

FND: Functional neurological disorder

IDYT: Idiopathic dystonia

IRAD: Italian registry of adult dystonia

IRFMD: Italian registry of functional motor disorders

LD: Laryngeal dystonia

ULD: Upper limb dystonia

OMD: Oromandibular dystonia

WC: Writer's cramp

INTRODUCTION

DYSTONIA

Definition of dystonia

The term dystonia was first introduced by Oppenheim in 1911 in the form *"dystonia musculorum deformans"*.[1] Previous medical description of dystonia was made by Gowers, Destarac, and Schwalbe who referred to the condition as *"tetanoid chorea"*, *"torticolis spasmodique"*, and *"tonic cramps"* respectively.[2–4] Interestingly, one the most famous artistic description of torcicollis was made by Dante Aligheri in *"La Divina Commedia (Inferno, Canto XX)"*:

"Come 'l viso mi scese in lor più basso,
mirabilmente apparve esser travolto
ciascun tra 'l mento e 'l principio del casso;

ché da le reni era tornato 'l volto,
e in dietro venir li convenia,
perché 'l veder dinanzi era lor tolto."

After Meige the term "dystonia" has been extensively used in the neurological studies in the form "torsion dystonia". Until the early 1980s, dystonia was considered a condition between organic disorder and psychiatric condition. David Marsden was the first neurologist to postulate that dystonia was a disorder related to the basal ganglia functioning. Marsden described dystonia as a syndrome characterized by sustained involuntary muscle contraction, that frequently causes twisting or

repetitive movements or abnormal postures.[5,6] He also highlighted that dystonia would be considered an involuntary movement. Marsden's theory is a keystone for the understanding of dystonia, and the recent definitions of dystonia were based on his concept.

Indeed, according to the recent and current definition *"dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation."* [7]

Epidemiology

Prevalence of dystonia in general population is probably underestimated, and it is not still clear if dystonia should be considered a rare condition. Findings from different epidemiological studies had a huge variability probably due to differences in methods and analysis.[8]

Overall, 27 studies assessed the prevalence of adult-onset dystonia: 2 population-based studies showed a high prevalence; 5 reported a prevalence ranging from 40 to 70 cases per million individuals; and the remain 20 estimated a prevalence ranging from 3 to 37 cases per million.[9] Within this context, a recent viewpoint has urged the necessity to really clarify the epidemiology of dystonia in order to better assess risk and protective factors, neurological changes over time, and disease-modifying treatment.[10]

Another important reason related to the great variability amongst epidemiological studies, is the lack of validated diagnostic criteria for most type of dystonia, and the presence of a significant proportion of individuals with mild symptoms who are usually not referred to neurology clinics.

With particular reference to adult-onset dystonia, focal presentation is more frequent than generalized dystonia, as well as woman are more affected than men. Among focal dystonia, cervical dystonia (CD) is the most frequent type, followed by blepharospasm (BSP). For adult-onset focal

forms the genetic causes are rare, however, a positive family history has been described in about a fifth of the patients.[8]

Clinical features

The main motor features of dystonia include dystonic postures and dystonic movements, which are two physical signs that can be recognized during neurological examination. Dystonic postures indicate that muscle contractions may be continuous (usually associated with a co-contraction of agonist and antagonist muscles), forcing the involved body part into sustained postures (i.e., body site is flexed or twisted along its longitudinal axis).[7,11,12] Dystonic movements may be present at rest and they are generally repetitive and patterned or twisting. Fatigue and stress may often worsen the phenomenology of the movements, as well as the simultaneous presence of a voluntary movement.[13,14] A remarkable feature of dystonia, especially upper limb dystonia (ULD), is the task specificity, meaning that the disorder appears only during the execution of specific motor activities (e.g., writer's cramp [WC]).[15–17] Neurologists should recognize other clinical signs that are usually reported in patients with dystonia:

i) Tremor: may appear as isolated tremor and is a feature of dystonic movements. This rhythmic movement is often worsened by attempts to keep the primary posture.[8,9]

ii) Motor overflow: diffusion of dystonic movements or posture to an anatomically distinct body region contiguous to those primarily affected.[8,9]

iii) *Geste antagoniste* or sensory trick: specific voluntary movements that relieve or temporarily abolish dystonia. These manoeuvres involve the affected body site and are usually graceful and natural (e.g., touching specific parts of the face, cheek, chin in CD; or shifting pen holding, and writing with a closed fist in WC). Some individuals may also manifest multiple sensory tricks and the phenomenology of the *geste* may vary from person-to-person.[18,19]

iv) Mirroring: involuntary unilateral posture or movements (with the same or similar features of patient's dystonia) involving the contralateral upper or lower limbs that can be elicited during the activation of the body part affected by dystonia.[8,9]

Dystonia is "isolated" when it is the only motor symptom, whereas it is called "combined" when additional movement disorders occur (e.g., myoclonus dystonia or dystonia parkinsonism).[7] Since the recognition of dystonia is mainly based on the clinical observation of the aforementioned physical signs, the diagnosis can be difficult when the dystonic movements occur in isolation or in a non-complete pattern. This is the reason why the diagnosis of dystonia can be missed or delayed very frequently.

