Neurological Sciences (2022) 43:6929–6945
https://doi.org/10.1007/s10072-022-06424-x

CONSENSUS PAPERS AND GUIDELINES

Diagnostic and therapeutic recommendations in adult dystonia: a joint document by the Italian Society of Neurology, the Italian Academy for the Study of Parkinson's Disease and Movement Disorders, and the Italian Network on Botulinum Toxin

Marcello Romano[1] · Sergio Bagnato[2] · Maria Concetta Altavista[3] · Laura Avanzino[4,5] · Daniele Belvisi[6,7] · Matteo Bologna[6,7] · Francesco Bono[8] · Miryam Carecchio[9] · Anna Castagna[10] · Roberto Ceravolo[11] · Antonella Conte[6,7] · Giuseppe Cosentino[12] · Roberto Eleopra[13] · Tommaso Ercoli[14] · Marcello Esposito[15] · Giovanni Fabbrini[6,7] · Gina Ferrazzano[6] · Stefania Lalli[16] · Marcello Maria Mascia[17] · Maurizio Osio[18] · Roberta Pellicciari[19] · Simona Petrucci[20,21] · Enza Maria Valente[22,23] · Francesca Valentino[24] · Mario Zappia[25] · Maurizio Zibetti[26] · Paolo Girlanda[27] · Michele Tinazzi[28] · Giovanni Defazio[14,15,16,17] · Alfredo Berardelli[6,7]

Received: 16 July 2022 / Accepted: 21 September 2022 / Published online: 3 October 2022

Abstract
The diagnostic framework and the therapeutic management of patients with adult dystonia can represent a challenge for clinical neurologists. The objective of the present paper is to delineate diagnostic and therapeutic recommendations for dystonia provided by a panel of Italian experts afferent to the Italian Society of Neurology, the Italian Academy for the Study of Parkinson's Disease and Movement Disorders, and the Italian Network on Botulinum Toxin. We first discuss the clinical approach and the instrumental assessment useful for diagnostic purpose. Then, we analyze the pharmacological, surgical, and rehabilitative therapeutic options for adult dystonia. Finally, we propose a hospital-territory network model for adult dystonia management.

Keywords Blepharospasm · Botulinum toxin · Cervical dystonia · Dystonia · Rehabilitation · Upper limb dystonia

Introduction

Dystonia is a movement disorder characterized by prolonged and/or intermittent muscle contractions that induce abnormal postures and repetitive movements [1–5]. Dystonia prevalence varies greatly in different epidemiological studies, partly due to methodological differences between studies. For this reason, it is not clear whether isolated forms of dystonia should be considered rare diseases. Of 27 studies assessing the prevalence of adult-onset dystonia, 20 provided a prevalence ranging from 3 to 37 cases per million individuals, 5 showed a prevalence ranging from 40 to 70 cases per million, and 2 population-based studies (performed in distant areas such as South Tyrol in Italy and the Faroe Islands) reported a high prevalence (7320 cases per million individuals over 50 years old in the Italian population and 8800 cases per million individuals over 40 years old in the Faroe Islands population) [6]. Finally, low prevalence estimates were found for early-onset dystonias (3–50 cases per million) [7, 8].

General clinical features

Dystonic movements are typically prolonged and patterned with a torsional component (a feature that distinguishes dystonic movements from other hyperkinetic movement disorders) and are usually associated with simultaneous contraction (co-contraction) of agonist and antagonist muscles [4, 9–11]. Dystonic movements are worsened by fatigue and stress, may be present at rest, and increase with voluntary movements [12, 13]. When dystonia is induced by a specific action only, it is referred to as task-specific dystonia (e.g., writer's cramp) [14].

✉ Alfredo Berardelli
alfredo.berardelli@uniroma1.it

Extended author information available on the last page of the article

In most cases, clinical observation is adequate to identify both dystonic postures and involuntary movements, the cardinal signs of dystonia. Other clinical signs to search for when dystonia is suspected include the following: (1) tremor: rhythmic movement produced by the activation of dystonic muscles, often exacerbated by attempts to maintain the primary posture; (2) overflow: diffusion of postures or dystonic movements to body regions contiguous to those primarily activated by dystonia; (3) antagonistic gestures, also called sensory tricks, or maneuvers that relieve dystonia: specific voluntary movements patients learn to use in order to temporarily stop or reduce the intensity of dystonia; (4) "mirroring": a phenomenon that mainly affects the upper limbs, characterized by involuntary movements or abnormal postures in the contralateral limb with respect to that affected by dystonia during the voluntary activation of the latter.

Classification

The current classification of dystonia used to guide patient therapeutic management is based on two diagnostic axes: clinical characteristics and etiology [4].

Axis I: Clinical features

In order to define the clinical characteristics of patients with dystonia, five descriptors have been used: age of onset, body distribution, temporal pattern, coexistence of other movement disorders, and occurrence of other neurological or systemic manifestations.

Age of onset

Age of onset has prognostic relevance since, in childhood onset particularly, it may determine a greater chance of identifying a specific cause and a greater probability of progression towards a generalized form. In contrast, adult-onset dystonias are usually focal or segmental.

Body distribution

In addition to diagnostic and therapeutic implications, description of the body distribution allows the spread of motor symptoms to be evaluated over time in each patient.

The current classification identifies the following forms: (1) focal: one body region is involved (blepharospasm (BS), oromandibular dystonia (OMD), cervical dystonia (CD), laryngeal dystonia, and upper/lower limb dystonia); (2) segmental: two or more contiguous body regions are involved (e.g., cranial and upper limb dystonia); (3) multifocal: two or more non-contiguous body regions are involved; (4) generalized: the trunk and at least two other sites are involved; (5) hemidystonia: more than one body region restricted to one body side is involved.

Temporal pattern

This descriptor refers both to progression of the disorder over time (disease course) and to phenomenological changes related to circadian rhythm, voluntary activity, external triggers, compensatory phenomena, sensory tricks, or psychological states (variability).

The disease course can be static or progressive, with four different patterns of variability: (1) persistent: substantial invariability of dystonia throughout the day; (2) action-specific: dystonia appears during a specific activity or task; (3) with diurnal fluctuations: recognizable circadian variations of severity and phenomenological characteristics; and (4) paroxysmal: sudden and self-limiting episodes usually induced by triggers.

Coexistence of other movement disorders

Dystonia may be an isolated entity or combined with other movement disorders, such as myoclonus and parkinsonism. In the combined form, dystonia may not be the main movement disorder.

Coexistence of other neurological or systemic manifestations

Additional neurological or systemic pathological manifestations allow the diagnostic pathway to be directed towards specific underlying pathologies.

Axis II: Etiology

The second axis, related to etiology of the dystonic disorder, is constantly evolving on the basis of new scientific achievements.

To date, two complementary characteristics can be used for classification: (1) morphological alterations, identified with neuroimaging techniques or inferred from pathology; and (2) inheritance patterns, definable through genetic, metabolic, or other tests.

Accordingly, the following subgroups can be identified: (1) degenerative forms: structural anomalies progressing over time; (2) static forms: non-progressive neuronal developmental abnormalities or acquired forms; and (3) absence of degeneration or structural lesions.

Acquired, hereditary, and idiopathic forms can be identified. Acquired forms include numerous pathological conditions caused by different brain injuries (vascular, toxic, metabolic, neoplastic, etc.). Inherited forms have a proven

genetic origin with autosomal dominant, autosomal recessive, X-linked, or mitochondrial transmission. No causes have been identified for idiopathic forms, which may be familial or sporadic.

Diagnosis

Clinical features of focal dystonias

Below we describe the main clinical features of BS, OMD, CD, laryngeal dystonia, and upper limb dystonia.

Blepharospasm

According to the diagnostic guidelines validated in 2013 [15], BS is characterized by involuntary narrowing or complete closure of the eyelid rim due to involuntary spasms. By definition, eyelid spasms are characterized by involvement of the orbicularis oculi muscle and by contraction of the corrugator supercilii muscle with lowering of the medial margin of the eyebrow. In BS, eyelid spasms are stereotyped, synchronous, symmetrical, and often prolonged. However, some patients present only with an increased blink rate [16]. The presence of an antagonistic gesture supports the dystonic origin of the disorder.

Differential diagnoses include uni/bilateral ptosis in patients with disorders of the neuromuscular junction, such as myasthenia gravis or other conditions such as hemifacial spasm (including the rare bilateral variant). An uncommon clinical variant of BS is apraxia of eyelid opening, which is characterized by the inability to open the eyes after voluntary or involuntary closure of the eyelid rim. This condition is plausibly due to excessive contraction of the pretarsal component of the orbicularis oculi muscle. Various clinical scales are used to assess BS severity, including the Jankovic Rating Scale (JRS) (Table 1), and the more recent Blepharospasm Severity Rating Scale (Table 2) [17]. Recently, a scale to assess the severity of apraxia of eyelid opening has also been introduced [18].

Cervical dystonia

To diagnose CD, positive and negative signs should be evaluated [4, 19]. The most important positive signs are repetitive/stereotyped movements of the head and/or neck and/or abnormal stereotyped postures, spontaneous or triggered by voluntary movement, with deviation of the head with respect to a neutral position. Tremor is a frequent associated feature [20, 21].

