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Review

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Keywords

Dystonia, genetic, phenomenology, classification, botulinum toxin, Deep brain stimulation.

Dystonia: Etiology, phenomenology, classification, and treatment of Dystonia

Etiología, fenomenología, clasificación y tratamiento de la distonía

Abstract

In the last 30 years not only have significant progress in the genetic and physiological aspects of dystonia but the diagnostic, classification and treatment approach. For years, oral medications were used exclusively, with the introduction of botulinum toxin and deep brain stimulation, in addition to advances in the understanding of the disease, it has had a positive impact on the quality of life of those who suffer from it and their families. In this article, we will carry out an integral update of the dystonia from its definition, phenomenology, classification, etiology, and treatment.

Palabras clave

Distonía, genética, fenomenología, clasificación, toxina botulínica, estimulación cerebral profunda.

Resumen

En los últimos 30 años no solo se han logrado avances importantes en los aspectos genéticos y fisiológicos de la distonía sino en el abordaje diagnóstico, clasificación y en el tratamiento. Durante años se utilizaron exclusivamente medicamentos orales, con la introducción de la toxina botulínica y la estimulación cerebral profunda, sumado a los avances en el entendimiento de la enfermedad, se ha logrado impactar positivamente en la calidad de vida de quienes la padecen y sus familias. En este artículo realizaremos una actualización integral de la distonía desde su definición, fenomenología, clasificación, etiología y tratamiento.

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Introducción

Dystonia is a hyperkinetic movement disorder that causes sustained or intermittent muscle contractions that produce repetitive movements, abnormal postures, or both.[1]

The prevalence and incidence of dystonia have been variable in different regions reflecting the different biological substrates of the disease, but this variability may also be related to the different methodological approaches of the studies. A meta-analysis by Steeves et al. estimates that the prevalence of primary dystonia is 16.43 per 100,000 inhabitants (95% CI 12.09-22.32). It is possible, however, that the diagnosis is underestimated. In the same study, they calculated a prevalence per 100,000 inhabitants of 15.4 (95% CI 12.1-19.5) for focal and segmental dystonia, 5.0 (95% CI 3.6-6.9) for cervical dystonia, and 4.2 (95% CI 2.9-6.2) for blepharospasm.[2] In Latin America, there are few epidemiological data on the prevalence of dystonia.[3,4] Dystonia can also be associated with non-motor symptoms in up to 70% of cases.[5] In this article we will review the definition, phenomenology, classification, diagnosis, and treatment.

1. Definition

This disease was first described by Schwalbe in 1908 when he published his thesis on a family with three affected children suffering from generalized primary dystonia. Three years later, Oppenheim described the same disorder in four patients and coined the word "dystonia" calling this syndrome "deforming muscular dystonia" or "progressive lordotic dysbasia."[6] Then, in 1975, David Marsden described dystonia as a disorder of organic origin, which also includes blepharospasm, spasmodic torticollis, and writer's cramp.[7,8] In 1984, Stanley Fahn proposed the first definition of dystonia as sustained muscular contractions that frequently cause torsion and repetitive movements or abnormal postures.[9,10]

This definition of dystonia remained in effect for more than 25 years. Since it did not comprehensively consider all aspects of dystonia, however, a consensus of experts got together in 2012 to develop a new definition. This classification was published in 2013 by the Movement Disorders Society, and defines the disease as follows: "Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation."[11] The word dystonia has been used to describe not only the motor phenomenology but also a clinical syndrome and now it is recognized as a disease that may be genetic, sporadic, but may also be secondary to other diseases such as Wilson's disease, immune encephalopathy, neuroferritinopathy, and cerebral palsy among others.[12]

2. Phenomenology

A fundamental characteristic that differentiates dystonia from other hyperkinetic movement disorders is its predictability and the pattern nature of muscle contractions. Dystonic postures can flex, extend, or twist a part of the body along its main axis. In axial dystonia, scoliosis and camptocormia are often observed. Dystonic postures can cause pain, especially cervical dystonia.[13] Dystonic movements have a torsional nature and usually a direction, they are repetitive, predictable and have a peak in which the movement is sustained and the direction is maintained for an instant. An example of this is cervical dystonia, in which the movements of the neck have a directional preponderance causing an abnormal position resulting in postures such as laterocollis (lateral tilt), retrocollis (backward tilt), torticollis (horizontal rotation), or anterocollis (anterior tilt). Other types of postures secondary to dystonic movements are ulnar deviation, plantar flexion, vocal fold adduction, and eye closure.[14]

The speed and rhythmicity of the movements can be variable. Though they are usually arrhythmic, they can also be rhythmic, this type of movement has been called dystonic tremor. Dystonia can be

difficult to differentiate from other movement disorders such as essential tremor, for it is necessary to take into account its directional character and the worsening of the amplitude of the tremor when the movement goes in the opposite direction to dystonia. Dystonic movements can be differentiated from other movement disorders such as chorea, in which the movements are unpredictable, follow a flow from proximal to distal, and are usually associated with loss of tone. It is also possible to differentiate dystonia from tics because in the former there is no urgency to perform the movement and there is no relief after executing it.[11]

Other features that support the diagnosis of dystonia have been described such as mirror dystonia, in which, while performing a motor task with one extremity, similar movements are observed but with dystonic characteristics in the contralateral limb.[15] There is also action dystonia or task-specific dystonia, where dystonia is activated or increased in intensity by a voluntary task. Dystonic movements can be attenuated by voluntary movements called antagonistic gestures or sensory trick phenomenon. The presence of these phenomena supports the diagnosis of dystonia.[16] In a series of cases, the existence of sensory tricks was reported in 71% of the patients with blepharospasm and in 84% of the subjects with cervical dystonia. It is believed that these phenomena inhibit cortical overflow associated with dystonia.[10] In some patients, simply thinking about the trick helps improve dystonia.