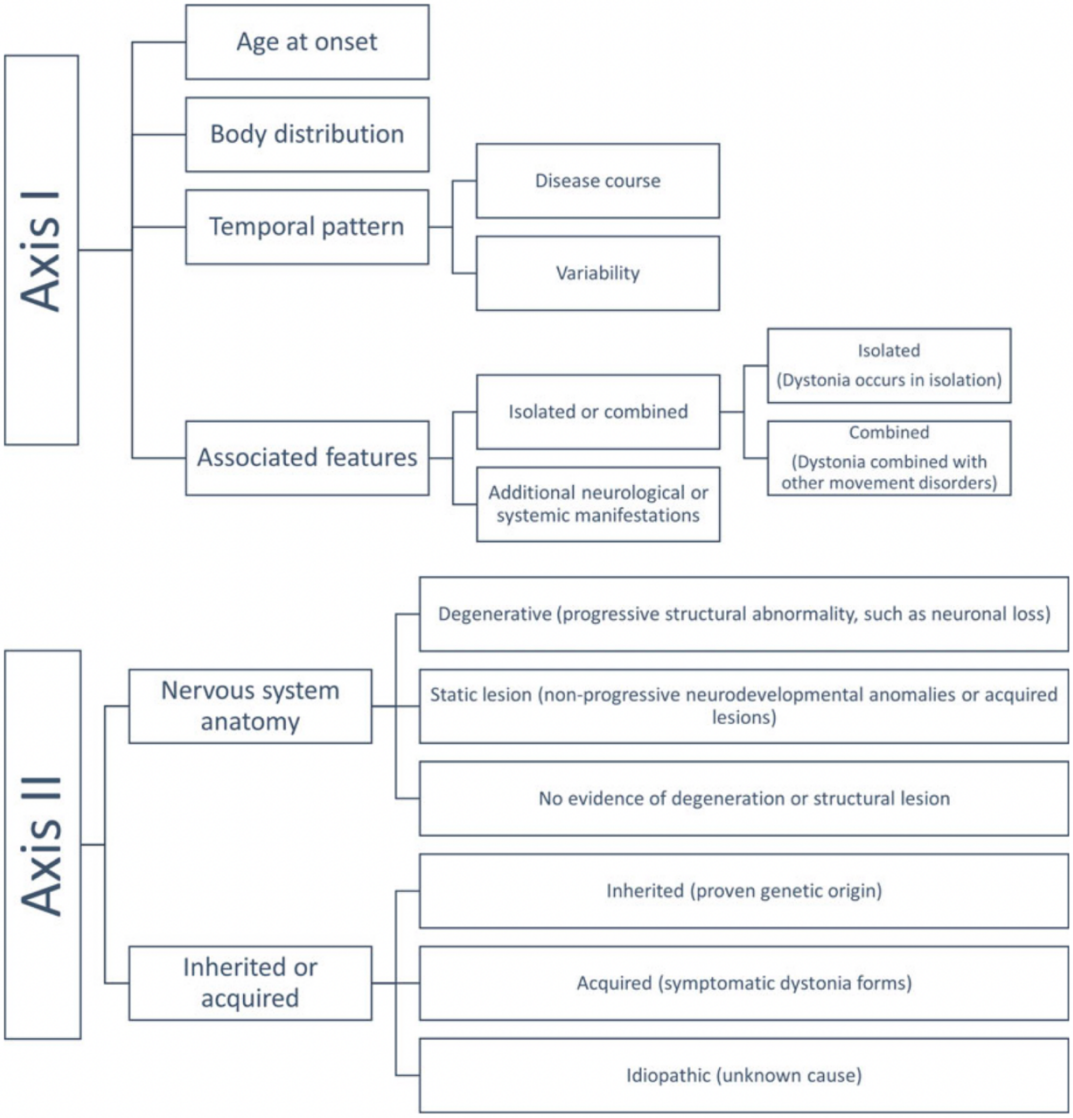
Classification

A recent classification of dystonia have been proposed in order guide clinician in patients' assessment.[7] The panel of expert identify two distinct axes (Figure 1):

i) Axis I shows clinical features (e.g. age at onset, body distribution, temporal pattern, cooccurrence of other movement disorders or of other neurological manifestations) and provides information at the time od examination.

ii) Axis II is focused on etiology and examines identifiable anatomical changes and pattern of inheritance.

Figure 1. Dystonia classification based on the hierarchical organization of the two axes (from Albanese et al. 2018).



At this point, some aspects of the classification should be highlighted.[7] Indeed, according to Axis I, five different age groups are identified for age at dystonia onset: infancy (birth to 2 years), childhood (3-12 years), adolescence (13-20 years), early adulthood (21-40 years) and late adulthood (>40 years). Following the definition provided by the experts, the body distribution of dystonia may be focal (only one body region is affected), segmental (two or more contiguous body regions are affected), multifocal (two noncontiguous or more body regions are involved), generalized (the trunk and at least two other sites are involved) or hemidystonia (more body regions restricted to one body side are involved). Interestingly body distribution can change over time and dystonia my spread from the original body site to another one.[15,20–22] As far as the etiology is concerned, Axis II provides helpful indications. Anatomical change and pattern of inheritance should be used together for etiological classification. Exploring the nervous system pathology may lead to the observation of degeneration (namely a progressive structural abnormality); static lesions; or the absence of degeneration/structural lesion. Moreover, dystonia may be i) inherited (dystonia forms of proven genetic origin), ii) acquired (dystonia due to a known specific cause); iii) idiopathic (unknown cause). Noteworthy several cases of focal or segmental isolated dystonia with onset in adulthood fall in the latter group.[7]

Diagnosis of dystonia

Due to the lack of validated diagnostic biomarkers, the diagnosis of dystonia is based on clinical examination and therefore may be challenging and open to bias.[23] This is the reason why many patients experienced numerous medical visits, delaying access to treatment.[24] It has been showed that experienced neurologists in movement disorders can diagnose dystonia with greater accuracy than general neurologists.[25]

The factors contributing to misdiagnosis of dystonia can be summarized in two main points: i) the huge variability in the clinical phenomenology of dystonia; ii) the existence of a bunch of medical conditions (i.e., pseudodystonia) mimicking the abnormal postures/movements induced by dystonia. Within this context, the most common neurological and non-neurological imitators of dystonia are: functional dystonia (FDYT); tics; head tilt; camptocormia/scoliosis; atlanto-axial and shoulder subluxation; Arnold-Chiari malformation; soft tissue neck mass; trigger digits; neuromuscular causes (such as myasthenia gravis etc.); spasms; orthopedic and rheumatological causes.[7]

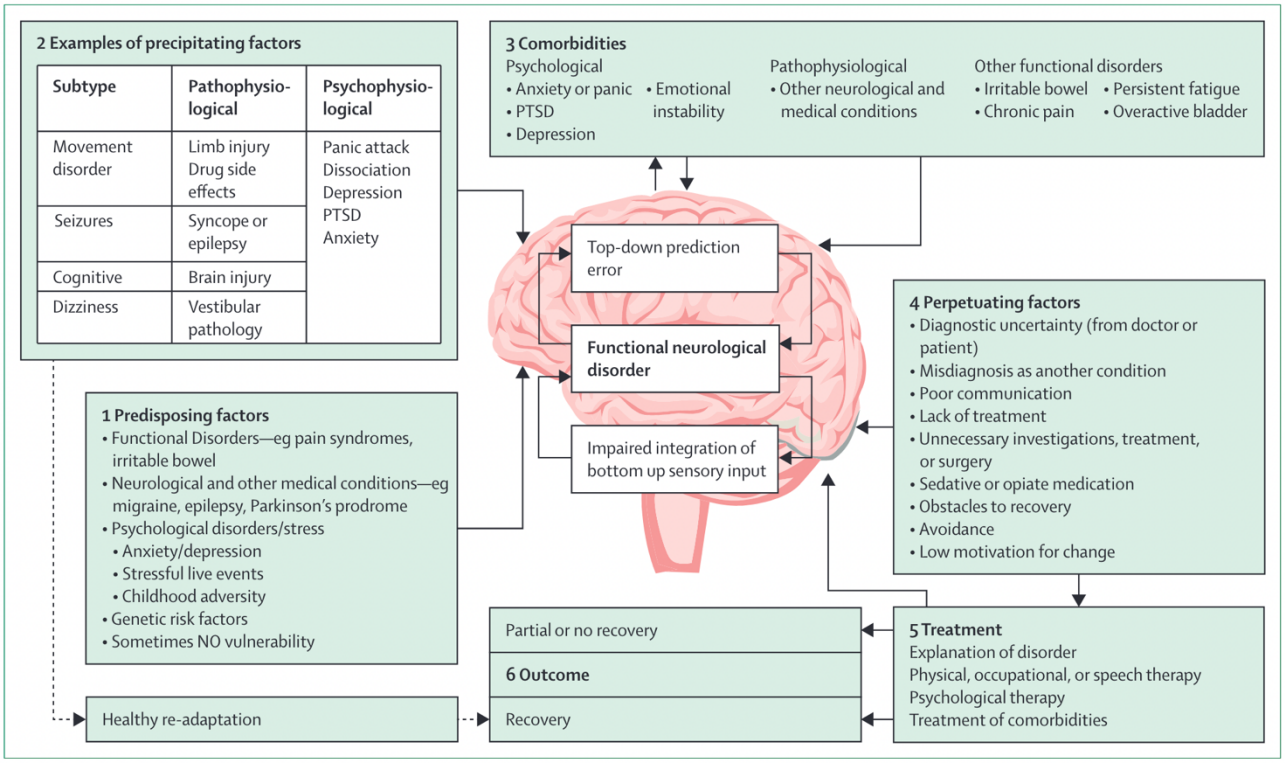
To date diagnostic guidelines have been proposed just for BSP[26,27] and laryngeal dystonia (LD)[28], whereas the lack of diagnostic guidelines for the other types is unmet need in the field. Recently a group of Italian Movement Disorder experts provided clinical diagnostic recommendations for CD, oromandibular (OMD), and limb dystonia.[23] These recommendation serve as basis for future validated diagnostic guidelines.