Multiple clinical phenotypes of CD may be differentiated, including torticollis (rotation of the head and neck with respect to the trunk), laterocollis (inclination of the head and neck on the shoulder), and antero- and retrocollis (anterior flexion and posterior extension of the head and neck on the trunk, respectively) [4, 22]. The presence of antagonistic

Table 1 Jankovic Rating Scale

Severity
None
☐ 0
Increased blinking present only with external stimuli (e.g., bright light, wind, reading, driving)
☐ 1
Mild but spontaneous eyelid fluttering (without actual spasm), definitely noticeable, possibly embarrassing, but not functionally disabling
☐ 2
Moderate, very noticeable spasm of eyelids, mildly incapacitating
☐ 3
Severe, incapacitating spasm of eyelids and possibly other facial muscles
☐ 4
Frequency
None
☐ 0
Slightly increased frequency of blinking
☐ 1
Eyelid fluttering lasting less than 1 s in duration
☐ 2
Eyelid spasm lasting more than 1 s, but eyes open more than 50% of waking time
☐ 3
Functionally "blind" due to persistent eye closure (blepharospasm) more than 50% of waking time
☐ 4

Table 2 Blepharospasm Severity Rating Scale

Intensity rating	
Item A1) Type of eyelid spasm	
☐ Brief (< 3 s duration) eyelid spasms with complete rim closure = score 1	
☐ Prolonged (≥ 3 s duration) eyelid spasms with partial rim closure = score 2	
☐ Prolonged (≥ 3 s duration) eyelid spasms with complete rim closure = score	3
Item A2) Apraxia of eyelid opening	
☐ Yes = score 2	
☐ No = score 0	
Item A3) OO spasms occur during writing	
☐ Yes = score 1	
☐ No = score 0	
Item A4) Average duration of prolonged eyelid spasm with complete rim closure recorded while patient at rest, eyes open, for 2 min. Calculate the correspondent tertile as follows:	
☐ I tertile = 3 to 4 s = score 1	
☐ II tertile = 4.1 to 5 s = score 2	
☐ III tertile = > 5 s = score 3	
Frequency rating	
Item B1) Count number of blinks + brief eyelid spasm/min (patient at rest, eyes open, for 2 min) and calculate the corresponding tertile as follows:	
☐ I tertile = 1 − 18 blinks + brief spasm / min = score 1	
☐ II tertile = 19 − 32 blinks + brief spasm / min = score 2	
☐ III tertile = > 32 blinks + brief spasm / min = score 3	
Item B2) Count number of prolonged eyelid spasm with complete rim closure/min (patient at rest, eyes open, for 2 min) and calculate the corresponding quartile as follows:	
☐ I tertile = 1–3/min = score 1	
☐ II tertile = 3.1–7/min = score 2	
☐ III tertile = > 7/min = score 3	

Total score = Intensity + Frequency = (A1 + A2 + A3 + A4) + (B1 + B2)

gestures (touching the chin, forehead, or nape, or supporting the head by touching the temples with the hand, etc.) is a positive sign supporting the diagnosis of CD [23].

Some clinical elements, called *negative signs*, suggest a non-dystonic nature in a suspected case of CD. Negative signs should be considered red flags in the differential diagnosis with other clinical conditions mimicking CD. Negative signs include (1) involuntary fixed posture, (2) weakness of cervical muscles (which can occur in patients with myasthenia gravis or motoneuron disease), and (3) the possibility to partially suppress dystonic movements/postures (a typical characteristic of tic disorders).

Several scales have been validated to evaluate CD severity: the Tsui Scale is one of the most widespread and easiest to apply (Table 3). Another commonly used scale is the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

Oromandibular, laryngeal, and upper limb dystonias

OMD, laryngeal (spasmodic dysphonia, SD), and upper limb dystonias do not share clinical diagnostic criteria. Therefore, the presence of stereotyped and repetitive movements, spontaneous or induced by a specific motor task, should be evaluated for diagnostic purposes.

From a clinical point of view, the main characteristics of the aforementioned forms of dystonia are (1) OMD with mouth opening or closing; (2) adductor or abductor SD; and (3) task-specific upper limb dystonia (writer's cramp, musician's dystonia), non-task-specific upper limb dystonia, and task-specific dystonic tremor (e.g., primary writing tremor).

In the clinical evaluation of OMD [24], SD [25], and upper limb dystonia [26, 27], it is very important to exclude non-neurological conditions that can mimic dystonic postures (pseudodystonias) [19].

No clinical scales have been validated to assess the severity of OMD and upper limb dystonia. In SD, the Voice Handicap Index is widely used (Table 4). To confirm OMD and SD diagnoses, a neurological evaluation should be integrated with clinical and instrumental evaluations by other specialists. In patients with suspected OMD, a maxillofacial/gnathological evaluation should be performed to exclude temporo-mandibular joint disorders such as bruxism or spontaneous dislocation of the mandibular condyles. In patients with SD, the

Table 3 Modified Tsui Scale for cervical dystonia

Amplitude of sustained movements		Duration of sustained movements	Shoulder elevation	Tremor	
Rotation	0 = absent	1 = intermittent	0 = absent	Severity	1 = mild
	1 = < 15 degree	2 = constant	1 = mild and intermittent		2 = severe
	2 = 15–30 degree		2 = mild and constant, or severe and intermittent	Duration	1 = constant
	3 = > 30 degree		3 = severe and constant		2 = continuous
Tilt	0 = absent				
	1 = < 15 degree				
	2 = 15–30 degree				
	3 = > 30 degree				
Ant/Retro	0 = absent				
	1 = < 15 degree				
	2 = 15–30 degree				
	3 = > 30 degree				
A = Rotation + Tilt + Ant/Retro		B = 1 − 2	C = 0 − 3	D = Severity (1 − 2) × Duration (1 − 2)	

Total score = [(A) × (B)] + (C) + (D)

diagnostic process includes phoniatric evaluation. To exclude other laryngeal pathologies, such as vocal cord paralysis or laryngeal lesions, a laryngoscopy is recommended, along with the video recording of phonation tests as necessary.

Non-motor symptoms of adult dystonias

Non-motor symptoms may precede the appearance of motor symptoms, and this supports the hypothesis that they are an integral manifestation of the disease itself and not a mere consequence of motor symptoms. Patients with BS often report burning and dry eyes, patients with CD often suffer from neck pain, and patients with SD may present with laryngeal irritation. In adults, focal dystonias are often complicated by anxiety and depression and sometimes by obsessive–compulsive disorder [28]. Sensory function alterations have also been described [29]. Finally, there are some cognitive function alterations (such as visuospatial processing, prospective memory), often subclinical, that may compromise the quality of life of patients with dystonia [30].

In conclusion, an overall clinical evaluation that includes both motor and non-motor aspects is essential for a better definition of the health status of patients with dystonia. However, a clinical scale with these characteristics is only available for CD [31].

Instrumental assessment

Clinical neurophysiology

Neurophysiological tests may play a role in the diagnosis of primary dystonia.

Surface electromyography (EMG) provides useful information about prolonged muscle activity with co-contraction of agonist and antagonist muscles or tremor activity [32]. EMG can also be useful in choosing the muscles to be treated with botulinum toxin inoculation (in order to have a better definition of the dystonic pattern, quantification of the degree of muscle activation, and a differential diagnosis between coactivation of antagonistic muscles and compensatory muscle activation) [33, 34]. Somatosensory evoked potentials and electroencephalography might be useful in case of dystonia associated with myoclonus in order to identify possible cortical generator of the hyperkinesia [35]. Other neurophysiological tests can be used to identify increased excitability in specific regions of the central nervous system (e.g., the blink reflex recovery cycle in patients with BS) [16].

Neuroimaging

Brain magnetic resonance imaging (MRI) is the main neuroradiological investigation used in clinical practice. In idiopathic forms and in most isolated genetic forms, brain MRI is normal, while in secondary forms it can help detect specific pathological abnormalities. MRI can also help identify forms of dystonia secondary to focal lesions (e.g., due to vascular accidents) in the basal ganglia, the most commonly involved brain region [36], or in other structures of the central nervous system, such as the cerebellum [37] or the white matter. Standard MRI protocol should use sequences able to identify focal or extensive signal alterations, diffuse or selective atrophies, and abnormal deposition of heavy metals and calcium. Most experts agree that brain MRI is always

Table 4 Voice Handicap Index 30

		Never	Almost never	Sometimes	Almost always	Always
Part I-F (functional)						
F1	My voice makes it difficult for people to hear me	0	1	2	3	4
F2	People have difficulty understanding me in a noisy room	0	1	2	3	4
F3	My family has difficulty hearing me when I call them throughout the house	0	1	2	3	4
F4	I use the phone less often than I would like to	0	1	2	3	4
F5	I tend to avoid groups of people because of my voice	0	1	2	3	4
F6	I speak with friends, neighbors, or relatives less often because of my voice	0	1	2	3	4
F7	People ask me to repeat myself when speaking face-to-face	0	1	2	3	4
F8	My voice difficulties restrict personal and social life	0	1	2	3	4
F9	I feel left out of conversations because of my voice	0	1	2	3	4
F10	My voice problem causes me to lose income	0	1	2	3	4
Part II-P (physical)						
P1	I run out of air when I talk	0	1	2	3	4
P2	The sound of my voice varies throughout the day	0	1	2	3	4
P3	People ask, "What's wrong with your voice?"	0	1	2	3	4
P4	My voice sounds creaky and dry	0	1	2	3	4
P5	I feel as though I have to strain to produce voice	0	1	2	3	4
P6	The clarity of my voice is unpredictable	0	1	2	3	4
P7	I try to change my voice to sound different	0	1	2	3	4
P8	I use a great deal of effort to speak	0	1	2	3	4
P9	My voice is worse in the evening	0	1	2	3	4
P10	My voice "gives out" on me in the middle of speaking	0	1	2	3	4
Part III-E (emotional)						
E1	I am tense when talking to others because of my voice	0	1	2	3	4
E2	People seem irritated with my voice	0	1	2	3	4
E3	I find other people don't understand my voice problem	0	1	2	3	4
E4	My voice problem upsets me	0	1	2	3	4
E5	I am less outgoing because of my voice problem	0	1	2	3	4
E6	My voice makes me feel handicapped	0	1	2	3	4
E7	I feel annoyed when people ask me to repeat	0	1	2	3	4
E8	I feel embarrassed when people ask me to repeat	0	1	2	3	4
E9	My voice makes me feel incompetent	0	1	2	3	4
E10	I am ashamed of my voice problem	0	1	2	3	4

recommended in patients with early-onset dystonia and in patients with other associated neurological signs. The diagnostic approach in adult-onset dystonia is more heterogeneous, especially in patients with focal or segmental dystonia. Some authors suggest that brain MRI should be performed only in the presence of hemidystonia at clinical onset or in patients with generalized dystonia [38], while other authors believe that it should be considered in every case to identify secondary forms, regardless of the affected body site. Brain MRI is especially important in the pediatric population given the higher incidence of metabolic pathologies and disorders associated with heavy metal accumulation that may present with isolated dystonia [39].