3. Classification

The current classification of dystonia divides it into two main axes: Axis 1 - Clinical Characteristics; Axis 2 - Etiology.

In axis 1, age at onset, body distribution, temporal pattern, and additional movement disorders or neurological features are included. The age at onset is subdivided into five groups, onset in infancy (from birth or lactation to 2 years), childhood (3-12 years), adolescence (13-20 years), early adulthood (21-40 years), and late adulthood (>40 years). In reference to body distribution, it is called focal dystonia when only one region is affected, it is segmental when two or more contiguous regions are affected, multifocal if two or more non-contiguous regions are affected, hemidystonia when it is limited to half the body, and generalized when it affects the trunk and at least two affected regions. The temporal pattern includes the disease course (static or progressive) and the variability of the symptoms (persistent, fluctuating, specific, and paroxysmal). Finally, it must be established whether dystonia is associated with other movement disorders.

In axis 2, dystonia is classified according to the etiology in nervous system pathology (degeneration, structural lesion or absence of both) and in hereditary or acquired causes (perinatal injury, infection, drugs, toxic, vascular, brain damage).[11] Table 1 summarizes the characteristics of axis 1, while Table 2 shows the components of axis 2. It is also important to perform the differential diagnosis with other entities that may be similar or mimic dystonia.[11]

4. Pathophysiology

The pathophysiology of dystonia is complex and involves multiple systems at the central and peripheral levels, as well as affecting different circuits in the basal ganglia, thalamus, cerebellum, and cortex: all of them involved in motor control and the inhibition of unwanted involuntary movements. However, in practical and simplified terms, the following main alterations are described:

a. Loss of inhibition

The nervous system is composed of excitatory and inhibitory circuits in equilibrium with each other. In dystonia, it seems that the inhibition is defective, which leads to loss of selectivity and excess of movement. For the construction of a motor act, there must be an excitatory signal for the desired movement and an inhibiting command for the unwanted movements. This occurs in the basal ganglia circuit through the direct and indirect pathways, respectively.[17] Additionally, there is also an inhibitory control called "surround inhibition" at the cortical level, which blocks the excitation of neuronal groups not required for the execution of a motor act. The loss of inhibition has also been

Table 1. Axis 1: Classification of dystonia according to clinical characteristics.

Age of onset	
PPresentation <2 years of age	Infant
Presentation 3-12 years of age	Childhood
Presentation 13-20 years of age	Adolescence
Presentation 21-40 years of age	Young adult
Presentation >40 years of age	Adult
Body distribution	
One affected body region	Focal
Two contiguous body regions	Segmentary
More than two non-continuous regions	Multifocal
Trunk and at least two affected regions	Generalized
An affected hemibody	Hemidystonia
Temporal pattern	
Course of the disease	Persistent Task-specific
Variability of symptoms	Diurnal fluctuations Paroxysmal
Coexistence of other neurological disorders	
Parkinsonism, myoclonias.	Neurological or systemic associated diseases Dystonia alone or in combination with other movement disorders.

Table 2. Axis 2: Classification of dystonia according to etiology.

Central nervous system disease	
Pathology of the nervous system.	Evidence of degeneration Structural lesion No evidence
Inherited or acquired	
Autosomal dominant, autosomal recessive, X-linked, mitochondrial.	Inherited
Perinatal injury, infection, drugs, toxic, vascular,	Acquired
neoplasms, brain tumor, psychogenic. Sporadic or familial.	Idiopathic

studied in more basic levels of motor control, such as at the medullary level. It was precisely in the medulla and brainstem where it was demonstrated for the first time. Some examples are loss of reciprocal inhibition in the forearm muscles of patients with focal hand dystonia as well as abnormalities opening and closing the eyelids due to loss of reciprocal inhibition and decreased inhibition of the blinking reflex seen in blepharospasm. This loss of reciprocal inhibition may be partly responsible for the antagonistic muscle co-contraction that characterizes dystonia.[18]

b. Sensory Alterations and in Sensory-Motor Integration

The sensory trick phenomenon is clear proof of the importance of perception in the expression of the disease, however, it is not yet understood. In some experiments the vibration of the affected arm can induce dystonia in patients with focal

dystonia of the hand; this can be blocked with diluted lidocaine, which may indicate that this phenomenon is mediated by afferent fibers from the neuromuscular spindle.[19] Sensory abnormalities have been observed, such as alterations in spatial localization and temporal discrimination, present in both hands of patients with focal dystonia of the hand and even in the hands of patients with blepharospasm and cervical dystonia.[20,21]

c. Abnormal Brain Plasticity

There is evidence in animal studies that suggest that neuronal plasticity is a key factor in the pathophysiology of dystonia. Long-term potentiation and depression models are typical models of plasticity in mammals and there is ample evidence that loss in this synaptic homeostasis is the cause of motor disorder.[22,23] It has been postulated that the synchronic and repetitive activity can produce afferences to the motor and sensitive area that produce a "bad adaptation" in the cortical plasticity. This has been observed in animal and human models in which abnormal remodeling of the primary somatosensory cortex occurs.[23] This excess of neuronal plasticity, together with the lack of factors that model the synaptic potentiation in cortico-striatal circuits, generates a tendency to form associations between sensory inputs and motor outputs that prevent a differentiation of the motor programs. During learning tasks, a fine regulation usually occurs that reduces interference between superimposed motor tasks by avoiding the combination of unwanted movements. This lack of inhibition and loss of homeostasis in brain plasticity can lead to the consolidation of abnormal motor engrams that contain redundant information causing the motor overflow that produces the typical dystonic phenomena.[22,23]

