

The Diagnostic Challenge of Primary Dystonia: Evidence from Misdiagnosis

Stefania Lalli, MD, PhD¹ and Alberto Albanese, MD^{1,2*}

¹Fondazione IRCCS Istituto Neurologico “Carlo Besta,” Milano, Italy

²Università Cattolica del Sacro Cuore, Milano, Italy

Abstract: Although the understanding of dystonia has improved in recent years, primary dystonia is still insufficiently recognized and patients may not receive the correct diagnosis, leading to transient or permanent misclassification of their symptoms. We reviewed cases of primary dystonia who were at first misdiagnosed and analyzed the reasons why the correct diagnosis was first missed and later retained. Primary dystonia is misdiagnosed mainly, but not exclusively, in favor of other movement disorders: Parkinson’s disease (PD), essential tremor, myoclonus, tics, psychogenic movement disorder (PMD), and even headache or scoliosis.

Accounts are more numerous for PD and PMD, where diagnostic tests, such as DAT scan and psychological assessment, support clinical orientation. The correct diagnosis was achieved in all cases following the recognition of inconsistencies in the first judgment and of distinctive clinical features of dystonia. These clues have been collected here and assembled into a diagnostic epitome. © 2010 Movement Disorder Society

Key words: dystonia; Parkinson’s disease; essential tremor; tic; psychogenic movement disorder; myoclonus

Dystonia is a disorder characterized by sustained muscle contractions usually producing twisting and repetitive movements or abnormal postures. Prevalence values for primary dystonia are between 0.2 and 5 cases per 100,000 for early-onset cases and between 3 and 732 cases per 100,000 for late-onset cases.¹ A possible explanation of this wide variability of incidence and prevalence values might be the difficulty or the delay of the clinical diagnosis. There is general agreement among movement disorder specialists that the diagnosis of dystonia may be underestimated.² It is also unknown how many patients with mild symptoms of dystonia fail to seek medical advice. An example of personal unawareness of dystonia is provided by a large Italian family linking to the DYT13 locus,³

where 2 of the 5 clinically definite cases and 1 of the 3 probable cases considered themselves unaffected.

Diagnostic difficulties are grounded on several reasons, including the wide ranging spectrum of dystonia. Conditions that are more common or better acknowledged than dystonia have higher chances to be suspected or diagnosed instead, at least initially. To overcome these difficulties, a diagnostic flow chart has been recently introduced.⁴ Its implementation in specific cases, however, depends on the possibility to consider dystonia as a possible diagnosis.

Under-recognition of dystonia raises the question regarding which other diagnoses are made in dystonia patients. We answer to this question by reviewing the available scientific evidence of misdiagnosed cases and examining the reasons why the correct diagnosis was not reached or was delayed. Because of the lack of well-designed clinical studies or large series, we evaluated all the available individual case reports, observational studies, and occasionally compared the evidence so collected with our direct experience. Computerized MEDLINE and EMBASE searches (no date restrictions up to December 2009) were conducted using a combination of textwords, MeSH and Emtree terms “dys-

*Correspondence to: Alberto Albanese, Fondazione Istituto Neurologico Carlo Besta, Via G. Celoria, 11, Milano 20133, Italy.
E-mail: alberto.albanese@unicatt.it

Potential conflict of interest: Nothing to report.

Received 21 September 2009; Revised 1 January 2010; Accepted 10 March 2010

Published online 18 May 2010 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.23137

tonia," "movement disorders," "Parkinson disease," "tremors," "tics," "myoclonus," "psychogenic," "headache," and "scoliosis" limited to human studies and English language. We also identified articles through searches of our own files as well as by collecting references from relevant articles. Books on movement disorders, personal experience, and comments collected from colleagues were also used to identify sources of evidence. The final reference list was generated on the basis of the relevance to the topic covered.

PARKINSON'S DISEASE

Dystonia is a feature of Parkinson's disease (PD) and is more common in patients with a younger age at disease onset. Dystonia secondary to PD usually begins in the legs, it is painful and is not relieved by sensory tricks; dystonic postures often start abruptly and progress to significant disability. Dystonia can be observed as part of the PD spectrum (e.g., blepharospasm and eyelid apraxia) and also following dopaminergic treatment or subthalamic nucleus stimulation.^{5,6}

Primary dystonia may be mistaken for PD mainly for two reasons. First, dystonic slowness can resemble bradykinesia observed in PD.⁷ Since a full set of maneuvers is required to detect the features of bradykinesia in some patients with PD,⁸ incomplete physical examination may lead to mistake dystonic slowness for bradykinesia. Second, dystonic tremor may be mistaken for parkinsonian tremor, particularly when it is observed at rest. In conditions of incomplete rest of the arm, the positional component of dystonia may lead to diagnose a parkinsonian rest tremor instead of dystonic tremor.