FUNCTIONAL MOTOR DISORDERS

Definition of functional motor disorders

Functional motor disorder (FMD) is a common presentation of functional neurological disorder (FND), presenting with diverse phenotypes such as tremor, dystonia, tics, weakness and gait disorder.[29,30] According to a recent review published in Lancet Neurology, the authors "*define the term FND to denote clinical syndromes consisting of symptoms and signs of genuinely experienced alterations in motor, sensory, or cognitive performance, which are distressing or impairing, and manifest one or more patterns of deficits that are consistent predominantly with dysfunction of the nervous system, and show variability in performance within the same task and between different tasks.*"[29] FND is a very common condition in clinical practice and it is considered the second most frequent reason for a new outpatient neurological consultation.[31] The etiology of FND is multifactorial and it has postulated that several factors may play an important role in the development of the disorder (Figure 2).

Figure 2. Multifactorial model explaining the complexity of FND (from Hallet et al. 2022)



Epidemiology

Although the lack of focused studies on the topic, FND seems to have similar prevalence across geographical areas.[29] FMD accounts for 2-10% of patients seen in movement disorder clinics.[32–34] Basic epidemiological features of FMD have been elucidated only recently by a large international study, called GAP study (Gender, Age and Phenotype study), confirming female preponderance (72.6%) and mean age at FMD onset of 39.6 $\pm$ 16.1 years.[30] Interestingly, men had a significantly later age of onset than women (41.0 years vs 39.1 years).[30]

Clinical features

FMDs manifest with involuntary various symptoms of altered movement (such as tremor, dystonia, weakness, gait disorders). The GAP study also described a clearer picture of FMD phenotype frequency: mixed FMD (23%), tremor (22%), weakness (18%), dystonia (12%), gait disorder (8%), myoclonus/jerks (5%), and parkinsonism (2%).[30] Compared the mean age of FMD onset, patients with gait disorders had a significantly later age at onset than tremor, while the mean ages at onset of weakness and dystonia were significantly younger.[30] Common features of FMDs included sudden onset of symptoms (71%), anxiety (52%), fatigue (45%), and pain (42%).[35] About 22% of FMD patients experienced neurological and non-neurological diseases, highlighting the important overlap among various conditions.[36] Moreover, the disorder may start in a single body site in about half of patients and then spread to additional body sites in 15–20% of cases.[37]

Diagnosis of functional motor disorders

Diagnosis by the text revision of DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*) no longer requires the presence of precipitating stressors, and FND is referred to as functional neurological symptom disorder (conversion disorder).[29] The diagnosis of FMD should not be considered a diagnosis of exclusion, and it should rely on positive clinical features for which laboratory findings may help.[38] According to Gupta-Lang criteria,[39] the two most important features that guide the clinical diagnosis of all FMDs are: i) inconsistency (i.e., clinical features may vary over time with susceptibility to distraction); ii) incongruence (i.e., signs are incompatible with known determined patterns). The diagnosis is often supported by positive clinical signs, such as the Hoover's sign for functional leg weakness, and the entrainment test for functional tremor.[38] Within this context, the examination can establish a "rule-in" (positive) rather than a "rule-out" (exclusionary) diagnosis for FMDs. The diagnosis of FMD, especially for some motor symptoms (such as FDYT), may be very challenging. However, clinicians should bear in mind that missing the diagnosis of FMD could be more frequent than making an erroneous diagnosis of FMD.[40]

STUDY AIMS

This work is organized in two different part (Study 1 and Study 2) and the overall aim of the work is to help clinicians to better diagnosis idiopathic dystonia (IDYT) and FDYT.

As the title suggests *"Sudden onset, fixed dystonia and acute peripheral trauma as diagnostic clues for functional dystonia"*, Study 1 is focused on the complex differential diagnosis between IDYT and FDYT. Indeed, the objective of the study is to identify clinical features suggestive of FYDT to guide physicians to distinguish FDYT from IDYT. The study has been already published in an international scientific journal specialized in movement disorders (*Movement Disorders Clinical Practice, Volume 8, Issue 7, October 2021, Pages 1107-1111*).[41] The study received the *"BRONZE award"* for the Best Research Article in *Movement Disorders Clinical Practice*, 2021-2022.

Study 2 *"Validation of a guideline to reduce variability in diagnosing cervical dystonia"* was designed to provide practical guidance for clinicians in confirming or refuting suspected CD, which is the most frequent type of dystonia. To date CD diagnosis is based on clinical examination and is therefore subjective, so a diagnostic test is still an unmet need. The final version of the study was submitted to an international scientific journal.