5. Etiology of Dystonia

Although most patients with dystonia are classified as sporadic, genetic factors are central to the development of isolated and combined primary dystonias. There are dystonias with autosomal dominant inheritance, however, some of them with low penetrance; therefore, not all carriers of the mutation will present the phenotype although they can potentially transmit it to their offspring. Dystonia may also be inherited in an autosomal recessive or X-linked manner.[24]

The most frequent isolated generalized dystonias are related to the genes DYT1, DYT4, and DYT6, being inherited in an autosomal dominant manner with incomplete penetrance secondary to mutations in TORIA, TUBA4, and THAP1, respectively.[24] Mutations in DYT5a and b (GCH1 and TH), DYT3, DYT12, and DYT16 can be accompanied by parkinsonism whereas DYT11 (SGCE) and DYT15 by myoclonias.[24,25] Table 3 summarizes some of the hereditary dystonias including the function of the encoded protein, its phenotype, and year of its description. Additionally, the autosomal recessive mutations of PARKIN and DJ1 seen in early-onset Parkinson's disease may also be accompanied by limb dystonia. It is important to note that in mutations that cause generalized dystonia such as DYT1, DYT4, and DYT6, in addition to reduced penetrance there is variable expressibility, so in some cases, the clinical expression can also be focal.

Genes associated with craniocervical dystonia have been recently described. The first new gene described was CIZ1 (DYT23) (Cip1- Interacting zinc finger protein 1). This mutation has been reported in adult-onset cervical dystonia.[26]

Mutations in ANO3 (DYT24) (Anoctamin 3) have been reported in predominantly craniocervical dystonia, with a wide age range of onset. ANO3 encodes a transmembrane protein that binds to calcium channels activated by calcium and that play an important role in transduction.[27]

Heterozygous mutations in the GNAL (DYT25) gene (Guanine nucleotide-binding protein subunit alpha L), which codes for the alpha subunit of the Golf protein, causes cervical dystonia.[28] The Golf protein has been found coupled to dopamine D1 and adenosine A2A receptors. These mutations have high penetrance but not complete.[29] Other genes related to cervical skull dystonia are: DYT 7, DYT 17, DYT 26, and DYT 27.[1,30]

In order to perform a phenotypic and genetic

Table 3. Hereditary dystonia, coded protein function, phenotype, and year of description.

Dystonia Type	Phenotype	Protein Function	Year
DYT-TOR1A (DYT1)	Generalized dystonia of early onset, usually starts in the lower limbs.	Located in the endoplasmic reticulum, ATPase associated with several cellular functions, could be considered to be a chaperone.	1997
DYT-THAP1 (DYT6)	Dystonia with onset in adolescence with mixed phenotype, cranial-cervical involvement.	Transcription factor. Regulates the expression of TOR1A.	2009
DYT-GNAL (DYT25)	Dystonia of adult onset, segmental, predominantly cranial and cervical .	Protein involved in transduction. Encodes for the alpha subunit of the Golf protein, which is coupled to D1 and A2A receptors.	2013
DYT-ANO3 (DYT24)	Late-onset craniocervical dystonia.	Transmembrane protein that binds to calcium channels activated by calcium, playing an important role in transduction.	2012
DYT-CIZ1 (DYT23)	Cranio-cervical dystonia.	Protein 1 interaction with zinc fingers.	2012
DYT-GCH1 (DYT5a)	Dystonia that responds to dopa. Typically with daytime fluctuation. Starts in lower limbs.	Enzyme involved in the synthesis of tetrahydrobiopterin.	1995
DYT-SGCE (DYT11)	Myoclonic dystonia. Predominance of dystonia and myoclonus in the cervical skull region and upper limbs. Responds to Alcohol.	Transmembrane protein that stabilizes sarcoglycan complex.	2001
DYT-PRKRA (DYT16)	Dystonia-Parkinsonism.	Protein kinase with function in response to cellular stress.	2008

approach, we studied dystonia according to whether it occurs in isolation, combined with myoclonus or Parkinsonism, or in a paroxysmal manner. Figure 1 shows the diagnostic approach through the phenotype. Additionally, it should be considered if the dystonia involves muscles in the cranial and cervical region, in the larynx, if it is generalized, focal, or multifocal, in order to perform an even more precise orientation. Figure 2 and Figure 3 show an approximation according to these more specific clinical characteristics of dystonia to guide and facilitate the genetic search.