There are reports of patients with genetically diagnosed DYT1 dystonia, who have long been considered to have PD.⁹ A DYT1 patient with adult-onset task-specific tremor was diagnosed as having benign tremulous PD. At 69 years, he presented evident rest tremor of both arms. The diagnosis of PD was retained until a DAT scan resulted normal. The issue whether patients with PD-like phenomenology and normal DAT scan (so-called SWEDD) may in fact be affected by dystonia has recently emerged.¹⁰ In the ELLDOPA study,¹¹ some patients diagnosed with early PD had normal β -CIT SPECT imaging, calling into question their diagnosis. One piece of evidence that SWEDD patients did not have PD was their lack of any clinical response to levodopa treatment. The possible occurrence of dystonic tremor in SWEDD patients is a recent finding¹⁰ based on the observation of ten subjects, who received

a diagnosis of PD at some point of their history and were later recognized to have dystonia. All the patients had asymmetric tremor, including a resting component, reduced arm swing on the same side, and sometimes facial hypomimia or jaw tremor, but no significant akinesia. Based on these observations, it has been elaborated that clinical peculiarities suggesting dystonic tremor in SWEDD patients are as follows: subtle dystonia, thumb extension tremor, "flurries" or task/position-specific tremor, head tremor, dystonic voice, no progression to develop features other than tremor and dystonia, no clear fatiguing or decrement of repetitive movements.¹⁰

A recent report described a 59-year-old man with a 6-month history of increasing tremor in the right hand, a slight tremor in the left hand, who was initially diagnosed with PD.¹² DAT scan was normal. A dystonic tremor was later diagnosed based on the observation of abnormal posturing of the right thumb in combination with a slowly progressive jerky, asymmetric, rest, and action tremor. In a series of 99 patients with an initial diagnosis of degenerative parkinsonism, ¹²³I-FP-CIT SPECT imaging remained normal throughout a period of 3 years in 21% of them.¹³ Three of these SWEDD patients were considered to have dystonia.

This evidence from multiple sources indicates that PD and other parkinsonian syndromes may be overdiagnosed disfavoring the recognition of dystonia. Table 1 lists a number of indicators that contributed to the diagnosis in the cases reviewed. Aside clinical features suggesting a diagnosis of dystonia, a normal DAT scan can rule out PD. This finding is not specific of primary dystonia and also occurs in dopa-responsive dystonia, essential tremor (ET), psychogenic tremor, or cases of vascular parkinsonism or of drug-induced parkinsonism.¹⁴ Other useful investigations are as follows: electrophysiological recording of dystonia features, tremor analysis, and the study of the cortical excitability.^{15,16}

ESSENTIAL TREMOR

The differential diagnosis between ET and dystonia may be difficult and their phenomenological overlap has been repeatedly reported. A tremor similar to ET may occur in dystonia and can be mistaken for nondystonic tremor, particularly when isolated.¹⁷ Head or voice tremors observed in tremulous forms of cervical dystonia can be very hard to distinguish from ET.¹⁸ In some cases, only family history orientates in favor of the correct diagnosis, particularly if family members are ascertained to have dystonia. The diagnosis of dys-

TABLE 1. A list of clues suggesting a diagnosis of primary dystonia in patients suspected to have a different condition