STUDY 1

Sudden onset, fixed dystonia and acute peripheral trauma as diagnostic clues for functional dystonia[41]

Inconsistency (i.e., changing patterns over time with susceptibility to distraction) and/or incongruence (i.e., a clinical picture incompatible with known determined patterns) are clinical features of neurological examination that support clinically definite diagnosis of FDYT according with the most recent set of diagnostic criteria proposed by Gupta and Lang.[39]

Demonstrating inconsistency/incongruence may be clinically challenging, however,[42,43] and straightforward laboratory-supported criteria for most forms of dystonia are lacking.[44] The only reliable neurophysiological discriminator between FDYT and IDYT proposed to date has been for blepharospasm.[45]

Medical history and clinical features that may reveal some clues to the diagnosis of FDYT include sudden symptom onset, evidence of fixed movement disorder, history of physical trauma, psychiatric diseases, and comorbid functional somatic disorders. Their validity in supporting a diagnosis of FDYT remains to be fully established. For this study, we compared the frequency of sudden symptom onset, evidence of fixed dystonia, and prior acute peripheral trauma in patients with adult-onset FDYT and IDYT. We also assessed their sensitivity and specificity either alone or combined. We did not assess psychiatric diseases and comorbid functional somatic disorders because of their high frequency in both FDYT and IDYT.[46]

Methods

The study relied on information from the Italian Registry of Functional Motor Disorders (IRFMD) and the Italian Registry of Adult Dystonia (IRAD), two multicenter initiatives coordinated by the Italian Academy for the Study of Parkinson's Disease and Other Movement Disorders (Accademia LIMPE-DISMOV RADAC project) and Fondazione LIMPE. Patients in the IRFMD were referred from 25 Italian centers for movement disorders with a diagnosis of clinically definite FMDs based on Gupta and Lang's diagnostic criteria.[39] The IRAD includes patients with adult-onset dystonia from 37 secondary/tertiary referral centers for movement disorders throughout Italy. Diagnosis was made according to published criteria.[7,26] Core assessment characterizing IRFMD and IRAD has been described in detail in other studies[35,47]; it comprises demographic, historical, and clinical information on the movement disorder and possible predisposing/precipitating factors.[36,48,49] Information was collected about dystonia at different body sites (upper and lower limbs, trunk, cervical, cranial among others), year of dystonia onset, and prior peripheral injury (at extracranial body sites). Onset of dystonia can be defined as acute (abrupt with deterioration within a few days or weeks) or slowly progressing.[35] Peripheral injury had to be severe enough to require medical attention, hospitalization, or surgery. Information about trauma included year and site of the injury. Dystonia was defined as fixed when immobile dystonic postures did not return to the neutral position at rest.[50] Patients with FDYT from the IRFMD were frequency matched by age and sex with patients with IDYT from the IRAD who were followed up at the same clinics. To include only patients who were idiopathic, tests for Wilson's disease, dopa-responsive dystonia, and common genetic variants (e.g., *TOR1A, THAP1*) were performed as appropriate. Patients screening positive on genetic testing were not included in the study sample.[15]

Statistical analysis was performed using the Stata 11 package (StataCorp, College Station, TX) and descriptive and inferential statistics as appropriate (*t* test, chi-square test, Fisher's exact test). Data are expressed as mean $\pm$ standard deviation unless otherwise indicated. Logistic regression

models for unequal case-control ratios were computed to assess the association between history of trauma and case-control status after adjusting for potentially confounding variables. Statistical significance was set at 0.05. To assess sensitivity and specificity, the gold standard was the diagnosis of FDYT or IDYT made at each site. Sensitivity was defined as the proportion of patients who screened positive among those given a diagnosis of FDYT (true positives/true positives + false negatives). Specificity was the proportion of patients who screened negative among those given a diagnosis of IDYT (true negatives/false positives + true negatives).

Results

In December 2020, the data on 113 patients with FDYT were extracted from the IRFMD, which included data from 410 patients with functional movement disorders,[36,51] and 125 patients with IDYT selected among the 1634 patients from the IRAD.[22] The two groups were similar for sex, age, and educational level but differed for disease duration, dystonia distribution, and frequency of focal dystonia, which was more frequent in the patients with IDYT (Table 1).

Table 1. Clinical and demographic features of patients with functional and idiopathic dystonia.

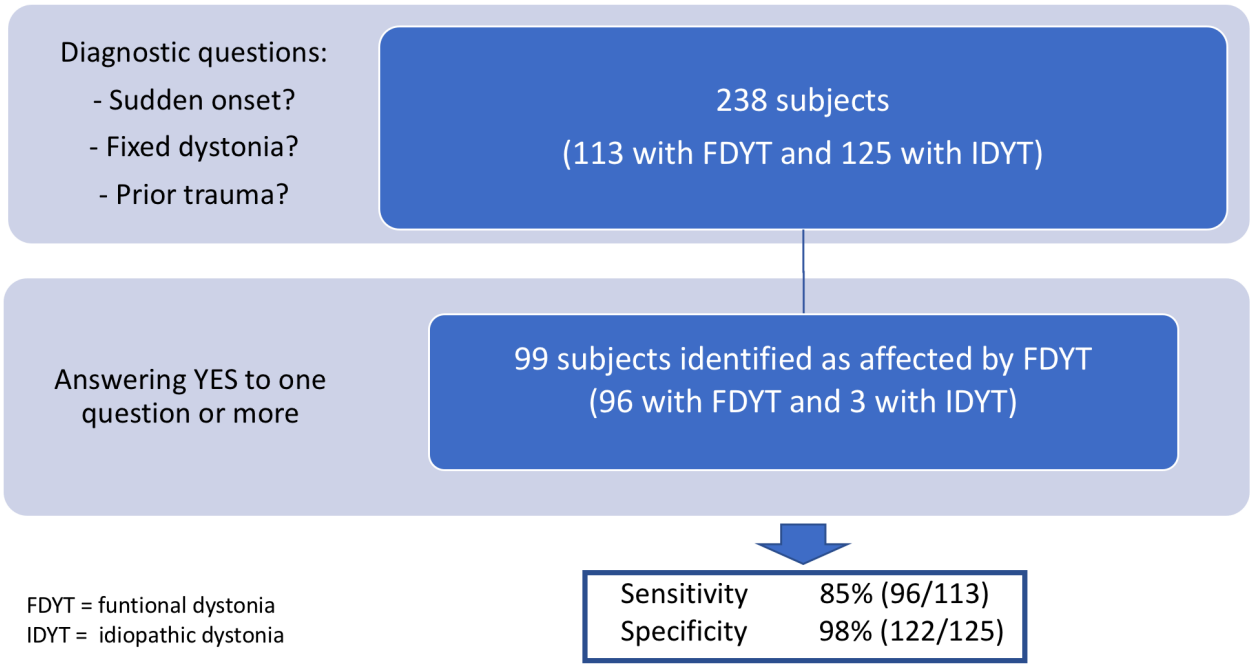
	Patients with functional dystonia (n=113)	**Patients with idiopathic dystonia (n=125)**	**P-value**
Women, no. (%)	87 (77)	94 (75)	0.4
Mean age, yrs.	47.2 ± 14.4	49.4 ± 10.0	0.2
Mean years of schooling	12.5 ± 4.1	12.3 ± 3.5	0.7
Mean age (years) at onset ± SD	41.3 ± 14.1	40.2 ± 10.6	0.3
Mean years of disease duration	5.9 ± 6.2	9.5 ± 8.0	0.0002
Focal dystonia, no. (%)	67 (59.3)	104 (83.2)	<0.0001
Site of dystonia, no. (%)			
- Upper Limbs	52 (46)	24 (19.2)	<0.0001
- Lower Limbs	43 (38.1)	6 (4.8)	<0.0001
- Trunk	22 (19.5)	5 (4)	<0.0001
- Cervical	41 (36.3)	84 (67)	<0.0001
- Cranial	8 (7.1)	36 (28.8)	<0.0001
- Other	11 (9.7)	0	<0.0001
Sudden dystonia onset, no. (%)	73 (65)	0	<0.0001
Fixed dystonia, no. (%)	56 (49.6)	0	<0.0001
History of peripheral trauma, no. (%)	22 (19.5)	3 (2)	<0.0001
Trauma and dystonia in the same body part, no. (%)	17 (15)	3 (2)	<0.0001
Time (months) elapsing between trauma in the same body part and dystonia onset ± SD (no.)	3.1 ± 6.9 (17)	2.7 ± 3.8 (3)	0.9