6. Non-motor characteristics of Dystonia

Clinical observation has allowed recognizing the coexistence of depression and anxiety in patients with dystonia. The prevalence of these disorders varies; however, it is estimated between 12 and 71% though most studies show a range between 25 and 50%, a similar percentage to patients with Parkinson's disease. In both cases, this frequency is higher than in healthy individuals and other medical conditions.[5] There are controversy and little knowledge about whether the neuropsychiatric symptoms are a consequence of the neurobiology of dystonia or if they are a secondary expression in coping with the severity of the disease. There is more evidence in favor of the fact that the alterations of affect are secondary to the alteration of the circuits involved in dystonia. In a study of 89 patients with focal dystonia, 57.3% had psychiatric disorders compared to 24% of healthy subjects and 34.6% of patients with hemifacial spasm.[31] In another study carried out in Germany, a prevalence of 70.3% was reported for psychiatric or personality disorders, with those in the anxious

spectrum being the most frequent.[32] Functional studies of dopamine transporters, as well as ligands of D2/D3 receptors, suggest a role of dopamine in the pathophysiology of depression in patients with cervical dystonia.[33] Another study compared the frequency of psychiatric symptoms in the initial evaluation with another subsequent evaluation at five years. It was reported that the prevalence was similar and that the symptoms did not change over time. In comparison, the motor evaluations presented improvement; this suggests that the presence of psychiatric symptoms are independent of the severity of motor symptoms.[34] For all the above, it is considered that neuro-psychiatric symptoms may be related to a process underlying the pathophysiology of dystonia. It is possible that elements of reactive depression triggered by a visible, disabling, and potentially painful disease may exacerbate affective symptoms like anxiety and depression, however, these aspects have a profound impact on the quality of life.[35]

In this regard, a study conducted in 50 Dutch patients with dystonia reported worse scores on the quality of life scale compared with patients diagnosed with a psychiatric illness. Additionally, the most important predictors of quality of life were the severity of their depression and pain, not the motor symptoms.[36]

Finally, some alterations in cognition have also been described, especially in executive functions such as mental flexibility, attentional deficits, and verbal fluency, among others.[37]

7. Treatment

In the last 25 years not only has it been possible to delve into the molecular aspects of dystonia, but at the same time, the therapeutic options have changed drastically. For decades, oral medications were used exclusively, though they had a limited benefit and important adverse effects. With the introduction of botulinum toxin application for the treatment of focal dystonias, and later with the advent of deep brain stimulation (DBS) surgery, the therapeutic approach of these entities has been modified, which in turn has improved the quality of life of the patients.[38]

Figure 1. Approach to Dystonia based on the Phenotype/Genotype Correlation.

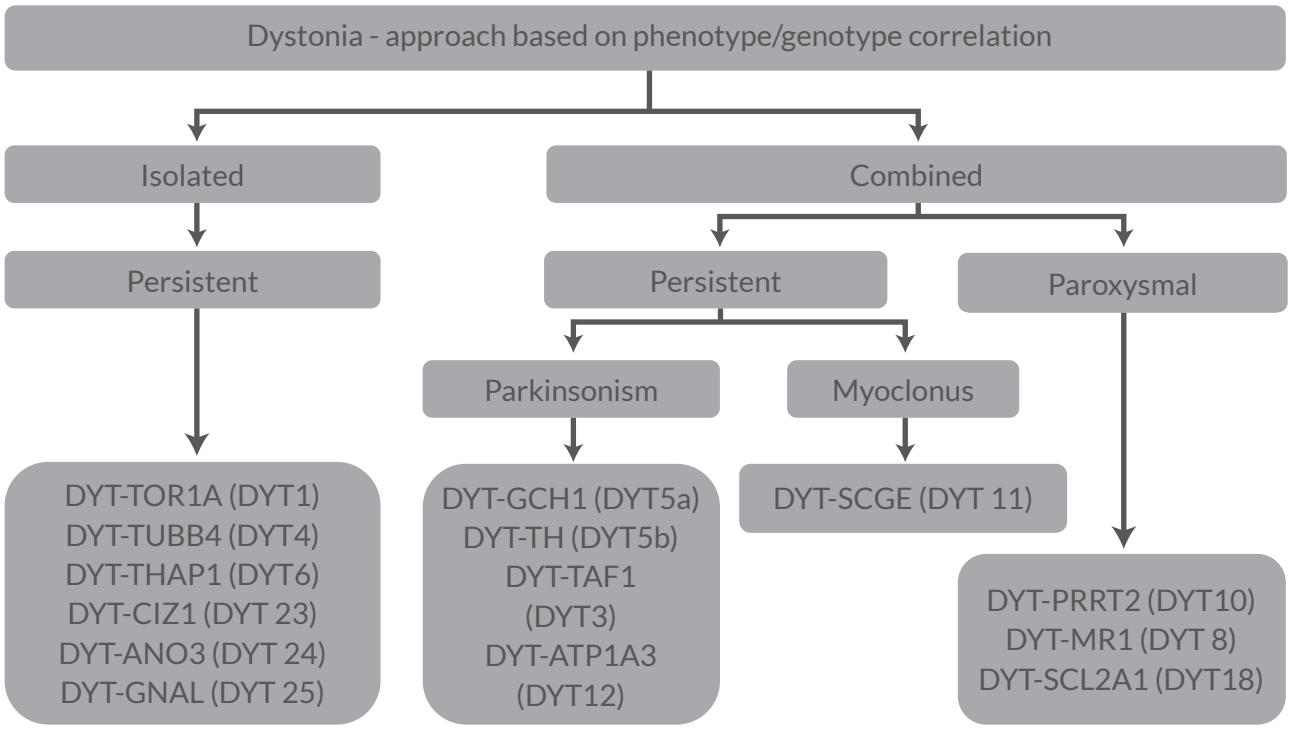


Figure 2. Genetic diagnosis approach according to the clinical characteristics of Dystonia (Isolated).