Clinical orientation	Clues suggesting primary dystonia
Parkinson's disease	Diagnostic inconsistencies • There is no progression to develop features other than tremor and dystonia¹⁰ • There is no clear fatiguing or decrement while performing repetitive movements¹⁰ • DAT scan is normal (SWEDD)¹⁰ • Features do not improve with dopaminergic treatment (consider acute challenge) Features suggesting the dystonic nature of movements or postures • There is thumb extension tremor, and tremor does not have a pill-rolling aspect¹⁰ • Tremor is task- or position-specific¹⁰ • There is head tremor¹⁰ • Voice is dystonic¹⁰ • EMG mapping supports a diagnosis of dystonia¹⁹ • Variability of tremor with positional arm changes
Essential tremor	Diagnostic inconsistencies • Head tremor is isolated¹⁸ • Patients with voice tremors cannot change pitch during vocalization¹⁸ • Tremor does not improve with ET therapy (i.e., propranolol, primidone) Features suggesting the dystonic nature of movements or postures • With head rotation there is clear asymmetry of tremor²⁰ • Tremor disappears with <i>geste</i> maneuver²¹ • There is neck pain or hypertrophy of neck muscles (particularly if asymmetric)²⁰ • EMG mapping or tremor analysis support a diagnosis of dystonia²² • Mirroring produces torsional movements • Family history is positive and dystonia has not been ruled out in other family members
Myoclonus	Diagnostic inconsistencies • EMG analysis does not show characteristic features of myoclonus²³ Features suggesting the dystonic nature of movements or postures • Abnormal postures are associated with myoclonus (perform mirroring and overflow maneuvers)¹⁷ • EMG mapping supports a diagnosis of dystonia¹⁹ • Family history is positive and dystonia has not been ruled out in other family members
Tics	Diagnostic inconsistencies • There are no behavioral comorbidities • There are no premonitory sensations Features suggesting the dystonic nature of movements or postures • Tics have a predictable and consistent pattern²⁴ • There is family history of dystonia²⁵ • EMG mapping supports a diagnosis of dystonia¹⁹
Psychogenic movement disorder	Diagnostic inconsistencies • Absence of possible secondary gain^{26,27} • Dystonic movements are consistent over time^{26,27} • Dystonic postures are consistent and congruous over time²⁸ Features suggesting the dystonic nature of movements or postures • The development of dystonic movement and postures is gradual and progressive^{26,27} • There is a combination of phasic movements and tonic dystonic postures^{26,27} • EMG mapping supports a diagnosis of dystonia (consider investigating cortical excitability)^{19,29}
Headache	Diagnostic inconsistencies • Headache is relieved by <i>gestes</i> maneuvers Features suggesting the dystonic nature of movements or postures • EMG mapping supports a diagnosis of dystonia¹⁹ • Focal pain over the splenius capitis or trapezius muscles is accentuated by palpation • There is hypertrophy of neck muscles (the splenius capitis may become palpable) • Response to botulinum toxin is excellent
Idiopathic scoliosis	Diagnostic inconsistencies • Family history is positive and dystonia has not been ruled out in other family members^{30,31} Features suggesting the dystonic nature of movements or postures • EMG mapping supports a diagnosis of dystonia¹⁹

The signs proposed in published papers are referenced.

tonia can be missed or delayed in a number of patients with task- and position-specific tremors, particularly primary writing tremor, occupational tremors, or isolated voice tremor, as typical features of dystonia may develop only many years after onset.²⁰ A consensus

statement of the Movement Disorder Society set criteria to classify tremor observed in patients or families affected by dystonia.¹⁵ This classification has not gained diffusion because all these forms are considered variants of primary dystonia, where the features of dys-

tonia and tremor may remain distinct until they eventually intermix. The review of misdiagnosed cases confirms that this classification schema is difficult to implement in clinical practice.

There are proven cases of primary focal dystonia, who initially received a diagnosis of ET due to the occurrence of isolated tremor of the trunk or neck. David Marsden observed patients with isolated “no-no” head tremor, with a presentation typical for ET, who eventually developed obvious cervical dystonia.²⁰ Furthermore, there is proof that a patient with DYT1 dystonia was misdiagnosed as having ET.³² She had a positive family history and at age 40 developed leg tremor while walking and at rest. She was initially diagnosed to have ET and was treated accordingly, but eventually received a diagnosis of dystonia upon re-examination at age 67. Cases of isolated arm tremor who later developed cervical dystonia are also published.³³ In a series comparing patients with ET of the upper limbs to patients with cervical dystonia and associated upper limb tremor, neurophysiological tests allowed to recognize differences useful for the differential diagnosis of tremulous upper limb movements.³⁴ It was also observed that upper limb tremor can precede the onset of cervical dystonia by more than 20 years, leading to nosologic misclassification.