Laboratory tests

Routine blood tests should be performed at the time of diagnosis. In addition to routine tests, the study of copper metabolism (serum copper and ceruloplasmin levels, 24-h urinary copper excretion) can be performed in pediatric and young patients to exclude Wilson's disease. In patients with dystonia-plus (dystonia combined with other neurological signs or symptoms) or in the presence of peculiar MRI findings, other tests may be required, including complete blood count in search of acanthocytes (neuroacanthocytosis), alpha fetoprotein plasma levels (ataxia with oculomotor apraxia and ataxia-telangiectasia), evaluation of antiphospholipid

antibodies, assessment of calcemia, phosphatemia, and parathyroid hormone (basal ganglia calcifications), and evaluation of creatine phosphokinase, blood lactate, and pyruvate dosage (mitochondrial diseases) [9].

Genetic tests

Genetic analysis should be performed when clinical data is suggestive of a hereditary form. Despite the growing role of molecular diagnosis, in clinical practice only patients with specific clinical and anamnestic characteristics should be referred for genetic testing. Mutations of genes associated with genetic dystonias (Table 5) may be searched with the next-generation sequencing (NGS) techniques [40, 41]. NGS should be reserved for subjects with a well-founded suspicion of a genetic form, especially in presence of neurological conditions in which dystonia is associated to other hyperkinetic or hypokinetic movement disorders or is part of a more complex clinical spectrum. NGS is able to analyze many genes associated with dystonias. NGS is superior to single-gene sequencing (Sanger sequencing), and its costs are now reduced due to a wider availability of the technologies necessary to carry out these investigations.

In general, the following are recommended: (1) to search for the common delGAG mutations in the *DYT-TOR1a* (*DYT1*) gene in early-onset isolated dystonia (before the age of 30 years) with initial involvement of the lower limbs, and in patients with clinical onset after 30 years but with a family history of early-onset autosomal dominant dystonia; (2) to search for mutations in the *DYT-THAP1* (*DYT6*) gene in patients with cranio-cervical dystonia, with or without generalization, with early onset and/or a family history of autosomal dominant dystonia; (3) to search for mutations in the *DYT-SGCE* (*DYT11*) gene in patients who, before the age of 18 years, show myoclonus involving the upper half of the body (head, neck, trunk, upper limbs), especially if it is transmitted in an autosomal dominant way and triggered by the action. If direct sequencing of the *DYT-SGCE* gene is negative, exclusion of exonic/multi-exonic/genomic mutations should be carried out using the multiplex ligation-dependent probe amplification (MLPA) technique; (4) to search for mutations in the *DYT-PRRT2* and *DYT-PNKD* (*MR-1*) genes in patients with kinesigenic and non-kinesigenic paroxysmal dystonia, respectively; (5) to search for mutations in the *DYT-SLC2A1* (*GLUT1*) gene in patients with exercise-induced paroxysmal dystonia, particularly if associated with a reduction in the cerebrospinal fluid/serum glucose ratio, epileptic seizures with pediatric onset, intellectual disability, and/or hemolytic anemia; (6) to evaluate the effect of dopaminergic therapy in all patients with early-onset dystonia, especially in the lower limbs and with circadian worsening, in order to direct genetic investigations towards dopa-responsive forms (*DYT-GCH-1* gene and others); (7) to search for mutations in the *KMT2B* gene in patients with early-onset severe generalized dystonia who are DYT1 negative and present with additional features, such as short stature, mild intellectual disability, or mild facial dysmorphic traits; (8) not to perform genetic tests on asymptomatic subjects (adults or children) in families with genetically ascertained dystonia; (9) not to perform genetic tests for common forms of focal dystonia in the absence of clear or strongly suspected inheritance.

Genetic counseling

Before referring a patient with dystonia for genetic testing, a consultation with a medical geneticist or a neurologist expert in movement disorder genetics is recommended in order to explain the purpose of the genetic test, any limitations of the methods used, and any prognostic or therapeutic implications in case of positive results.

All genetic investigations require informed consent indicating the analysis to be performed, which should be clearly explained by the neurologist or geneticist. The same person who referred the patient for the analysis should preferably explain the content of the report. Genetic counseling must be available to explain the genetic report and the prognostic and therapeutic implications in each specific case. This is particularly relevant in terms of response to some medical (e.g., dopa-responsive dystonia) or surgical therapies (patients with DYT-TOR1a dystonia have an excellent and long-lasting response to deep brain stimulation) [42]. If a mutation in a gene associated with dystonia is identified, it is important to explain both the risk of transmitting the disease and the risk of first-degree relatives being carriers of the same mutation and developing the disease. Genetic tests are never indicated in under-18 subjects without clinical evidence of dystonia, even if they are children/relatives of patients with genetically proven dystonia.

In the event of difficult-to-interpret results (variants of uncertain significance), it is particularly important to extend the genetic analysis to other family members in order to identify the possible pathogenicity of the identified genetic variant.

Dystonia therapy

The therapeutic strategy for dystonia must be individualized and specific to each patient, particularly with regard to age (pediatric, juvenile, adult), topographical distribution of dystonic symptoms (focal, segmental, or generalized), and potential risks and adverse effects of treatment (focal or systemic) (Table 6).

Table 5 Common forms of hereditary dystonic syndromes grouped according to axis I criteria

Gene/Protein	Proposed name	Inheritance	Phenomenology
Isolated hereditary dystonic syndromes			
DYT1 (TOR1A/torsin A)	DYT-TOR1A	AD	Generalized dystonia with early onset. Typically starts in the limbs and spreads to the neck and face. Alternative phenotypes are described
DYT4 (TUBB4/tubulin beta 4)	DYT-TUBB4A	AD	Rare form of dystonia with onset with spasmodic dysphonia, cranio-cervical involvement, and possible secondary generalization
DYT6 (THAP1/THAP domain with apoptosis-associated protein 1)	DYT-THAP1	AD	Onset in adolescence, generalized or segmental involvement with predominantly cranio-cervical and laryngeal involvement
DYT24 (ANO3/anoctamin 3)	DYT-ANO3	AD	Adult-onset cranio-cervical dystonia with laryngeal involvement and tremor in the upper limbs
DYT25 (GNAL/guanine nucleotide-binding protein subunit alpha L)	DYT-GNAL	AD	Adult-onset cranio-cervical dystonia with typical involvement of the larynx, trunk and limbs
Combined hereditary dystonic syndromes			
DYT5a (GCH1/GTP cyclohydrolase 1)	DYT/PARK-CGH1	AD	Childhood or juvenile onset, responsive to L-dopa, with parkinsonism and diurnal fluctuations
DYT5b	DYT/PARK TH	AR	Milder form of dopa-responsive dystonia with childhood/juvenile onset
DYT3 (TAF1/TATA box-binding protein-associated factor 1	DYT/PARK TAF1	XD	Segmental or generalized dystonia with severe oromandibular involvement and parkinsonism unresponsive to L-dopa. Endemic in Panay (Philippines), where it is known as lubag
DYT12 (ATP1A3/ATPase Na^+/K^+ transporting subunit alpha 3)	DYT/PARK ATP1A3	AD	Polymorphic phenotypes: rapid onset dystonia-parkinsonism, alternating hemiplegia of childhood and CAPOS syndrome (cerebellar ataxia—areflexia—optic atrophy—sensorineural deafness)
PARK2 (Parkin/E3 ubiquitin ligase)	PARK-Parkin	AR	Parkinsonian syndrome with juvenile onset with prolonged response to dopaminergic therapy and dystonia prevalent in the lower limbs
DYT11 (SGCE/epsilon-sarcoglycan)	DYT-SGCE	AD	Myoclonic dystonia with prevalent involvement of the neck and upper limbs
N/D (NKX2.1/homeobox protein Nkx-2.1	CHOR-NKX2-1	AD	Onset with chorea that may progress to myoclonic dystonia during the disease course
N/D (ADCY/adenylate cyclase 5)	CHOR-DYT-ADCY5	AD	Variable phenotypes: paroxysmal or persistent chorea with childhood onset; dystonia
DYT10 (PRRT2/proline-rich transmembrane protein 2)	PxMD-PRRT2	AD	Paroxysmal dystonia and choreoathetosis
DYT8 (MR1/myofibrillogenesis regulator 1)	PxMD-PNKD	AD	Paroxysmal non-kinesigenic dystonia, chorea, athetosis or ballism precipitated by specific factors (alcohol, caffeine, stress, hunger, fatigue, tobacco)
DYT18 (SLC2A1/glucose transporter protein type 1)	PxMD-SLC2A1	AD	Chorea and dystonia induced by exercise
Hereditary dystonic syndromes associated with additional neurological disorders			
SCA3 (ATXN3/ataxin-3)	SCA_ATXN3	AD	Ataxic syndrome that can present with parkinsonism, dystonia, chorea, and spasticity. Neuropathy or lower motor neuron involvement
SCA17 (TBP/TATA box-binding protein)	SCA-TBP	AD	Ataxic syndrome that can present with chorea and dystonia; can be associated with dementia and psychosis
N/D (TIMM8A/mitochondrial import inner membrane translocase subunit Tim8 A)	DYT-TIMM8A	XD	Mohr-Tranebjaerg syndrome: dystonia associated with other clinical features such as sensorineural deafness, visual and/or cognitive impairment, behavioral disorders, pyramidal signs