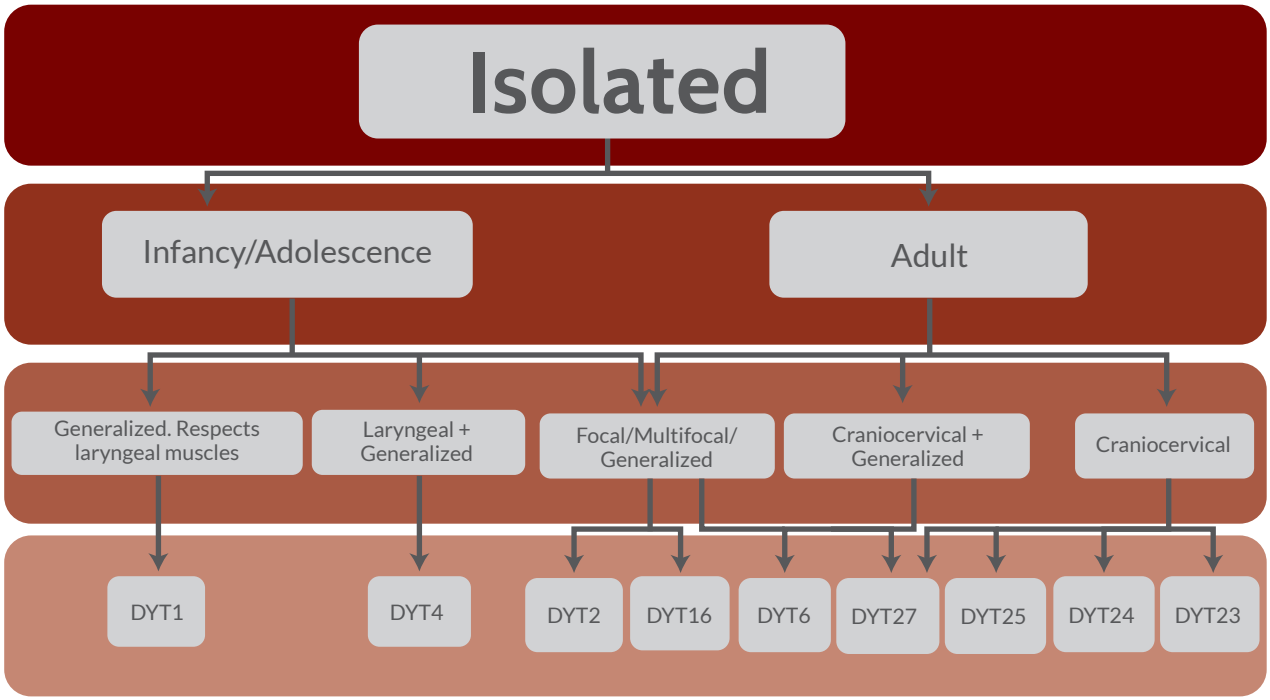
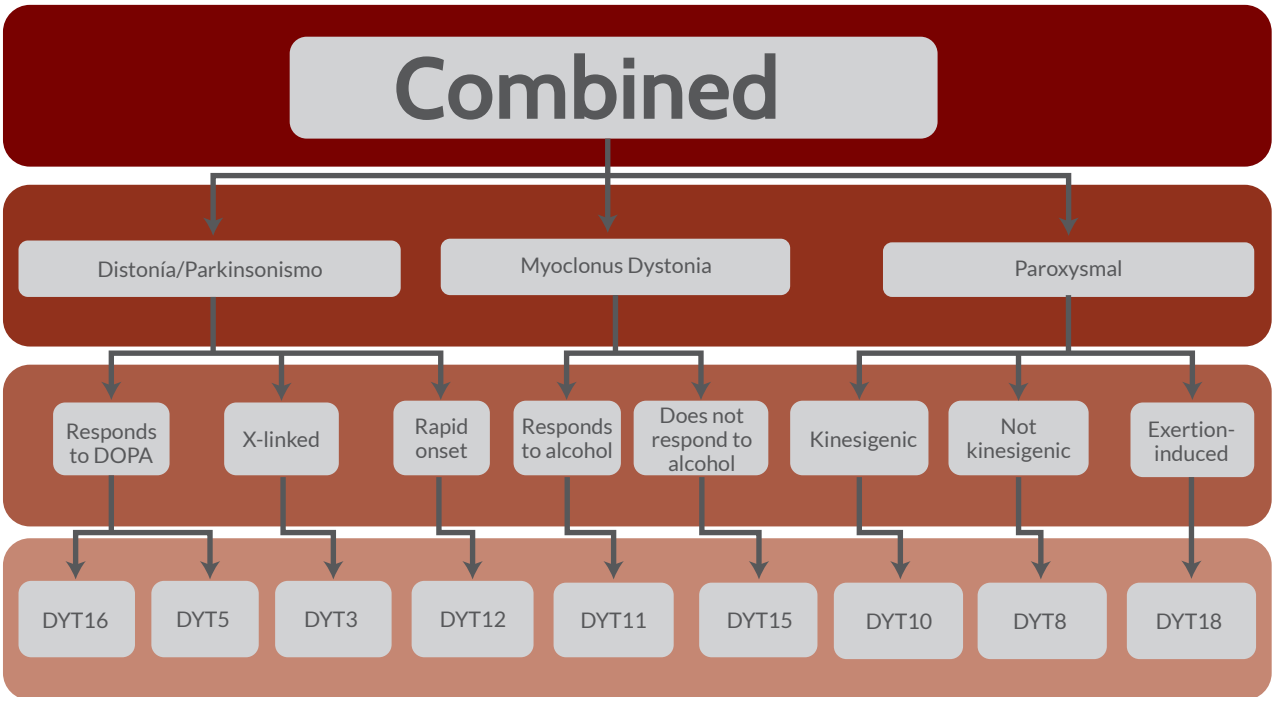


Figure 3. Genetic diagnosis approach according to the clinical characteristics of Dystonia (Combined).