There are also a number of ET cases where dystonia features were not specifically ruled out. First, in a recent epidemiological study, subjects were diagnosed as having ET in the presence of an action tremor of the head, limbs, or voice without any recognizable cause.³⁵ These inclusion criteria did not consider features suggestive of dystonia, such as, head tremor, voice tremor, very asymmetric limb tremor, and dystonia in a family member (34% of the patients reported at least one first-degree relative with a tremulous disorder). Second, a review of a videotape used to exemplify ET³⁶ revealed dystonia features in four clips. These consisted in the following: lateral shift and bending of the head in primary position (clip 4), marked asymmetry of hands tremor (clips 6 and 8), and posturing of fingers with outstretched arms (clip 1). Third, in a recent retrospective study of a large cohort of patients diagnosed to have ET, it was found that upper limb mirror movements were three times more common than in controls.³⁷ The mirror movement had a torsional and sustained character in some patients (see patient 3), whereas in others, they consisted in mild flexion of fingers or toes. Mirror movements are a typical, albeit not exclusive, feature of dystonia.³⁸ The observation of a high incidence of mirroring, and particularly of torsional mirroring, suggests

a diagnosis of primary dystonia. The clinical clues that help recognizing dystonia in patients suspected to have ET are summarized in Table 1.

MYOCLONUS

Patients with myoclonus dystonia (M-D, DYT11) present a combination of myoclonus and dystonia, whereas no dystonia is observed in essential myoclonus³⁹; in many cases, myoclonic jerks can be distinguished from fast “jerky” dystonic movements based on clinical and electrophysiological features.⁴⁰ However, rapid jerky movements may occur in dystonia patients without myoclonus,¹⁷ and, particularly if affecting a limb, these are likely to be mistaken for myoclonic jerks. EMG recording can provide arguments in favor of the diagnosis of dystonia, if a duration of muscle spasms longer than 200 ms is recorded.²³ It has been shown, in fact, that patients with “jerky primary dystonia” (also called “myoclonic dystonia”) may have EMG bursts of short duration (50–250 ms), leading to confusion with the EMG features of myoclonus.⁴¹ Genetic studies have clarified that “jerky dystonia” is not associated with mutations in the ϵ -sarcoglycan gene.⁴²

As demonstrated by genetic studies, clinical diagnostic criteria for M-D have lead to misclassification. In a large cohort of M-D patients, half of those who received a definite clinical diagnosis turned out to be negative for mutations in the ϵ -sarcoglycan gene.⁴³ On the other hand, genetic studies have also shown that mistakes in favor of myoclonus have been made in patients with “jerky” DYT1 dystonia. Early-onset action myoclonus of the right hand during writing was the presentation of DYT1 dystonia patient, who also received the additional diagnosis of possible psychogenic tremor.⁴⁴ Another DYT1 patient developed “jerky tremor” of the trunk and gait difficulties at 9 years of age and remained unchanged for 40 years before she eventually received the DYT1 diagnosis at age 71.⁴⁵

It has been recently recognized that jerks observed in children with dystonia are related with four possible conditions: myoclonus dystonia (DYT11), myoclonic dystonia (jerky primary dystonia), benign hereditary chorea, or primary dystonia with poly-mini myoclonus.⁴⁶ This wide diagnostic spectrum highlights the variety of phenotypes potentially associated with myoclonic-like movements in dystonia patients. The electrophysiological studies may help confirm a diagnosis of myoclonus dystonia whereby myoclonus can remain isolated, rhythmic or more frequently arrhythmic, usu-

ally with a frequency never exceeding 10 Hz. These different patterns can coexist. The criteria supporting a diagnosis of dystonia in patients who are suspected of having myoclonus are highlighted in Table 1.

TICS

Tics are brief and intermittent movements usually abrupt in onset and rapid; but they may be slower and cause a briefly sustained abnormal posture resembling dystonia (“dystonic tics”).²⁴ In people with excessive blinking, it may be difficult to distinguish dystonic movements from motor tics and both may improve after botulinum toxin treatment, regardless of the precise diagnosis. Unlike tics, which usually change their pattern over time, dystonic movements are predictable and consistent during a period of observation. Furthermore, there is no strong urge to perform dystonic movements and no relief after execution; these are aspects of tics, which make them assume a “semivoluntary” or at least intentional nature usually not observed in dystonia.

Simple motor tics are quite common and may coexist with dystonia. The differential diagnosis between motor tics and dystonia has never been studied in large patient cohorts and criteria to separate the two entities are missing. There is evidence to suggest a possible misdiagnosis of dystonia in favor of tics in the cranial district. It has been observed that eye tics have an increased incidence in families of patients with adult-onset cranial dystonia,²⁵ raising the doubt that the two entities may not be satisfactorily distinguished. A family has been reported in which 5 subjects in three generations were affected by eye-winking tics; 2 of the patients also had cranial-cervical dystonia (including Meige’s syndrome and torticollis).⁴⁷ If current diagnostic criteria for dystonia are used to review the clinical features of these 5 subjects,⁴ 4 of them (cases 1–4) might be considered to have features of dystonia. Table 1 enlightens criteria proposed to distinguish tics from dystonia in difficult clinical cases.