Table 5 (continued)

Gene/Protein	Proposed name	Inheritance	Phenomenology
N/D (DCAF17/nuclear transmembrane protein)	NBIA/DYT-DCAF17	AR	Woodhouse-Sakati syndrome: dystonia associated with other clinical features, such as dysarthria, deafness, epilepsy, cognitive impairment, hypogonadism, alopecia, diabetes mellitus, dysthyroidism
NBA1 or *PKAN* (NBIA/DYT PANK2/pantothenate kinase 2)	NBIA/DYT-PANK2	AR	Dystonia with childhood or adolescent onset, associated with dysarthria, rigidity, pyramidal signs, and cognitive impairment
NBIA2, *PARK14*, or *PLAN* (PLA2G6/A2 phospholipase)	NBIA/DYT/PARK-PLA2G6	AR	Dystonia often associated with chorea, parkinsonism, dementia, pyramidal signs, and psychiatric disorders

AD, autosomal dominant; *AR*, autosomal recessive; *XD*, X-linked dominant

Current treatments for dystonia include oral medications, botulinum toxin, non-invasive neuromodulation, invasive neuromodulation, and rehabilitation [9]. Dystonia treatment should improve abnormal movements and pathological postures and relieve pain. Moreover, treatment should prevent comorbidities such as contractures and orthopedic complications. An effective therapeutic approach can also improve the mood disorders and anxiety often associated with dystonic symptoms.

Oral drug therapy

A specific therapy, based on pathogenetic mechanisms, exists only for a small and heterogeneous group of rare neurological disorders in which dystonia is part of a multisystemic syndrome or can be isolated [9, 43]: (1) Dopa-responsive dystonia is a genetically heterogeneous group of dystonias caused by various defects in dopamine biosynthesis presenting as progressive dystonia in children and young adults. Levodopa combined with a peripheral decarboxylase inhibitor is an effective treatment. Starting dosage is a half tablet of levodopa-carbidopa 100 mg/25 mg twice a day, which can be increased to 20 mg/kg/day of levodopa divided into three doses. In children, the recommended dosage is 1–3 mg/kg/day divided into three doses. Side effects may include nausea, vomiting, orthostatic hypotension, and psychosis. (2) Wilson's disease is an inherited autosomal recessive disease caused by mutations in the *ATP7B* gene resulting in a variety of movement disorders that frequently includes dystonia. Treatment includes specific drugs such as copper chelators and/or zinc therapy to reduce copper intestinal absorption.

Dystonia as a clinical manifestation of autoimmune movement disorders is treatable with drugs specific to the different pathologies. Antibacterial therapy is important in the treatment of dystonic postures in Sydenham's chorea, while immunomodulating agents are indicated for this group of dystonias.

Symptomatic oral drugs represent the most common therapy in dystonia and may improve symptoms in some patients with generalized or segmental dystonia. Oral drugs include the following:

Anticholinergic drugs These are considered the most effective oral drugs in the treatment of dystonia. The effectiveness of anticholinergic drugs is related to their effects on the hyperactivity of striatal cholinergic interneurons. Trihexyphenidyl is the anticholinergic drug with the most scientific evidence of effectiveness. It is indicated in generalized and segmental dystonias in both pediatric and adult patients. Dosages range from 1 mg twice a day to 80 mg per day divided into three doses, though dosage should be increased very slowly. Side effects are common for high dosages and include cognitive disorders, sedation, dry mouth, constipation, blurred vision, and urinary retention.

Baclofen Oral baclofen, a $GABA_B$ receptor agonist, increases GABAergic sensorimotor inhibition in the basal ganglia. The daily dose ranges between 25 and 120 mg. Side effects include nausea, sleepiness, dizziness, generalized fatigue, and an excessive reduction in muscle tone. Baclofen can be administered intrathecally by spinal infusion pumps in axial and lower limb dystonia.

Benzodiazepines The effectiveness of these drugs is due to their binding to $GABA_A$ receptors, which increases inhibitory signals. Benzodiazepines are considered second- or third-choice agents in the treatment of dystonia. Clonazepam and diazepam are the most used benzodiazepines due to their long pharmacological half-life, and they are indicated in acquired hemidystonia. The daily dosage of clonazepam is up to 3.5 mg, and frequent side effects include sleepiness, dizziness, ataxia, fatigue, depression, and behavioral disorders. Clonazepam can also be used in myoclonus-dystonia.

Table 6 Practical recommendations for therapeutic intervention for dystonia

	First choice	Additional approaches
Blepharospasm	BoNT class II evidence	
Oromandibular dystonia	BoNT class II evidence	DBS (Gpi or STN)
Cervical dystonia	BoNT type A class I evidence	DBS Gpi Sensory motor re-training Multisensory feedback (SPRInT)
Laryngeal dystonia	BoNT class II evidence	Speech therapy
Upper limb dystonia (focal hand or musician's hand dystonia)	BoNT class II evidence	Rehabilitation training Sensorimotor re-training
Lower limb dystonia	BoNT class III evidence	
Generalized dystonia	DBS: • Gpi • STN and thalamus Other surgical procedures	Oral (anticholinergic, baclofen, benzodiazepines, levodopa, tetrabenazine)
Genetic generalized dystonia DYT-TOR1A KMT2B	DBS: • Gpi, • STN and thalamus	
Segmental dystonia	BoNT type A	Oral (anticholinergic, baclofen, benzodiazepines, levodopa, tetrabenazine)
	DBS: • Gpi, • STN and thalamus	Thalamotomy and pallidotomy
Combined dystonia • Dystonia + Parkinsonism	Oral (levodopa + carbidopa, dopaminergic agonists, anticholinergic)	
• Myoclonus-dystonia	Zonisamide Clonazepam Other drugs	
• Dystonia with spasticity	Baclofen (oral, intrathecal and intraventricular) BoNT	
Late-onset dystonia (antipsychotic drugs)	Tetrabenazine DBS Gpi (variable results)	
Paroxysmal disorders • Paroxysmal kinesigenic dyskinesia	Low dose carbamazepine Ketogenic diet	
• Paroxysmal exercise-induced dystonia	Levodopa Dopaminergic or anticholinergics	
Dopa-responsive dystonia	Levodopa Dopaminergic antagonists Anticholinergics 5 Hydroxy-tryptophan	
Wilson's disease	Oral (copper chelanting agents and zinc) Liver transplant DBS	

BoNT, botulinum toxin; *DBS*, deep brain stimulation; *GPi*, globus pallidus internus; *SPRInT*, Sensorimotor Perceptive Rehabilitation Integrated; *STN*, subthalamic nucleus

Dopaminergic drugs Dopaminergic neurotransmission enhancement by coactivation of D1 and D2 receptors is a useful therapeutic strategy in generalized dystonia. Levodopa and other dopaminergic agonists are used for symptomatic therapy of acquired dystonia, myoclonus-dystonia, and dystonia-parkinsonism. The starting dosage is a half tablet of levodopa-carbidopa 100 mg/25 mg twice a day and can be increased to 20 mg/kg/day of levodopa divided into three doses.

Antidopaminergic drugs Tetrabenazine, a vesicular monoamine transporter-2 (VMAT2) inhibitor, is indicated in late-onset dystonia. Tetrabenazine can be started with a dosage of 25 mg 1–3 times a day. The daily dose can be further increased by 25 mg every 3 or 4 days up to a maximum daily dose of 200 mg.

Antiepileptic drugs Low doses of carbamazepine (200–400 mg/day) are indicated for the treatment of dystonic

spasms in paroxysmal kinesigenic dystonia. Zonisamide may be useful in the treatment of myoclonus-dystonia.

Botulinum toxin therapy

Botulinum neurotoxin (BoNT) is an excellent therapeutic tool in dystonia [44–47]. BoNT injection is a highly targeted therapy that reduces the risk of adverse systemic effects, which are common with oral drug therapies. Local injection of BoNT into overactive muscles reduces excessive muscle activation and, in some cases, also pain and disability. BoNT acts through mechanisms operating at peripheral and central levels [44].

BoNT treatment is the first-choice therapy for most focal and segmental dystonias. BoNT type A and B are the two serotypes used in the treatment of focal adult dystonias. The corresponding commercial products of botulinum toxin A are onabotulinumtoxinA (Botox, Allergan), abobotulinumtoxinA (Dysport, Ipsen), and incobotulinumtoxinA (Xeomin, Merz). The BoNT type B commercial product is rimabotulinumtoxinB (NeuroBloc, Eisai). Biological activity, measured in units, differs among the different products. Therefore, it is important to be aware of the properties of the various formulations and that toxin units are not interchangeable among the different commercial products (Table 7).

BoNT should be used as the first therapeutic option for cervical dystonia (class I evidence). It is recommended for BS, OMD, focal upper limb dystonia, and laryngeal dystonia (class II evidence) and can be considered for focal lower limb dystonia (class III evidence). BoNT should not be used in patients with neuromuscular transmission disorders or in the presence of signs of infection at the injection site. BoNT treatment should be adapted to the characteristics of each patient. Therefore, the choice of BoNT product, dosage, muscles treated, and modalities and intervals of BoNT administration varies according to the individual patient's needs and can be modified over time. Ultrasound and/or EMG guidance is important to obtain satisfactory results. The effects appear within a week, and last for about 12 weeks.