Oral Medications

The efficacy of high-dose trihexyphenidyl for the treatment of generalized primary dystonia was established in a prospective, double-blind study by Burke et al. in 1986.[39] Since then, few oral medications have been successful in the treatment of dystonia. Oral pharmacological treatment has not changed much over the years, currently, anticholinergics (especially trihexyphenidyl) and baclofen are used in addition to benzodiazepines and levodopa.

Levodopa for the treatment of dystonia that responds to dopa (DYT5) has allowed demonstrating a significant benefit in this group of patients.[40] Tetrabenazine and clozapine can be used for secondary dystonia and metabolic syndromes such as glutaric acidemia, among others.[38,41]

Intrathecal infusion of baclofen

The intrathecal infusion of baclofen has also been used for the treatment of generalized dystonia refractory to oral medications. However, it has been shown to be more beneficial in patients with dystonia associated with spasticity or pain.[42,43]

Botulinum toxin

The treatment of focal dystonia, previously limited to oral medications, has been transformed by the introduction of botulinum toxin. Since the 1980s, the application of botulinum toxin has become a first-line treatment for the various forms of focal dystonia.[44–46] This treatment is used locally, having high efficacy and causing minimal side effects. Table 4 summarizes the recommendations of the American Association of Neurology for the use of botulinum toxin in different locations of dystonia and spasticity.[47] The toxin blocks the vesicular release of acetylcholine at the neuromuscular junction, causing temporary local chemo-denervation and muscle weakness, reducing excessive dystonic muscle activity.[48]

Botulinum toxin is a protein extracted from the bacterium Clostridium botulinum of which eight different antigenic variants are currently known (denominated from A to G), which share similar structural characteristics.[49] Out of those toxins, type A and type B toxins are currently in use (OnabotulinumtoxinA-Botox,AbobotulinumtoxinA - Dysport, IncobotulinumtoxinA - Xeomin, RimabotulinumtoxinB - Myobloc). The toxin consists of a light and heavy chain linked by a disulfide bond. The light chain acts on different proteins according to the toxin subtype. The light chain of toxin A acts on the protein SNAP-25 (associated with the synaptosome), which is necessary for the fusion of the vesicle with the presynaptic membrane.[48,49]

Botulinum toxin penetrates into the presynaptic terminal of the neuromuscular junction by binding the heavy chain to a specific receptor of the plasma membrane to be captured by endocytosis. Botulinum toxin is a protein that is foreign to the immune system, therefore neutralizing antibodies can be produced to block its effect. The risk for these antibodies to be generated is application at short intervals, usually less than three months, and high total doses. Clinically, this resistance can be suspected when the patient does not show improvement and does not develop weakness or atrophy in the injected muscles.[49–51]

Deep brain stimulation (DBS)

In the mid-20th century, the surgical treatment of generalized dystonia consisted of surgical lesions, classically thalamic. Thalamotomy provided significant benefit for dystonia in some patients; however, it frequently caused permanent disabling neurological effects. After observing that pallidotomy in patients with Parkinson's disease improved dyskinesias, interest in the globus pallidus was aroused as a surgical target in dystonia. After the introduction of DBS for the treatment of essential tremor and Parkinson's disease in the mid-1990s, this therapy was established as an alternative to ablative procedures for the treatment of movement disorders. Parallel bilateral stimulation began to be used for the treatment of generalized dystonia about a decade ago.[52]

In patients with primary generalized dystonia, especially those with dystonia DYT1, the response is dramatic.[53] Studies of bilateral DBS of the internal globus pallidus (Gpi) for the treatment of

Table 4. Level of recommendation of the American Association of Neurology for the use of botulinum toxin in different sites for dystonia and spasticity.

Indication	Onabotulinum	Incobotulinum	Abobotulinum	Rimabotulinum
	Type A	Type A	Type B	Type B
Blepharospasm	Level B	Level B	Level C	Level U
Cervical dystonia	Level B	Level B	Level A	Level A
Upper limb spasticity	Level A	Level A	Level A	Level B
Lower limb spasticity	Level A	Level U	Level A	Level U

Level A effective recommendation means that the intervention should be offered.
Level B probably effective recommendation means that the intervention should be considered.
Level C possibly effective recommendation means that the intervention could be considered.
Level U insufficient recommendation evidence means that there is no evidence to support or refute the effectiveness of the intervention.

primary dystonia show a significant reduction of 50-80% in dystonic symptoms[54–56] and a significant improvement in function and quality of life.[56,57]

This therapeutic strategy has also become a crucial treatment option for patients with primary generalized dystonia refractory to pharmacological management. In addition, long-term follow-up studies have reported sustained clinical improvement in patients with follow-ups at 5 and 10 years.[55–59] However, there are some considerations for the selection of patients, on whom the success of the procedure depends. [54,60]