Plus-minus values are the mean ± standard deviation (SD)

Limb/trunk dystonia was more frequent in the FDYT group, and cranial-cervical dystonia was more frequent in the IDYT group (Table 1). Sudden onset of dystonia, evidence of fixed dystonia, and acute peripheral trauma before dystonia onset were more frequent in the FDYT group (Table 1). This finding was confirmed after limiting the analysis to trauma to the dystonic body part (Table 1) and adjusting for disease duration, age, and sex on logistic regression analysis (adjusted odds ratio, 5.8; 95% confidence interval, 1.6–20.9; P = 0.007).

No study variable alone reached a satisfactory combination of sensitivity/specificity (sudden onset of dystonia: sensitivity, 65% [73/113] and specificity, 100% [125/125]; fixed dystonia: sensitivity, 50% [56/113] and specificity, 100% [125/125]; prior trauma: sensitivity, 15% [17/113] and specificity, 98% [122/125]). However, screening positive to at least 1 of the 3 variables yielded 85% sensitivity (96/113) and 98% specificity (122/125) (Figure 3).

Figure 3. Diagnosing functional dystonia.



Discussion

Our findings indicate that sudden dystonia onset and fixed dystonia are more likely to occur in FDYT and that acute peripheral trauma may be significantly associated with FDYT.[43,50] Novel findings indicate that each variable differentiated FDYT from IDYT with 15% to 65% sensitivity, but none of these clinical features alone was crucial for diagnosing FDYT. Nonetheless, each of the 3 variables carried a negligible risk of misclassifying FDYT cases and reached 98% to 100% specificity. Although no study variable alone achieved satisfactory sensitivity and specificity, screening positive to at least 1 of the 3 clinical features can correctly diagnose FDYT in more than 8/10 patients who have the condition (85% sensitivity) and can correctly identify as not having FDYT about 10/10 subjects not affected by the condition (98% specificity). The sensitivity and specificity levels were shared by those reported for a recently published decision tree that classified FDYT using a complex case-finding procedure based on the serial application of about seven historical/clinical features and diagnostic confirmation subsequently informed by recognition of incongruence/inconsistence on neurological examination.[52] At variance with such an approach, however, our algorithm is considerably simpler and based on the combination of only three historical/clinical features.

Our study has several strengths. First, the populations of FDYT and IDYT were from multicenter settings and probably representative of the general population of cases with similar demographic/clinical features.[35,47] The older age at onset of patients with FDYT compared with the other reported cohorts probably reflects the inclusion of only adult-onset patients in the source registries. The frequency of sudden onset and fixed dystonia in our sample was consistent with previous series, whereas the trauma frequency was lower.[50] Unlike other studies, however, we limited recall bias by not including patients with mild trauma. Physical injury was more commonly recorded preceding weakness than dystonia.[53] Second, the standard for comparison was dystonia status based on clinical examination by neurologists applying stringent diagnostic criteria. In addition, both groups of patients with FDYT and IDYT were followed up by the same neurologists at the same center,

which provided accuracy in data collection. The low frequency of peripheral trauma to a specific body part in the IDYT group was consistent with the observations of several large controlled studies and demonstrated a negligible effect of peripheral trauma on topographically related IDYT.[54,55]

The present study also has some limitations. Patients participating in the study were diagnosed with clinically definite FMDs according to the Gupta and Lang criteria.[39] hese criteria are largely based on incongruence/inconsistency that may incorporate some of the issues we studied such as sudden onset and fixed dystonia. This may lead to the "circular argument" of diagnosing FMDs with new sets of criteria based on existing criteria. However, our aim was to measure the accuracy of these 3 simple aids alone in recognizing FDYT diagnosed according with the current gold standard, that is, clinical diagnosis established by expert neurologists who relied on several additional aspects of incongruence/inconsistency and positive clinical signs.[19,38,56] Moreover, because the patients and the physicians involved in the study were from the same country, data from other populations of patients and movement disorder specialists are needed to confirm the present results. Also, because our study focused on dystonia, not all findings may be extensible to other functional movement disorders. Disease duration was significantly lower in the FDYT group, even though the estimated association between FDYT and trauma did not change after adjusting for disease duration. Body distribution of dystonia differed in the FDYT and the IDYT groups, which probably reflects the frequency distribution of dystonia in the general population of adult-onset cases with functional and idiopathic dystonia. Although we did not match patients with FDYT and IDYT by distribution of dystonia, we were confident that our study variables, in particular sudden onset of dystonia and evidence of fixed dystonia, were probably independent of the body localization of dystonia. Nevertheless, we acknowledge that the higher frequency of limb dystonia in the FDYT group may limit the generalizability of findings to all forms of FDYT.

In conclusion, our findings extend the current diagnostic approach to FDYT by showing that clinical information about symptom onset, fixed dystonia, and previous peripheral trauma may provide key clues for diagnosing FDYT in addition to incongruence/inconsistence. In this context,

this large cohort corroborates the existing knowledge and presents sensitivity and specificity figures for a few historical/clinical features that can aid clinicians to establish a positive diagnosis for FDYT.