PSYCHOGENIC MOVEMENT DISORDERS

Dystonia is the second most common phenotype of psychogenic movement disorders (PMD) seen at specialist centers.⁴⁸ Patients with clinical features of dystonia may be suspected to have a PMD if the clinical features are inconsistent over time, dystonic movements and postures are incongruous, dystonia is fixed or paroxysmal, and there are other bizarre involuntary movements, including gait disturbance.²⁶ Additional

proposed features include foot dystonia in adults, dystonia at rest, and incongruous contraction of antagonist muscles with apparent agonist action.²⁷ These features are by no means specific and PMD remain one of the most challenging conditions encountered by clinicians.

In a series of 84 patients affected by primary dystonia, 37 were originally misdiagnosed as being psychogenic.⁴⁹ More recent examples of dystonia mistaken for a PMD are also available, such as a case of focal lower limb primary dystonia who was long considered psychogenic and was later successfully addressed to deep brain stimulation treatment.⁵⁰ In a Sardinian family with 4 definitely affected members and a typical DYT1 phenotype, 1 GAG mutation carrier presented with a movement disorder matching diagnostic criteria for clinically established psychogenic dystonia.⁵¹ This case highlights the uncertainties surrounding diagnostic criteria for PMD.

Post-traumatic dystonia refers to a further area of diagnostic vagueness and patients with this syndrome may be inappropriately considered to have PMD. In the “dystonia-causalgia” syndrome, spasms are associated with “fixed” tonic postures and often follow a peripheral injury;⁵² passive range of movement is reduced, there are no sensory tricks or gestes antagonistes, and there may be association of a complex regional pain syndrome. In a large series of patients with fixed dystonia, 37% fulfilled criteria for psychogenic dystonia, whereas in 10% of the prospectively studied and in 45% of those studied retrospectively, there was no evidence of a PMD.²⁸ These patients with fixed dystonia presented abnormalities of cortical excitability similar to those observed in primary mobile dystonia of undisputed organic nature.⁵³ Electrophysiological studies might help to differentiate organic from psychogenic forms of dystonia. It has been recently observed that abnormal plasticity is a hallmark of organic dystonia, whereas in psychogenic patients, plasticity may be normal.²⁹ Indicators for the diagnosis of organic dystonia in patients suspected to have a PMD are listed in Table 1.

Another post-traumatic movement disorder with fixed upper limb and neck dystonia has been considered to be psychogenic based on the observation of a conversion “V” profile on scales 1 and 3 of the Minnesota Multiphasic Personality Inventory (MMPI).⁵⁴ Other studies of post-traumatic cervical dystonia failed to identify any correlation with psychological or psychiatric features.^{55,56} There are also reports of patients with the phenotype of post-traumatic cervical dystonia, but no preceding trauma, who had no features suggestive of a psychogenic etiology.⁵⁷

DISEASES OTHER THAN MOVEMENT DISORDERS

Headache

The association between headache and craniocervical dystonia provides a still incomplete diagnostic puzzle.⁵⁸ The inclusion of headache in the differential diagnosis of dystonia is an intriguing and controversial topic. The International Classification of Headache Disorders (ICHD-II) has established a definite set of headaches associated with craniocervical dystonia denominated "headache attributed to craniocervical dystonia (code 11.2.3)."⁵⁹ Some patients with headache present mild head posturing and protective gestures that may raise suspicion of an underlying mild dystonia. Pain is a common feature in patients with cervical dystonia, whereas it is rare in other focal dystonias;⁶⁰ it is referred to the back of the head and neck and contributes significantly to disability, a feature that could mislead the clinician.

Response to treatment is not helpful to orientate the diagnosis. Botulinum toxin injections are used to manage patients with headache as well as those with cervical dystonia; the doses used and the injection sites are quite similar. Remarkably, the duration of pain relief is comparable in both conditions.^{61–63}

Idiopathic Scoliosis

Adolescent idiopathic scoliosis is a lateral curvature of the spine measuring greater than 10° in the coronal plane detected before the onset of skeletal maturity, which is not secondary to any known cause.⁶⁴ Adult scoliosis, instead, can be divided in two broad categories: idiopathic scoliosis and de novo degenerative scoliosis.⁶⁵ Idiopathic scoliosis, whether of adolescents or adults, has no known cause and patients with this condition are often referred to orthopedic surgeons for assessment.