It is considered that there are a few good outcome predictors for DBS, among which are a lower severity, early age at the time of surgery, carrying a DYT1 mutation, shorter disease duration, and absence of fixed skeletal deformities. Regarding the duration of symptoms, there is controversy in the literature. An observational study found that the duration of symptoms rather than age at the time of surgery was inversely correlated with the outcome. Skeletal deformities were generally associated with worse outcomes. Therefore, it is considered that age should not be used as inclusion or exclusion criteria for Gpi DBS, as both children and adults can benefit from the procedure.[61] It is important to note that there are not enough data for recommendations in children under seven years of age; however, the surgical option could be considered before the development of fixed skeletal deformities or other complications such as cervical myelopathy.[62,63]

The use of DBS for the treatment of generalized primary dystonia, especially DYT1 has been widely accepted. There are questions about its effectiveness in secondary forms. The data regarding the efficacy of deep brain stimulation for secondary dystonia in the reports of individual cases or small series of cases with different forms of secondary dystonia range from no benefit to dramatic improvement. Cases with good response have been reported as dystonia due to hereditary-degenerative diseases such as PKAN (Pantothenate kinase-associated neurodegeneration) and Lubag Syndrome (X-linked dystonia-parkinsonism).[64,65]

The detection of psychiatric comorbidity, including depression and suicide attempts, is important in the preoperative evaluation. If psychiatric symptoms are considered serious this may be a contraindication for surgery. Comorbidities such as hypertension and cognitive deterioration should be taken into account when analyzing risks and benefits. Careful evaluation of other neurological disorders should be included in the evaluation, especially in cases of secondary dystonia.[63] It is important to emphasize that pharmacological

medical treatment must always be offered before considering surgery. General clinical experience suggests that patients with dystonia should receive the appropriate medications, even reaching the maximum tolerated dose of currently available drugs. Children usually tolerate high doses of anticholinergics, which can be very beneficial, whereas high doses are not well tolerated in adults due to adverse effects on cognitive functions. This therapy should always be started thinking about the possibility of subsequent surgery, given that it is clear that fixed skeletal deformities should be avoided, as they worsen the prognosis.[66]

Conclusions

Dystonia today constitutes a fundamental field of study in the hyperkinetic movement disorders through which we can approach the understanding of the functioning and integrity of the motor systems at the level of the basal ganglia, cerebral cortex, and cerebellum. Its recognition and adequate classification allow a better diagnostic and genetic approach, making it easier to choose the most appropriate pharmacological, therapeutic, or surgical intervention which will impact the patient's quality of life.

Conflicts of interest
We declare that this research has no conflicts of interest.