STUDY 2

Validation of a guideline to reduce variability in diagnosing cervical dystonia

Cervical dystonia, the most frequent form of focal dystonia, is characterized by a variable pattern of neck muscle involvement, leading to clinically heterogeneous directional presentations, such as torticollis, laterocollis, retrocollis, or anterocollis.[57] Patients may also have additional signs and symptoms, including shoulder elevation, neck/shoulder pain, or head tremor, and may benefit from the use of sensory tricks.[18,49,58]

Due to the lack of a diagnostic test, CD diagnosis is based on clinical examination and is therefore subjective.[59] As an example, a study on CD incidence in northern California found that up to 65% of patients may be incorrectly diagnosed prior to receiving a correct diagnosis.[60] Diagnostic errors may largely be due to the clinical variability of CD but also to the existence of several related conditions, for example, pseudodystonia mimicking the abnormal movements or postures of CD.[61,62] In the case of CD, dystonia mimics may include head tremor;[63] neck chorea producing nonrepetitive head movements;[64] neck tics associated with ability to mentally suppress the spasms;[65] orthopedic neck diseases (like atlanto-axial and shoulder subluxation, or fracture of the cervical vertebrae), rheumatologic neck diseases, and posterior fossa tumors, all leading to tonic postures or movement of the head;[66] lower motor neuron disease/myopathy/myasthenia gravis inducing weakness of the neck muscles opposite to the abnormal posture;[67,68] and ocular torticollis characterized by diplopia caused by the voluntary correction of the abnormal neck posture.[69]

Methods

Participants were identified from among outpatients attending the movement disorder clinic of the University of Cagliari and Sapienza University of Rome. Inclusion criteria for both case and control subjects were age 18 or older, any sex, and the willingness and mental/physical ability to sign informed consent and participate in the protocol. Case patients were enrolled if they had a diagnosis of focal idiopathic CD made by an experienced movement disorder neurologist.[23] Exclusion criteria were secondary CD and co-existing medical conditions/surgical interventions that could confound assessment of CD. Botulinum neurotoxin (BoNT) treatment was performed at least 12 weeks before the examination. The control group included normal subjects and a group of patients with head/neck impairment that could be confused with CD,[62] i.e., isolated head tremor; nonrepetitive head movements due to chorea; head tics associated with the ability to mentally suppress spasms; fixed involuntary neck postures due to orthopedic neck diseases (like atlanto-axial and shoulder subluxation or cervical vertebrae fracture), rheumatologic neck diseases, or posterior fossa tumors; focal weakness of the neck muscles opposite the side of abnormal posture due to lower motor neuron disease/myopathy/myasthenia gravis; and diplopia caused by the voluntary correction of abnormal neck posture due to ocular torticollis. To assess diagnostic accuracy we focused on the following clinical items: (i) presence of repetitive, patterned head/neck movements/postures inducing head/neck deviation from neutral position (item 1, derived from the 2013 revised definition of dystonia);[7] (ii) sensory trick (item 2); and (iii) red flags related to conditions mimicking dystonia that would be expected to be absent in dystonia (items 3 to 6). In the latter group, we took into account fixed head/neck deviation from neutral position (item 3, a feature distinguishing dystonia from orthopedic or rheumatologic diseases inducing fixed postures); focal weakness of neck muscles antagonizing the abnormal head/neck posture (item 4, a feature that may prove useful to differentiate lower motor neuron diseases/myopathy from dystonia); diplopia induced by voluntary correction of the abnormal head/neck posture (item 5, a feature that may distinguish CD from ocular torticollis); and ability to

voluntarily suppress spasms defined as an inner volitional effort rather than voluntary compensatory frontalis muscle overactivity (item 6, a feature that is potentially useful to distinguish dystonia and tics). Attention was paid to distinguish suppressibility by willpower alone from compensatory movements that often counteract dystonic movements or postures and are also the result of voluntary action. There was no duration requirement for voluntary suppression. Participants were video recorded according to a standardized protocol in order to assess all the major/distinctive clinical features possibly contributing to CD diagnosis. The video protocol included standard maneuvers triggering involuntary head movements, sensory trick if present, and the strength of neck muscles under voluntary contraction. Subjects were also asked by the examiner about: (i) occurrence of diplopia induced by voluntary correction of the abnormal head/neck posture, and (ii) capability to voluntarily suppress involuntary neck movements. Inter/intra-rater agreement was assessed among three independent raters who did not belong to the centers participating in the project. The number of videos included in the reliability study (64 video recordings of 43 CD patients, 6 normal controls, and 15 disease controls) exceeded that based on recommended subject-to-item ratios (which usually consider the assessment of 5-10 subjects for each item of a new scale) and on the number of items (n. 4) to be assessed by the three observers. Item 5 (diplopia induced by voluntary correction of the abnormal head/neck posture) and item 6 (inability to voluntarily suppress spasms) were not included in the reliability analysis because questions about these items were asked by the site examiner but not captured in the video. Agreement among raters was assessed by k index, which measures the level of agreement beyond chance and ranges from -1 (perfect disagreement) to +1 (perfect agreement). A k index >0.4 (indicating moderate to substantial/almost perfect agreement) was considered to be satisfactory. To estimate sensitivity and specificity, the gold standard was the diagnosis made at each site by the senior neurologists. Sensitivity was defined as the proportion of subjects who screened positive from among those who had a diagnosis of CD on clinical examination (true positives/true positives + false negatives). Specificity was the proportion of subjects who screened negative from

among those who were determined to not have CD on clinical examination (true negatives/false positives + true negatives).

Results

The validation sample included 43 patients with idiopathic CD (age at onset 53.3 ± 9.5 years) and 21 control subjects. The control group included: 6 normal subjects, 2 patients with isolated head tremor, 2 with dyskinesia/chorea, 3 with tics, 2 with head ptosis due to myasthenia or amyotrophic lateral sclerosis, 4 with orthopedic/rheumatologic neck diseases, and 2 with ocular torticollis. The case and control groups were similar for sex and age.

Inter-rater agreement was substantial to almost perfect for all four tested items (Item 1: $k = 0.82$, $p < 0.0001$; item 2: $k = 0.87$, $p < 0.0001$; item 3: $k = 1.00$, $p < 0.0001$; item 4: $k = 0.86$, $p < 0.0001$).

Considering only item 1 ("stereotyped, patterned, involuntary head/neck movements or postures inducing head/neck deviation from neutral position"), the three observers achieved 98% mean sensitivity and 49% mean specificity (Table A); analyzing item 2 alone (i.e., sensory trick), mean sensitivity was 75% and mean specificity was 84%; finally, mean sensitivity and mean specificity of the red flags group (namely items 3 to 6), were 55% and 71% respectively (Table A).

Table A. Sensitivity and specificity of clinical diagnostic items 1, 2 and 3 to 6.