Cervical dystonia About 80% of patients report a good or very good therapeutic effect. The use of EMG to guide BoNT injection and to select muscles to treat results in a greater degree of clinical improvement. Adverse events include weakness and reduced neck stability (9%), dry mouth (19%), and dysphagia (14%).

Blepharospasm The choice of dosage and muscles to treat based only on clinical examination of muscle activity is an adequate approach. The selection of the orbital or eyelid portions of the orbicularis oculi muscle to be injected depends on clinical presentation. Pretarsal injection of BoNT has been shown to offer additional benefit to patients with poor response to previous treatments. Adverse effects can occur in 3–25% of injections and can include bruises, lagophthalmos, ptosis, entropion, and diplopia.

Oromandibular dystonia BoNT therapy is considered the first-line treatment for OMD. Approximately 2/3 of patients receiving BoNT experience moderate or good clinical improvement. The greatest benefit is obtained in the form with jaw closure. The most frequent adverse effects are dysphagia and dysarthria.

Laryngeal dystonia This type of dystonia can present as adductor or abductor SD. BoNT injection in adductor SD has a mean benefit duration of 15 weeks and produces a mean benefit of 90%. Side effects include a wheezing voice in 25% of patients and transient coughing while drinking fluids in 10% of patients. Patients with abductor SD report an improvement in 70% of cases. The average duration of benefits is approximately 10 weeks. Side effects include transient dysphagia (6%) and wheezing during physical exertion (2%).

Upper limb dystonia Upper limb dystonia can be divided into task-specific forms (e.g., writer's cramp or musician's hand dystonia) and non-task-specific forms. BoNT injection is the treatment of choice for upper limb dystonia. However, the reported response rate to BoNT injection is about 50%. The most common adverse effect is muscle weakness in the first weeks, followed by a period of clinical benefit. The use of anatomical landmarks alone is not adequate in treating the muscles involved in upper limb dystonia, and an auxiliary technique such as EMG, ultrasound, or muscle stimulation should be used to guide injections.

Table 7 Botulinum toxin type A and B formulations

	Onabotulinum BoNT type A	Abobotulinum BoNT type A	Incobotulinum BoNT type A	Rimabotulinum BoNT type B
Commercial name	Botox	Dysport	Xeomin	NeuroBloc
Available dosages (units)	100	500	100	1000, 2500, 5000
Storage	Refrigerated	Refrigerated	Room temperature	Refrigerated
Equivalent dose[a]	1	2.5–3	1	40

[a]As the first formulation approved, onabotulinum has a power unit equal to 1

Lower limb dystonia The efficacy of BoNT in isolated lower limb dystonia and isolated exercise-associated lower limb dystonia has a class III level of scientific evidence. However, BoNT injections in the lower limb muscles may improve step length and gait speed as well as pain and mobility parameters.

For further details about BoNT dosages and infiltration techniques to use in different dystonias, please refer to the publications reported in the references.

Surgical treatment

Deep brain stimulation is effective for the treatment of moderate and severe generalized, segmental, and cervical dystonias [48]. The globus pallidus is the most studied target and it remains the first treatment choice. Deep brain stimulation of the globus pallidus internus may result in a significant reduction in dystonia with functional improvement and a positive impact on quality of life [49]. Long-term efficacy was confirmed at 3 and 5 years of follow-up. Some clinical and demographic factors predict a better outcome after this intervention, including short disease duration, young age at the time of surgery, and isolated forms of dystonia (i.e., not associated with other neurological signs, such as spasticity) [50, 51]. In addition to idiopathic dystonias, some acquired dystonias may respond to deep brain stimulation, e.g., late-onset dystonia caused by antipsychotic drugs. In dystonia associated with infantile cerebral palsy, results are variable. Finally, deep brain stimulation is effective in some genetic dystonias, particularly generalized dystonia associated with DYT-TOR1A mutations and KMT2B-related dystonia [52, 53]. The presence of fixed postures with skeletal alterations or tendon retractions should be considered a negative prognostic factor for clinical outcome. In patients treated with deep brain stimulation, the phasic dystonic component improves in the first few weeks after starting stimulation, while tonic postures can improve even after months of chronic stimulation [54].

Although rare, dystonia can evolve towards a *status dystonicus* [55] in which generalized dystonia is acutely associated with hyperthermia, respiratory failure, rhabdomyolysis, myoglobinuria, and renal failure. This condition requires immediate hospitalization in an intensive care unit for mechanical ventilation, sedation with intravenous midazolam, intrathecal baclofen administration, and the evaluation of neurosurgery with deep brain stimulation [56, 57].

The most frequent side effects of deep brain stimulation are related to the device (infection, short circuit, displacement). In contrast, stimulus-related side effects are often mild and may be treated by changing the stimulation parameters. Surgical therapy with deep brain stimulation involves a very limited number of patients and is available in only a few centers in Italy. Deep brain stimulation implant requires periodic adjustments of the stimulation parameters. However, since most neurologists do not have the specific skills necessary to adjust stimulation parameters, treatment may be limited to specialized centers.

Other "ablative" neurosurgical interventions can be performed in patients in whom the placement of intracerebral electrodes is contraindicated. Pallidotomy and thalamotomy with radiofrequencies or gamma knife are the most common surgical alternatives to deep brain stimulation. For safety reasons, these interventions are typically unilateral (i.e., applied to the globus pallidus or to specific nuclei of the thalamus contralateral to the side most affected by dystonia) [58]. In recent years, a new method, magnetic resonance–guided focused ultrasound (MRgFUS), has been developed, which allows millimeter lesions to be performed in deep brain targets using focused ultrasound. MRgFUS has been approved for the treatment of essential tremor and Parkinson's disease with prevalent tremor, allowing a thalamotomy to be performed under magnetic resonance guidance without opening the skull. Its use in treating dystonia has also been studied [59].

Rehabilitation in adult dystonias

Growing evidence suggests that dystonia is a sensorimotor disorder [60, 61]. This supports the idea that rehabilitation strategies aimed at modulating sensorimotor integration can improve motor symptoms in patients with dystonia [62]. In complex cases, a multidisciplinary approach is required, including physical therapy, speech therapy, occupational therapy, and behavioral and psychological techniques [63].

Current evidence indicates that rehabilitation may be effective in reducing dystonic movements (especially as an adjunct treatment to BoNT) [64] and in restoring correct postures and voluntary motor control. Rehabilitation has demonstrated to be useful in increasing pain control and preventing secondary osteoarticular complications. In a survey conducted by the American Dystonia Society, 74% of patients with CD and 62% of patients with upper limb dystonia referred for physiotherapy treatment reported an improvement in symptoms. Some controlled studies have shown that physiotherapy can increase the effectiveness of BoNT, with a possible reduction in the dosage needed and treatment frequency. Some specific rehabilitative approaches for different forms of focal dystonia have been published [65–71], though a consensus in this field is still lacking.

Outpatient rehabilitation treatment should be provided with a personalized approach (preferably within the patient's community). The frequency and intensity of the treatment should be based on the severity of the individual case. Some patients need rehabilitative treatment for months or years, while a few weeks may be adequate for others.

The rehabilitation approach, indicated especially for CD and upper limb dystonia, should include a series of specific interventions aimed at sensorimotor re-training. Daily home self-performed exercises [60] can favor the consolidation of sensorimotor strategies learned during sessions guided by expert physiotherapists, who can also help identify compensatory sensory tricks to manage the disorder in daily life.

In patients with laryngeal dystonia, speech therapy may be useful. In task-specific dystonias, such as writer's cramp and other types of occupational focal dystonias (e.g., musician's dystonia, typist's cramp), rehabilitation is an important part of the treatment. In this context, various physiotherapy programs have been developed based on the concept of relearning normal movements and aimed at improving independence and precision of finger and wrist movements and training antagonist muscles [72]. Mirror therapy and motor imagery have been demonstrated to be a useful option [73]. For OMD, there are also strategies to promote sensory tricks in order to reduce dystonic spasms, such as chewing gum and biting toothpick sticks. Touching the periocular region can improve BS.

Many patients also need neuropsychological rehabilitation to improve visuospatial functions that are often altered, for example, in patients with CD. In patients with anxiety, significant mood deflection, social isolation, and reduced self-esteem and in those who lack compensatory strategies, it would be useful to include the acquisition of relaxation and stress management techniques or behavioral psychotherapy interventions in the interdisciplinary rehabilitation program [74].

Other neurorehabilitative techniques are based on possible modifications that EMG feedback [75–78] or multisensory feedback [79, 80] can induce on central nervous system structures. Integrated treatment with BoNT and sensorimotor rehabilitation based on relearning exercises guided with multisensory feedback (SPRInT) was more effective than BoNT alone in improving difficulties in activities of daily living in a cohort of patients with CD longitudinally evaluated over 6 months [81]. SPRInT program feedback exercises aim to promote the reconstruction of motor and visuospatial mental images in order to increase body axis perception and improve motor control and spatial interaction.

Telerehabilitation can be a possible tool for remotely treating CD patients [82].

Proposal of a hospital-territory network model for adult dystonia management

To limit the critical issues currently present in the management of adult dystonias (diagnostic uncertainties, availability of adequate therapies, lack of multidisciplinary and multi-professional management, and lack of adequate rehabilitation structures and centers able to provide and manage therapies in advanced stages) and to standardize the level of assistance in the regional/national territory, a network model is proposed.