There is evidence that idiopathic scoliosis may represent an initial manifestation of dystonia. Approximately 30% of adult patients with idiopathic scoliosis have a family history, suggesting the presence of a genetic cause.²⁷ There are no systematic reviews on the occurrence of isolated scoliosis in families that segregate for primary dystonia, although isolated scoliosis may be the presenting feature of dystonia in DYT1 carriers⁶⁶ and in patients with DOPA-responsive dystonia.^{67,68} An Irish family has been described in which 4 members had adult-onset cervical or brachial dystonia; 2 of these affected individuals also had coexistent adolescent-onset scoliosis and 4 other members of the

same family had isolated scoliosis with onset in childhood or adolescence.⁶⁹

Scoliosis has a high incidence in patients with cervical dystonia, because an imbalance of the spine at the cervical level may impact on all of its extension. Scoliosis was noted in 39% of 300 patients with cervical dystonia;⁷⁰ in another series, adolescent idiopathic scoliosis occurred in 16.5% of 296 cervical dystonia patients compared with 3% of 150 controls with back pain.⁷¹ In a case-control study,³¹ childhood or adolescent scoliosis occurred significantly more frequently in a group of 72 patients with cervical dystonia than among 144 control subjects with other neurological conditions. Whether scoliosis is genetically linked to cervical dystonia is still a debated issue. There is evidence that childhood- and adolescent-onset scoliosis is more frequent than expected in primary adult-onset cervical dystonia, possibly due to a common genetic mechanism.³¹ Thence, a neurological assessment for dystonia may be warranted in all subjects with primary scoliosis. The evidence supporting a diagnosis of dystonia in patients presenting with scoliosis is listed in Table 1.

DIFFERENTIAL DIAGNOSIS

Despite all recent advances in neurophysiology, imaging and genetics, the diagnosis of primary dystonia remains primarily a clinical exercise. Lower edge dystonic phenomenology, such as increased blinking, hoarse voice, or task-specific motor impairment, may be overlooked. At the initial presentation of the disease diagnostic uncertainty may be high and other features may mislead to diagnose another disease. Primary focal dystonia may be confounded particularly in favor of other movement disorders with overlapping clinical features. Rhythmic dystonic movements may raise suspicion of tremor, either essential tremor or parkinsonian tremor; dystonic slowness may lead to the suspicion of PD bradykinesia; jerky dystonic movements may resemble myoclonus. Dystonic postures are not always easy to distinguish from dystonic tics. Remissions, inconsistencies, and associated features may lead to suspect a psychogenic movement disorder, whereas neck pain may favor a misdiagnosis of tension headache.

The diagnostic workout should actively consider possible phenomenological inconsistencies and search for features of dystonia in such cases. Figure 1 reports a list of signs that may mislead the diagnosis if features of dystonia are not thoroughly evaluated. Increased awareness on potential diagnostic errors may derive from improved diagnostic skills, ultimately con-

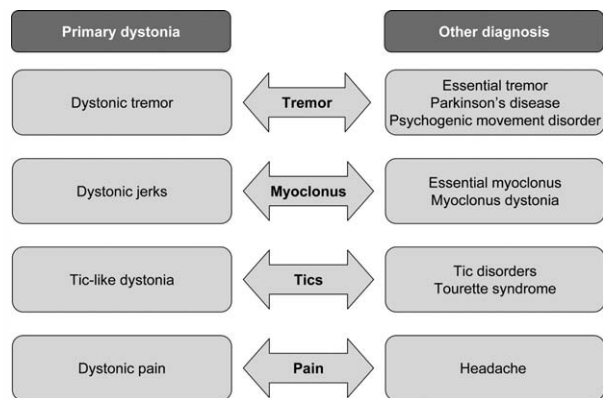


FIG. 1. Symptoms and signs that require interpretation to orient the diagnosis toward primary dystonia or another condition. Diagnostic inconsistencies and features of dystonia derived from published literature are listed in Table 1.

tributing to increased recognition of mild or nonprogressive cases.

Author Roles: Stefania Lalli was involved in writing of the first draft, bibliographic search, and execution of the manuscript. Alberto Albanese was involved in conception, organization, review, and critique of the manuscript.

Financial Disclosures: This work was funded in part by grants from the Italian Ministry of University and Research and the Italian Ministry of Health. Stefania Lalli: None. Alberto Albanese: Occasional consultancy advisory boards and honoraria from Lundbeck, Allergan, and Merz.

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