	Sensitivity			**Specificity**			**Average Sensitivity**	**Average Specificity**
	Observer 1	*Observer 2*	*Observer 3*	*Observer 1*	*Observer 2*	*Observer 3*		
Repetitive, patterned head/neck movements/postures inducing head/neck deviation from neutral position (Item 1)	100% (43/43)	97.6% (42/43)	95.3% (41/43)	42.8% (9/21)	52.3% (11/21)	52.3% (11/21)	97.6%	49.1%
Sensory trick (Item 2)	74.4% (32/43)	74.4% (32/43)	76.7% (33/43)	81% (17/21)	81% (17/21)	90.1% (19/21)	75.1%	84%
Red flags related to conditions mimicking dystonia (Item 3 to 6)	58% (25/43)	51% (22/43)	53.5% (23/43)	81% (17/21)	71.4% (15/21)	62% (13/21)	54.7%	71%

Owing to the unsatisfactory levels of sensitivity and specificity, we tested whether combining the selected items would improve diagnostic sensitivity/specificity (Table B). First, we combined the item that reached the greatest sensitivity, that is item 1, with item 2 or the red flags group (item 3 to 6): the combination item 1 + item 2 yielded 74% mean sensitivity and 89% mean specificity (Table B); the combination item 1 + red flags group of items yielded 54% mean sensitivity and 95% mean specificity. Thereafter, we tested the algorithm including all the items and starting with item 1 that reached the greatest sensitivity. The second step was recognition of sensory trick, the item reaching the greatest specificity. In the absence of a sensory trick, including in the algorithm the red flags group of items, yielded the 84% mean sensitivity and 84% mean specificity (Table B).

Table B. Sensitivity and specificity of combination of clinical diagnostic items.

	Sensitivity			Specificity			Average Sensitivity	Average Specificity
	Observer 1	*Observer 2*	*Observer 3*	*Observer 1*	*Observer 2*	*Observer 3*		
Repetitive, patterned head/neck movements/postures inducing head/neck deviation from neutral position (Item 1) + Sensory trick (Item 2)	74.4% (32/43)	72.1% (31/43)	72.1% (31/43)	85.6% (18/21)	85.6% (18/21)	95.2% (20/21)	73.5%	88.8%
Repetitive, patterned head/neck movements/postures inducing head/neck deviation from neutral position (Item 1) + Red flags related to conditions mimicking dystonia (Item 3 to 6)	58.1% (25/43)	51.2% (22/43)	51.2% (22/43)	95.2% (20/21)	100% (21/21)	90.1% (19/21)	53.5%	95.1%
Repetitive, patterned head/neck movements/postures inducing head/neck deviation from neutral position (Item 1) + Sensory trick (Item 2) + Red flags related to conditions mimicking dystonia (Item 3 to 6)	86% (37/43)	81.4% (35/43)	83.7% (36/43)	81% (17/21)	85.6% (18/21)	85.6% (18/21)	83.7%	84.1%

Finally, the prior algorithm was further checked by omitting one of the red flags at a time. As reported in Table C, the best combination of sensitivity and specificity was observed when item 6 ("capability to voluntarily suppress spasms") was excluded.

Table C. Sensitivity and specificity of clinical diagnostic items 1 to 6, omitting one of the red flags at a time (items 3 to 6).

	Sensitivity			Specificity			Average Sensitivity	Average Specificity
	Observer 1	*Observer 2*	*Observer 3*	*Observer 1*	*Observer 2*	*Observer 3*		
All items except item 3 (fixed head/neck deviation from neutral position)	86% (37/43)	81.4% (35/43)	83.7% (36/43)	71.4% (15/21)	81% (17/21)	76.2% (16/21)	83.7%	76.2%
All items except item 4 (focal weakness of neck muscles antagonizing the abnormal head/neck posture)	88.4% (38/43)	83.7% (36/43)	83.7% (36/43)	81% (17/21)	85.6% (18/21)	85.6% (18/21)	85.3%	84.1%
All items except item 5 (diplopia induced by voluntary correction of the abnormal head/neck posture)	86% (37/43)	81.4% (35/43)	83.7% (36/43)	66.7% (14/21)	76.2% (16/21)	81% (17/21)	83.7%	74.6%
All items except item 6 (ability to voluntarily suppress spasms)	97.6% (42/43)	95.3% (41/43)	95.3% (41/43)	76.2% (16/21)	85.7% (18/21)	81% (17/21)	96.1%	81%

Discussion

Among the clinical items herein tested, items 1 to 4 (i.e., repetitive, patterned head/neck movements/postures inducing head/neck deviation from neutral position; sensory trick; tonic head/neck deviation from neutral position; and focal weakness of neck muscles antagonizing the abnormal head/neck posture) were evaluated for reliability and were found to have almost perfect interrater agreement. Items 5 and 6 (i.e., diplopia induced by voluntary correction of the abnormal head/neck posture; and ability to voluntarily suppress spasms) were not tested for reliability because they were assessed by a patient's answer to a standardized question.

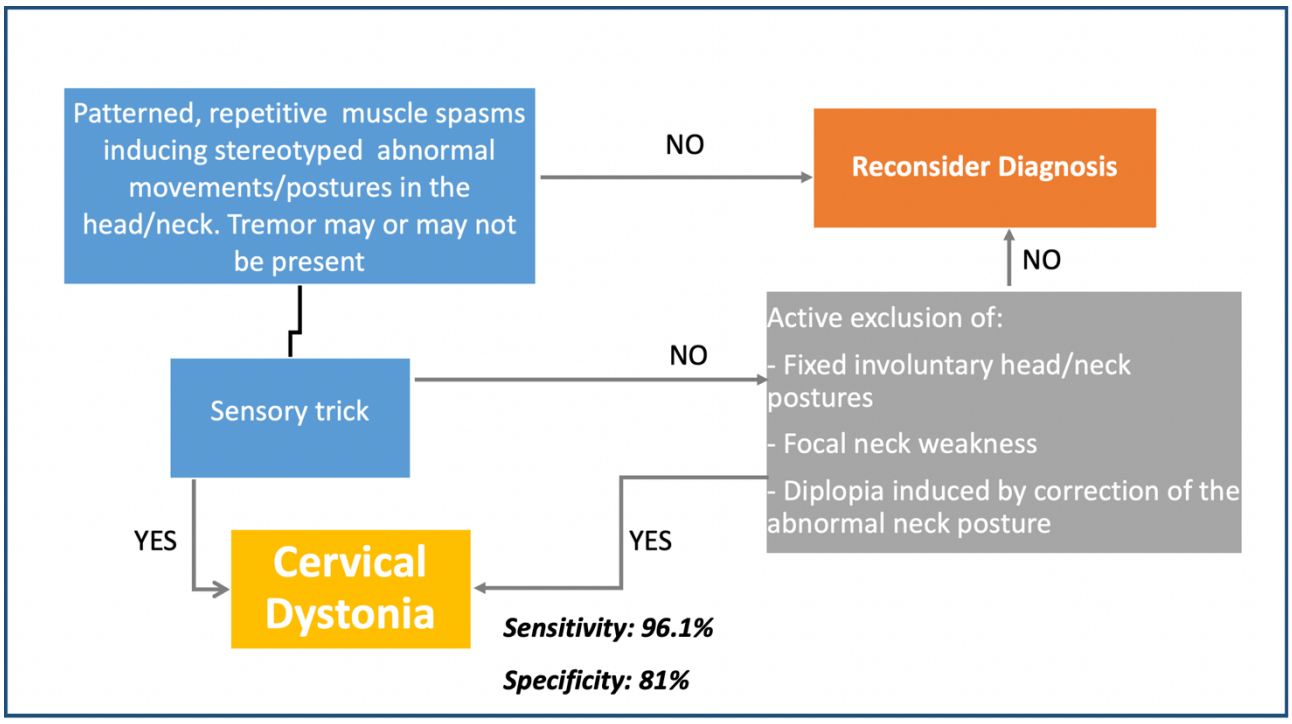
With regard to accuracy, the item "patterned, repetitive head/neck movements/postures inducing head deviation from neutral position" achieved very high sensitivity (98% on average), thus confirming the suggestion present in the 2013 definition of dystonia that assigns a crucial role to this item in diagnosing and differentiating CD from other neck movement disorders like chorea and tremor.[7] Nevertheless, the 49% specificity indicated a high risk of misclassifying several cases. Neither sensory trick nor red flags alone provided satisfactory sensitivity and specificity.