Each node of the network is represented by a public or private hospital with at least one neurologist expert in movement disorders and able to provide BoNT treatment. Neurologists expert in movement disorders interface with a multi-professional team (neurophysiologist (neurophysiology laboratory), neuroradiologist (computed tomography/MRI), neuropsychologist (neurocognitive test), psychiatrist, and specialists in the rehabilitation field) for a multidisciplinary evaluation (diagnosis and follow-up) of patients with adult dystonia. These professional figures may also be present in different structures, including territorial ones, as long as they are functionally connected. This network should be coordinated by a neurologist with expertise in movement disorders. Within this network, pathways for appropriate diagnostic investigations, treatment of motor and non-motor symptoms, and access to rehabilitation should be implemented. These pathways should be organized in existing or specifically developed informatic networks.

The entry point of the dystonia assistance network is through the general practitioner (GP) and/or territorial neurologist (outpatient or hospital specialist). When the presence of adult dystonia is suspected, the GP or territorial neurologist should refer the patient to the nearest hospital or territorial node of the network.

The network should provide a sufficient number of nodes based on the population density and geography of the territory. To better define the number of nodes and their locations, a survey on the current distribution of patients and resources should be carried out.

The network must include a limited number of structures offering advanced services for select patients. In particular, it would be useful to have a facility for genetic testing and a regional center for stereotaxic surgery.

The implementation of the network requires training neurologists and other health professionals in the diagnosis, follow-up, and therapy of adult dystonias. Network activities are coordinated by a central hub that, with the help of all the nodes in the network, develops and updates regional protocols for the diagnosis and treatment of dystonia and defines and manages a standardized electronic clinical file. Finally, the central hub implements network monitoring of the following indicators every 6–12 months: (1) number of newly diagnosed cases; (2) total number of cases; (3) number and type of clinical and instrumental multi-professional evaluations; (4) number of clinical follow-ups.

The network collaborates with patient associations in planning strategies, training personnel, and disseminating information campaigns.

The actors in this pathway have scientific, clinical, and organizational responsibility for all projects aimed at the functioning of the network, in close collaboration with health management.

This document represents a recommendation that can be further developed at the national, regional, or local level in all of its parts according to specific needs and objectives.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by Alfredo Berardelli, Marcello Romano, and Sergio Bagnato and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethical approval None.

Conflict of interest The authors declare no competing interests.

References

1. Albanese A, Lalli S (2009) Is this dystonia? Mov Disord 24:1725–1731. https://doi.org/10.1002/mds.22597
2. Albanese A, Asmus F, Bhatia KP, Elia AE, Elibol B, Filippini G, Gasser T, Krauss JK, Nardocci N, Newton A, Valls-Solé J (2011) EFNS guidelines on diagnosis and treatment of primary dystonias. Eur J Neurol 18:5–18. https://doi.org/10.1111/j.1468-1331.2010.03042.x
3. Albanese A, Sorbo FD, Comella C, Jinnah HA, Mink JW, Post B, Vidailhet M, Volkmann J, Warner TT, Leentjens AF, Martinez-Martin P, Stebbins GT, Goetz CG, Schrag A (2013) Dystonia rating scales: critique and recommendations. Mov Disord 28:874–883. https://doi.org/10.1002/mds.25579
4. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK (2013) Phenomenology and classification of dystonia: a consensus update. Mov Disord 28:863–873. https://doi.org/10.1002/mds.25475
5. Jinnah HA, Berardelli A, Comella C, Defazio G, Delong MR, Factor S, Galpern WR, Hallett M, Ludlow CL, Perlmutter JS, Rosen AR, Investigators DC (2013) The focal dystonias: current views and challenges for future research. Mov Disord 28:926–943. https://doi.org/10.1002/mds.25567
6. Defazio G, Berardelli A (2021) Is adult-onset dystonia a rare disease? Time for Population-Based Studies. Mov Disord 36:1119–1124. https://doi.org/10.1002/mds.28560
7. Defazio G, Abbruzzese G, Livrea P, Berardelli A (2004) Epidemiology of primary dystonia. Lancet Neurol 3:673–678. https://doi.org/10.1016/S1474-4422(04)00907-X
8. Defazio G (2010) The epidemiology of primary dystonia: current evidence and perspectives. Eur J Neurol 17(Suppl 1):9–14. https://doi.org/10.1111/j.1468-1331.2010.03053.x
9. Balint B, Mencacci NE, Valente EM, Pisani A, Rothwell J, Jankovic J, Vidailhet M, Bhatia KP (2018) Dystonia Nat Rev Dis Primers 4:25. https://doi.org/10.1038/s41572-018-0023-6
10. LeDoux MS (2012) Dystonia: phenomenology. Parkinsonism Relat Disord 18:162–164. https://doi.org/10.1016/S1353-8020(11)70050-5
11. Grütz K, Klein C (2021) Dystonia updates: definition, nomenclature, clinical classification, and etiology. J Neural Transm (Vienna) 128:395–404. https://doi.org/10.1007/s00702-021-02314-2
12. Wagle Shukla A, Brown R, Heese K, Jones J, Rodriguez RL, Malaty IM, Okun MS, Kluger BM (2016) High rates of fatigue and sleep disturbances in dystonia. Int J Neurosci 126:928–935. https://doi.org/10.3109/00207454.2015.1085035
13. Berlot R, Rothwell JC, Bhatia KP, Kojović M (2021) Variability of movement disorders: the influence of sensation, action, cognition, and emotions. Mov Disord 36:581–593. https://doi.org/10.1002/mds.28415
14. Stahl CM, Frucht SJ (2017) Focal task specific dystonia: a review and update. J Neurol 264:1536–1541. https://doi.org/10.1007/s00415-016-8373-z
15. Defazio G, Hallett M, Jinnah HA, Berardelli A (2013) Development and validation of a clinical guideline for diagnosing blepharospasm. Neurology 81:236–240. https://doi.org/10.1212/WNL.0b013e31829bfdf6
16. Conte A, Defazio G, Ferrazzano G, Hallett M, Macerollo A, Fabbrini G, Berardelli A (2013) Is increased blinking a form of blepharospasm? Neurology 80:2236–2241. https://doi.org/10.1212/WNL.0b013e318296e99d
17. Defazio G, Hallett M, Jinnah HA, Stebbins GT, Gigante AF, Ferrazzano G, Conte A, Fabbrini G, Berardelli A (2015) Development and validation of a clinical scale for rating the severity of blepharospasm. Mov Disord 30:525–530. https://doi.org/10.1002/mds.26156
18. Ferrazzano G, Muroni A, Conte A, Ercoli T, Tamburini G, Fabbrini G, Berardelli A, Defazio G (2020) Development of a clinical rating scale for the severity of apraxia of eyelid opening, either isolated or associated with blepharospasm. Mov Disord Clin Pract 7:950–954. https://doi.org/10.1002/mdc3.13083
19. Defazio G, Albanese A, Pellicciari R, Scaglione CL, Esposito M, Morgante F, Abbruzzese G, Bentivoglio AR, Bono F, Coletti Moja M, Fabbrini G, Girlanda P, Lopiano L, Pacchetti C, Romano M, Fadda L, Berardelli A (2019) Expert recommendations for diagnosing cervical, oromandibular, and limb dystonia. Neurol Sci 40:89–95. https://doi.org/10.1007/s10072-018-3586-9
20. Hvizdošová L, Nevrlý M, Otruba P, Hluštík P, Kaňovský P, Zapletalová J (2020) The prevalence of dystonic tremor and tremor associated with dystonia in patients with cervical dystonia. Sci Rep 10:1436. https://doi.org/10.1038/s41598-020-58363-2
21. Defazio G, Conte A, Gigante AF, Fabbrini G, Berardelli A (2015) Is tremor in dystonia a phenotypic feature of dystonia? Neurology 84:1053–1059. https://doi.org/10.1212/WNL.0000000000001341
22. Chen Q, Vu JP, Cisneros E, Benadof CN, Zhang Z, Barbano RL, Goetz CG, Jankovic J, Jinnah HA, Perlmutter JS, Appelbaum MI, Stebbins GT, Comella CL, Peterson DA (2020) Postural directionality and head tremor in cervical dystonia. Tremor Other Hyperkinet Mov 10. https://doi.org/10.7916/tohm.v0.745
23. Lee SW, Cho HJ, Shin HW, Hallett M (2021) Sensory tricks modulate corticocortical and corticomuscular connectivity in cervical dystonia. Clin Neurophysiol 132:3116–3124. https://doi.org/10.1016/j.clinph.2021.08.019
24. Saraf U, Chandarana M, Divya KP, Krishnan S (2022) Oromandibular dystonia - a systematic review. Ann Indian Acad Neurol 25:26–34. https://doi.org/10.4103/aian.aian_242_21
25. Simonyan K, Barkmeier-Kraemer J, Blitzer A, Hallett M, Houde JF, Jacobson Kimberley T, Ozelius LJ, Pitman MJ, Richardson RM, Sharma N, Tanner K, The NIH/NIDCD Workshop on Research Priorities in Spasmodic Dysphonia/Laryngeal Dystonia (2021) Laryngeal dystonia: multidisciplinary update on

terminology, pathophysiology, and research priorities. Neurology 96:989–1001. https://doi.org/10.1212/WNL.0000000000011922
26. Defazio G, Ercoli T, Erro R, Pellicciari R, Mascia MM, Fabbrini G, Albanese A, Lalli S, Eleopra R, Barone P, Marchese R, Ceravolo R, Scaglione C, Liguori R, Esposito M, Bentivoglio AR, Bertolasi L, Altavista MC, Bono F, Pisani A, Girlanda P, Berardelli A, Participants IDR (2020) Idiopathic non-task-specific upper limb dystonia, a neglected form of dystonia. Mov Disord 35:2038–2045. https://doi.org/10.1002/mds.28199
27. Norris SA, Jinnah HA, Klein C, Jankovic J, Berman BD, Roze E, Mahajan A, Espay AJ, Murthy AV, Fung VSC, LeDoux MS, Chang FCF, Vidailhet M, Testa C, Barbano R, Malaty IA, Bäumer T, Loens S, Wright LJ, Perlmutter JS (2020) Clinical and demographic characteristics of upper limb dystonia. Mov Disord 35:2086–2090. https://doi.org/10.1002/mds.28223
28. Fabbrini G, Berardelli I, Moretti G, Pasquini M, Bloise M, Colosimo C, Biondi M, Berardelli A (2010) Psychiatric disorders in adult-onset focal dystonia: a case-control study. Mov Disord 25:459–465. https://doi.org/10.1002/mds.22983
29. Stamelou M, Edwards MJ, Hallett M, Bhatia KP (2012) The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. Brain 135:1668–1681. https://doi.org/10.1093/brain/awr224
30. Romano R, Bertolino A, Gigante A, Martino D, Livrea P, Defazio G (2014) Impaired cognitive functions in adult-onset primary cranial cervical dystonia. Parkinsonism Relat Disord 20:162–165. https://doi.org/10.1016/j.parkreldis.2013.10.008
31. Comella CL, Fox SH, Bhatia KP, Perlmutter JS, Jinnah HA, Zurowski M, McDonald WM, Marsh L, Rosen AR, Waliczek T, Wright LJ, Galpern WR, Stebbins GT (2015) Development of the comprehensive cervical dystonia rating scale: methodology. Mov Disord Clin Pract 2:135–141. https://doi.org/10.1002/mdc3.12131
32. Grippe T, Cunha NSCD, BrandÃo PRP, Fernandez RNM, Cardoso FEC (2020) How can neurophysiological studies help with movement disorders characterization in clinical practice? A review. Arq Neuropsiquiatr 78:512–522. https://doi.org/10.1590/0004-282X20190195
33. Nijmeijer SW, de Bruijn E, Forbes PA, Kamphuis DJ, Happee R, Koelman JH, Tijssen MA (2014) EMG coherence and spectral analysis in cervical dystonia: discriminative tools to identify dystonic muscles? J Neurol Sci 347:167–173. https://doi.org/10.1016/j.jns.2014.09.041
34. Nijmeijer SWR, de Bruijn E, Verhagen R, Forbes PA, Kamphuis DJ, Happee R, Tijssen MAJ (2017) Koelman JHTM (2017) Spectral EMG changes in cervical dystonia patients and the influence of botulinum toxin treatment. Toxins (Basel) 9(9):256. https://doi.org/10.3390/toxins9090256
35. Popa T, Milani P, Richard A, Hubsch C, Brochard V, Tranchant C, Sadnicka A, Rothwell J, Vidailhet M, Meunier S, Roze E (2014) The neurophysiological features of myoclonus-dystonia and differentiation from other dystonias. JAMA Neurol 71:612–619. https://doi.org/10.1001/jamaneurol.2014.99
36. Bhatia KP, Marsden CD (1994) The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 117:859–876. https://doi.org/10.1093/brain/117.4.859
37. Bologna M, Berardelli A (2018) The cerebellum and dystonia. Handb Clin Neurol 155:259–272. https://doi.org/10.1016/B978-0-444-64189-2.00017-2
38. Fung VS, Jinnah HA, Bhatia K, Vidailhet M (2013) Assessment of patients with isolated or combined dystonia: an update on dystonia syndromes. Mov Disord 28:889–898. https://doi.org/10.1002/mds.25549
39. Fabbrini G, Conte A, Ferrazzano G, Esposito M, Albanese A, Pellicciari R, Di Biasio F, Bono F, Eleopra R, Ercoli T, Altavista MC, Berardelli A, Defazio G, Italian Dystonia Registry participants (2021) Neuroimaging in idiopathic adult-onset focal dystonia. Neurol Sci 42:2947–2950. https://doi.org/10.1007/s10072-020-05025-w
40. Harbo HF, Finsterer J, Baets J, Van Broeckhoven C, Di Donato S, Fontaine B, De Jonghe P, Lossos A, Lynch T, Mariotti C, Schöls L, Spinazzola A, Szolnoki Z, Tabrizi SJ, Tallaksen C, Zeviani M, Burgunder JM, Gasser T, EFNS, (2009) EFNS guidelines on the molecular diagnosis of neurogenetic disorders: general issues, Huntington's disease, Parkinson's disease and dystonias. Eur J Neurol 16:777–785. https://doi.org/10.1111/j.1468-1331.2009.02646.x
41. Müller U (2005) The monogenic primary dystonias. Brain 132:2005–2025. https://doi.org/10.1093/brain/awp172
42. Brüggemann N, Kühn A, Schneider SA, Kamm C, Wolters A, Krause P, Moro E, Steigerwald F, Wittstock M, Tronnier V, Lozano AM, Hamani C, Poon YY, Zittel S, Wächter T, Deuschl G, Krüger R, Kupsch A, Münchau A, Lohmann K, Volkmann J, Klein C (2015) Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia. Neurology 84:895–903. https://doi.org/10.1212/WNL.0000000000001312
43. Jinnah HA (2020) Medical and surgical treatments of dystonia. Neurol Clin 38:325–348. https://doi.org/10.1016/j.ncl.2020.01.003
44. Currà A, Berardelli A (2009) Do the unintended actions of botulinum toxin at distant sites have clinical implications? Neurology 72:1095–1099. https://doi.org/10.1212/01.wnl.0000345010.98495.fc
45. Anandan C, Jankovic J (2021) Botulinum toxin in movement disorders: an update. Toxins (Basel) 13(1):42. https://doi.org/10.3390/toxins13010042
46. Scontrini A, Conte A, Fabbrini G, Colosimo C, Di Stasio F, Ferrazzano G, Berardelli A (2011) Somatosensory temporal discrimination tested in patients receiving botulinum toxin injection for cervical dystonia. Mov Disord 26:742–746. https://doi.org/10.1002/mds.23447
47. Castelão M, Marques RE, Duarte GS, Rodrigues FB, Ferreira J, Sampaio C, Moore AP, Costa J (2017) Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev 12(12):CD003633. https://doi.org/10.1002/14651858.CD003633.pub3
48. Hu W, Stead M (2014) Deep brain stimulation for dystonia. Transl Neurodegener 3:2. https://doi.org/10.1186/2047-9158-3-2
49. Rodrigues FB, Duarte GS, Prescott D, Ferreira J, Costa J (2019) Deep brain stimulation for dystonia. Cochrane Database Syst Rev 1(1):CD012405. https://doi.org/10.1002/14651858.CD012405.pub2
50. Moro E, LeReun C, Krauss JK, Albanese A, Lin JP, Walleser Autiero S, Brionne TC, Vidailhet M (2017) Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. Eur J Neurol 24:552–560. https://doi.org/10.1111/ene.13255
51. Bronte-Stewart H, Taira T, Valldeoriola F, Merello M, Marks WJ Jr, Albanese A, Bressman S, Moro E (2011) Inclusion and exclusion criteria for DBS in dystonia. Mov Disord 26(Suppl 1):S5-16. https://doi.org/10.1002/mds.23482
52. Artusi CA, Dwivedi A, Romagnolo A, Bortolani S, Marsili L, Imbalzano G, Sturchio A, Keeling EG, Zibetti M, Contarino MF, Fasano A, Tagliati M, Okun MS, Espay AJ, Lopiano L, Merola A (2020) Differential response to pallidal deep brain stimulation among monogenic dystonias: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 91:426–433. https://doi.org/10.1136/jnnp-2019-322169
53. Rajan R, Garg K, Saini A, Radhakrishnan DM, Carecchio M, Bk B, Singh M, Srivastava AK (2021) GPi-DBS for KMT2B-associated dystonia: systematic review and meta-analysis. Mov Disord Clin Pract 9:31–37. https://doi.org/10.1002/mdc3.13374