Since these accuracy estimates were unsatisfactory, we tested whether combining the selected items improved diagnostic sensitivity/specificity. We observed that combining item 1 (the item that reached the greatest sensitivity) and sensory trick (the item that reached the greatest specificity) increased specificity to 89% but decreased sensitivity to 74%. This was probably because sensory trick is a feature largely specific for dystonia but is not present in all CD patients.[18] It should be noticed that also among control subjects, patients with tic, myasthenia, and ocular torticollis reported that touching the neck was a sensory trick. In tic patients, we could not be sure that this was a true trick or the result of the voluntary spasm suppression characteristic of tics.[65] In the other controls, tactile stimulation/local compression of the muscle may have led to the alleviation of muscle weakness and improvement in neck position.

In the absence of a sensory trick, active exclusion of the red flags (item 3 to 6) yielded 84% mean sensitivity and 84% mean specificity. Finally, we tested shorter versions of the algorithm by

excluding one of the red flags at a time. The best combination of sensitivity and specificity was obtained when the item "ability to mentally suppress spasms" was omitted. This is a feature that is potentially useful in distinguishing dystonia and tics, because tics are voluntarily suppressible while dystonia is not. The lack of utility of this item may be difficult to ascertain, and the result may depend closely on how the question is asked.[70] Some patients with CD may interpret the ability to voluntarily suppress symptoms in different ways. They may believe that "voluntary" includes compensatory movements that counteract dystonic movements or postures or they may believe that suppressibility can be partial. In fact, several CD patients reported voluntary suppressibility, which may reflect these differences of interpretation. Regardless of the explanation, the average 96% sensitivity and 81% specificity obtained with this algorithm means that it can correctly diagnose CD in more than 9/10 patients who have the condition and correctly identify 8/10 subjects who do not have the condition (Figure 4).

Figure 4. Proposed algorithm for the diagnosis of cervical dystonia.



Our study has several strengths. First, the validation procedure included patients with CD (whose demographic and clinical characteristics resembled those of patients reported in other published series), healthy controls, and subjects with a variety of neck disorders mimicking CD. Second, the standardized videotape protocol reproduced all major features seen during clinical examination. However, the present study also has some limitations. We did not evaluate whether incorporating the proposed guideline was better than providing only brief training without specific criteria to the raters. Nevertheless, there are several lines of evidence indicating that, in the absence of specific criteria, there is variability in the diagnostic approach of physicians, regardless of their expertise.[25,27] Our aim was to provide a valid and practical guideline capable of reducing variability among physicians. There may also be variability in the interpretation of patients to answer standardized questions on video examination. Probably a live examination would provide better outcome than video examination. Likewise, specificity will probably be better in real life than in this sample where the number of mimics closely matched the number of cases. Finally, since all patients and evaluating physicians involved in the study were from the same country, the results of the study need to be confirmed in different patient and physician populations.

Despite these limitations, this study demonstrates two relevant points. First, an accurate diagnosis of CD is not possible if we refer only to the core clinical feature of CD as proposed in the 2013 revised classification of dystonia,[7] i.e., “patterned and repetitive movements/postures in the head/neck” as well as to the combination of this item and sensory trick. Second, a higher diagnostic accuracy can be achieved if we also consider clinical features related to dystonia mimics that should be absent in dystonia. The diagnostic algorithm without the item “ability to voluntarily suppress spasms” was sensitive and specific enough to be proposed as a guideline for presumptive diagnosis of CD, though it needs to be further expanded and validated in a larger international sample.

CONCLUSIONS AND PERSPECTIVE

The present work sheds more light on the complex topic of the diagnosis of dystonia. The organization of the work in in two different part (Study 1 and Study 2) allowed to better focus on one topic at time. Indeed, the algorithms proposed in Study 1 and Study 2 provide a helpful tool for clinicians in their practice.

Study 1 (*Sudden onset, fixed dystonia and acute peripheral trauma as diagnostic clues for functional dystonia)* identifies clinical features suggestive of FDYT to guide physicians to distinguish FDYT from IDYT. Indeed, sudden onset of dystonia, presence of fixed dystonia, and acute peripheral trauma were more common in the FDYT group rather than in patients with IDYT. However, none of those study variables alone achieved a satisfactory level of sensitivity and specificity. Screening positive to at least 1 of those 3 variables can correctly diagnose FDYT in more than 8/10 patients who have the condition (85% sensitivity) and can correctly identify as not having FDYT about 10/10 subjects not affected (98% specificity). The proposed algorithm is simple and easy to apply to patients, due to the fact it relays on only 3 historical/clinical features.

Study 2 (*Validation of a guideline to reduce variability in diagnosing cervical dystonia*) provides a guideline for clinicians in confirming or refuting suspected CD. The validation of diagnostic guideline for the most frequent type of dystonia was an urgent need for the field, demonstrating that an accurate diagnosis of CD is not possible if we refer only to the core clinical definition of the 2013 revised classification.[7] The proposed guideline obtains an average 96% sensitivity and 81% specificity which means that it can correctly diagnose CD in more than 9/10 patients who have the condition and correctly identify 8/10 subjects who do not have it. Therefore, the algorithm is sensitive and specific enough to be proposed as a guideline for presumptive diagnosis of CD.

The novel findings of this work may really help both clinicians and researchers in recognizing dystonia. An accurate diagnosis of dystonia is a mandatory feature to set reliable clinical trial, as well as for measuring therapeutic outcomes. In order to strengthen this work, these findings need to be further expanded and validated in a larger international sample.

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