54. Fox MD, Alterman RL (2015) Brain stimulation for torsion dystonia. JAMA Neurol 72(6):713–719. https://doi.org/10.1001/jamaneurol.2015.51
55. Fasano A, Ricciardi L, Bentivoglio AR, Canavese C, Zorzi G, Petrovic I, Kresojevic N, Kostić VS, Svetel M, Kovacs N, Balas I, Roubertie A, Mishra D, Mariotti P, Temudo T, Nardocci N (2012) Status dystonicus: predictors of outcome and progression patterns of underlying disease. Mov Disord 27:783–788. https://doi.org/10.1002/mds.24981
56. Lobato-Polo J, Ospina-Delgado D, Orrego-González E, Gómez-Castro JF, Orozco JL, Enriquez- Marulanda A (2018) Deep brain stimulation surgery for status dystonicus: a single-center experience and literature review. World Neurosurg 114:e992–e1001. https://doi.org/10.1016/j.wneu.2018.03.129
57. Allen NM, Lin JP, Lynch T, King MD (2014) Status dystonicus: a practice guide. Dev Med Child Neurol 56:105–112. https://doi.org/10.1111/dmcn.12339
58. Cury RG, Kalia SK, Shah BB, Jimenez-Shahed J, Prashanth LK, Moro E (2018) Surgical treatment of dystonia. Expert Rev Neurother 18:477–492. https://doi.org/10.1080/14737175.2018.1478288
59. Fasano A, Llinas M, Munhoz RP, Hlasny E, Kucharczyk W, Lozano AM (2017) MRI-guided focused ultrasound thalamotomy in non-ET tremor syndromes. Neurology 89:771–775. https://doi.org/10.1212/WNL.0000000000004268
60. Abbruzzese G (2003) Berardelli A (2017) Sensorimotor integration in movement disorders. Mov Disord 18:231–240. https://doi.org/10.1002/mds.10327
61. Conte A, Belvisi D, De Bartolo MI, Manzo N, Cortese FN, Tartaglia M, Ferrazzano G, Fabbrini G (2018) Berardelli A (2018) Abnormal sensory gating in patients with different types of focal dystonias. Mov Disord 33:1910–1917. https://doi.org/10.1002/mds.27530
62. Avanzino L, Fiorio M (2014) Proprioceptive dysfunction in focal dystonia: from experimental evidence to rehabilitation strategies. Front Hum Neurosci 8:1000. https://doi.org/10.3389/fnhum.2014.01000
63. Bradnam LV, Meiring RM, Boyce M, McCambridge A (2021) Neurorehabilitation in dystonia: a holistic perspective. J Neural Transm (Vienna) 128(4):549–558. https://doi.org/10.1007/s00702-020-02265-0
64. Tassorelli C, Mancini F, Balloni L, Pacchetti C, Sandrini G, Nappi G, Martignoni E (2006) Botulinum toxin and neuromotor rehabilitation: an integrated approach to idiopathic cervical dystonia. Mov Disord 21(12):2240–2243. https://doi.org/10.1002/mds.21145
65. De Pauw J, Van der Velden K, Meirte J, Van Daele U, Truijen S, Cras P, Mercelis R, De Hertogh W (2014) The effectiveness of physiotherapy for cervical dystonia: a systematic literature review. J Neurol 261(10):1857–1865. https://doi.org/10.1007/s00415-013-7220-8
66. Boyce MJ, Canning CG, Mahant N, Morris J, Latimer J, Fung VS (2012) Active exercise for individuals with cervical dystonia: a pilot randomized controlled trial. Clin Rehabil 27(3):226–235. https://doi.org/10.1177/0269215512456221
67. Prudente CN, Zetterberg L, Bring A, Bradnam L, Kimberley TJ (2018) Systematic review of rehabilitation in focal dystonias: classification and recommendations. Mov Disord Clin Pract 5(3):237–245
68. Smania N, Corato E, Tinazzi M, Montagnana B, Fiaschi A, Aglioti SM (2003) The effect of two different rehabilitation treatments in cervical dystonia: preliminary results in four patients. Funct Neurol 18(4):219–225
69. Queiroz MAR, Chien HF, Sekeff-Sallem FA, Barbosa ER (2012) Physical therapy program for cervical dystonia: a study of 20 cases. Funct Neurol 27(3):187–192
70. Counsell C, Sinclair H, Fowlie J, Tyrrell E, Derry N, Meager P, Norrie J (2016) Grosset D (2016) A randomized trial of specialized versus standard neck physiotherapy in cervical dystonia. Parkinsonism Relat Disord 23:72–79. https://doi.org/10.1016/j.parkreldis.2015.12.010
71. Bleton JP (2010) Physiotherapy of focal dystonia: a physiotherapist's personal experience. Eur J Neurol 17(SUPPL. 1):107–112. https://doi.org/10.1111/j.1468-1331.2010.03061
72. Schramm A, Bäumer T, Fietzek U, Heitmann S, Walter U, Jost WH (2015) Relevance of sonography for botulinum toxin treatment of cervical dystonia: an expert statement. J Neural Transm (Vienna) 122(10):1457–1463. https://doi.org/10.1007/s00702-014-1356-2
73. Ramella M, Borgnis F, Giacobbi G, Castagna A, Baglio F, Cortesi M, Converti RM (2021) Modified graded motor imagery for musicians' focal dystonia: a case series. Med Probl Perform Art 36(1):10–17. https://doi.org/10.21091/mppa.2021.1002
74. Cleeland CS (1973) Behavioral technics in the modification of spasmodic torticollis. Neurology 23:1241–1247
75. Duddy J, Lellan Mc (1995) Lack of influence of EMG feedback in relaxation training for spasmodic torticollis. Clin Rehabil 9:297–303. https://doi.org/10.1177/026921559500900404
76. Jahanshahi M, Sartory G, Marsden CD (1991) EMG biofeedback treatment of torticollis: a controlled outcome study. Biofeedback Self Regul 16:413–448. https://doi.org/10.1007/BF00999994
77. Korein J, Brudny J (1976) Integrated EMG feedback in the management of spasmodic torticollis and focal dystonia: a prospective study of 80 patients. Res Publ Assoc Res Nerv Ment Dis 55:385–426
78. Brudny J, Grynbaum BB, Korein J (1974) Spasmodic torticollis: treatment by feedback display of the EMG. Arch Phys Med Rehabi 55:403–408
79. Harrison DW, Garrett JC, Henderson D, Adams HE (1985) Visual and auditory feedback for head tilt and torsion in a spasmodic torticollis patient. Behav Res Ther 23:87–88. https://doi.org/10.1016/0005-7967(85)90147-0
80. Leplow B (1990) Heterogeneity of biofeedback training effects in spasmodic torticollis: a single-case approach. Behav Res Ther 28:359–365. https://doi.org/10.1016/0005-7967(90)90091-v
81. Castagna A, Caronni A, Crippa A, Sciumè L, Giacobbi G, Corrini C, Montesano A, Ramella M (2020) Sensorimotor Perceptive Rehabilitation Integrated (SPRInt) program: exercises with augmented movement feedback associated to botulinum neurotoxin in idiopathic cervical dystonia—an observational study. Neurol Sci 41(1):131–138. https://doi.org/10.1007/s10072-019-04061-5
82. Castagna A, Saibene E, Ramella M (2021) How do I rehabilitate patients with cervical dystonia remotely? Mov Disord Clin Pract 8(5):820–821. https://doi.org/10.1002/mdc3.13212

Authors and Affiliations

Marcello Romano[1] · Sergio Bagnato[2] · Maria Concetta Altavista[3] · Laura Avanzino[4,5] · Daniele Belvisi[6,7] · Matteo Bologna[6,7] · Francesco Bono[8] · Miryam Carecchio[9] · Anna Castagna[10] · Roberto Ceravolo[11] · Antonella Conte[6,7] · Giuseppe Cosentino[12] · Roberto Eleopra[13] · Tommaso Ercoli[14] · Marcello Esposito[15] · Giovanni Fabbrini[6,7] · Gina Ferrazzano[6] · Stefania Lalli[16] · Marcello Maria Mascia[17] · Maurizio Osio[18] · Roberta Pellicciari[19] · Simona Petrucci[20,21] · Enza Maria Valente[22,23] · Francesca Valentino[24] · Mario Zappia[25] · Maurizio Zibetti[26] · Paolo Girlanda[27] · Michele Tinazzi[28] · Giovanni Defazio[14,15,16,17] · Alfredo Berardelli[6,7]

1 Neurology and Stroke Unit, Villa Sofia Cervello Hospital, Palermo, Italy

2 Unit of Neurophysiology and Unit for Severe Acquired Brain Injuries, Rehabilitation Department, Giuseppe Giglio Foundation, Cefalù, Italy

3 Neurology Unit, San Filippo Neri Hospital ASL, Italian Network on Botulinum Toxin (RITB SIN), Rome, Italy

4 Department of Experimental Medicine, Human Physiology Section, University of Genoa, IRCCS San Martino Polyclinic, Genoa, Italy

5 IRCCS San Martino Polyclinic, Genoa, Italy

6 Department of Human Neurosciences, Sapienza University of Rome, Viale dell' Università 30, 00185 Rome, Italy

7 IRCCS Neuromed, Pozzilli, IS, Italy

8 Botulinum Toxin Center, Neurology Unit, Mater Domini University Hospital, Italian Network On Botulinum Toxin (RITB SIN), Catanzaro, Italy

9 Parkinson and Movement Disorders Unit, Study Center On Neurodegeneration (CESNE), Department of Neuroscience, University of Padua, Padua, Italy

10 IRCCS Fondazione Don Carlo Gnocchi Onlus, Milan, Italy

11 Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

12 Department of Brain and Behavioral Sciences, University of Pavia, IRCCS Mondino Foundation, Pavia, Italy

13 Parkinson and Movement Disorders Unit, Department of Clinical Neuroscience, IRCCS Foundation Carlo Besta Neurological Institute, Milan, Italy

14 Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

15 U.O.C. of Neurophysiology, A.O.R.N. A. Cardarelli, Naples, Italy

16 Department of Neurology, IRCCS Humanitas Research Hospital, via Manzoni 56, 20089 Rozzano, Milan, Italy

17 Institute of Neurology, Azienda Ospedaliero Universitaria Di Cagliari, SS 554 km 4.500, 09042 Cagliari, Italy

18 Department of Neurology, Luigi Sacco Hospital, University of Milan, Milan, Italy

19 Department of Basic Science, Neuroscience, and Sensory Organs, University Aldo Moro, Bari, Italy

20 Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

21 Medical Genetics and Advanced Cell Diagnostics Unit, S, Andrea University Hospital, Rome, Italy

22 Neurogenetics Research Center, IRCCS Mondino Foundation, Pavia, Italy

23 Department of Molecular Medicine, University of Pavia, Pavia, Italy

24 IRCCS Mondino Foundation, Pavia, Italy

25 Department of Medical, Surgical Sciences and Advanced Technologies G.F. Ingrassia, Section of Neurosciences, University of Catania, Via Santa Sofia 78, Catania, Italy

26 II University Division of Neurology of A.O. City of Health and Science, Turin, Italy

27 Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

28 Department of Neuroscience, Biomedicine, and Movement, University of Verona, Verona, Italy