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References

1. Ozelius LJ, Lubarr N, Bressman SB. Milestones in dystonia. *Mov Disord.* 2011;26(6):1106-1126.
2. Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary dystonia: A systematic review and meta-analysis. *Mov Disord.* 2012;27(14):1789-1796.
3. Alegría MA, Rodríguez VM, Zavala RA, López RM. Distonía cervical. *Rev Mex Neurocienc.* 2009;10(2):90-102.
4. Troiano R, Micheli FE, Alarco F. *Movement disorders in Latin America.* 2006;12:125-138.
5. Kuyper DJ, Parra V, Aerts S, Okun MS, Kluger BM. Nonmotor manifestations of dystonia: A systematic review. *Mov Disord.* 2011;26(7):1206-1217.
6. H O. About a rare spasm disease of childhood and young age (Dysbasia lordotica progressiva, dystonia musculorum deformans). *Neurol Cent.* 1911;30:1090-1107.
7. CD Marsden. Dystonia: The Spectrum of the Disease. *Res Nerv Ment Dis.* 1976;55:351-367.
8. Albanese A. How many dystonias? Clinical evidence. *Front Neurol.* 2017;8:18.
9. Fahn S ER. Definition of dystonia and classification of the dystonic states. *Adv Neurol.* 1976;14:1-5.
10. Albanese A, Lalli S. Update on dystonia. *Curr Opin Neurol.* 2012;25(4):483-490.
11. Albanese A, Bhatia K, Bressman SB, *et al*. Phenomenology and classification of dystonia: A consensus update. *Mov Disord.* 2013;28(7):863-873.
12. Jinnah HA, Delong MR, Hallett M. The dystonias: Past, present, and future. *Mov Disord.* 2013;28(7):849-850.
13. Albanese A. *Dystonia : clinical approach.* 2007;13:356-361.
14. LeDoux MS. Dystonia: phenomenology. *Parkinsonism Relat Disord.* 2012;18:S162-S164.
15. Sitburana O, Chen Wu LJ, Sheffield JK, Davidson A, Jankovic J. Motor overflow and mirror dystonia. *Park Relat Disord.* 2009;15(10):758-761.
16. Frucht SJ. The definition of dystonia: Current concepts and controversies. *Mov Disord.* 2013;28(7):884-888.
17. Quartarone A, Hallett M. Emerging concepts in the physiological basis of dystonia. *Mov Disord.* 2013;28(7):958-967.
18. Breakefield XO, Blood AJ, Li Y, Hallett M, Hanson PI, Standaert DG. The pathophysiological basis of dystonias. *Nat Rev Neurosci.* 2008;9(3):222-234.
19. Kaji R, Rothwell SJC, Katayama M, Ikeda T. *Tonic Vibration Reflex and Muscle Afferent Block in Writer ' s Cramp.* 1995:155-162.
20. Tinazzi M, Fiorio M, Fiaschi A, Rothwell JC, Bhatia KP. *CME Sensory Functions in Dystonia : Insights from Behavioral Studies.* 2009;24(10):1427-1436.
21. Bara-Jimenez W, Shelton P, Hallett M. Spatial discrimination is abnormal in focal hand dystonia. *Neurology.* 2000;55(12):1869-1873.
22. Quartarone A, Bagnato S, Rizzo V, *et al*. Abnormal associative plasticity of the human motor cortex in writer's cramp. *Brain.* 2003;126(12):2586-2596.
23. Quartarone A, Pisani A. Abnormal plasticity in dystonia: Disruption of synaptic homeostasis. *Neurobiol Dis.* 2011;42(2):162-170.
24. Ozelius LJ, Bressman SB. Genetic and clinical features of primary torsion dystonia. *Neurobiol Dis.* 2011;42(2):127-135.
25. Klein C. Genetics in dystonia. *Park Relat Disord.* 2014;20(SUPPL.1):S137-S142.
26. Xiao J, Uitti RJ, Zhao Y, *et al*. Mutations in CIZ1 Cause Adult Onset Primary Cervical Dystonia. 2012; 71(4):458-469
27. Bras J, Sheerin U, Charlesworth G, *et al*. Mutations in ANO3 Cause Dominant Craniocervical Dystonia : Ion Channel Implicated in Pathogenesis. 2012:1041-1050.
28. Fuchs T, Saunders-pullman R, Masuho I, *et al*. Mutations in GNAL cause primary torsion dystonia. *Nat Genet.* 2013; 45(1): 88–92.
29. Lohmann K, Klein C. Update on the genetics of Dystonia. *Curr Neurol Neurosci Rep.* 2017;17(3):26
30. Camargos S, Cardoso F. Understanding dystonia: diagnostic issues and how to overcome them. *Arq Neuropsiquiatr.* 2016;74(11):921-936.
31. Fabbrini G, Berardelli I, Moretti G, *et al*. Psychiatric disorders in adult-onset focal dystonia: A case-control study. *Mov Disord.* 2010;25(4):459-465.
32. Lencer R, Steinlechner S, Stahlberg J, *et al*. Primary focal dystonia: evidence for distinct neuropsychiatric and personality profiles. *J Neurol Neurosurg Psychiatry.* 2009;80(10):1176-1179.
33. Zoons E, Tijssen MAJ, Dreissen YEM, Speelman JD, Smit M, Booij J. The relationship between the dopaminergic system and depressive symptoms in cervical dystonia. *Eur J Nucl Med Mol Imaging.* 2017;44(8):1375-1382
34. Berardelli I, Ferrazzano G, Pasquini M, Biondi M, Berardelli A, Fabbrini G. Clinical course of psychiatric disorders in patients with cervical dystonia. *Psychiatry Res.* 2015;229(1-2):583-585.
35. Zurowski M, Mcdonald WM, Fox S, Marsh L. Psychiatric comorbidities in dystonia: Emerging concepts. *Mov Disord.* 2013;28(7):914-920.

36. Smit M, Kuiper A, Han V, *et al*. Psychiatric co-morbidity is highly prevalent in idiopathic cervical dystonia and significantly influences health-related quality of life: Results of a controlled study. *Parkinsonism Relat Disord.* 2016;30:7-12.
37. Lange F, Seer C, Dengler R, Dressler D, Kopp B. Cognitive Flexibility in Primary Dystonia. *J Int Neuropsychol Soc.* 2016;22(6):662-670.
38. Adam O, Jankovic J. Treatment of dystonia. *Parkinsonism Relat Disord.* 2007;13(1):94-121.
39. Burke RE FS. Double-blind evaluation of trihexyphenidyl in dystonia. *Adv Neurol.* 1983;37:189-192.
40. Hwang WJ, Calne DB, Tsui JKC, Fuente-ferna R De. *The long-term response to levodopa in dopa-responsive dystonia.* 2001;8:18-22.
41. Jankovic J. Medical treatment of dystonia. *Mov Disord.* 2013;28(7):1001-1012.
42. Woolf SM, Baum CR. Baclofen. *Uses and Complications.* 2017;33(4):271-275.
43. Monbaliu E, Himmelmann K, Lin J, *et al*. *Clinical presentation and management of dyskinetic cerebral palsy.* 2017:741-749.
44. Jabbari B. *Reviews History of Botulinum Toxin Treatment in Movement Disorders.* 1989:1-9.
45. Müller J, Kemmler G, Wissel J, *et al*. The impact of blepharospasm and cervical dystonia on health-related quality of life and depression. *J Neurol.* 2002;249(7):842-846.
46. Su MV, Direcci REZ, Investigaci DE, *et al*. Impact of Neu-botulinumtoxinA on the Severity and Quality of Life of Cervical Dystonia Patients. *Arq Neuropsiquiatr.* 2016;10(6):188-194.
47. Simpson DM, Hallett M, Ashman EJ, *et al*. Practice guideline update summary : *Botulinum neurotoxin for the treatment of blepharospasm , cervical dystonia , adult spasticity , and headache Academy of Neurology.* 2016;86(19):1818-1826.
48. Jankovic J. Botulinum Toxin : State of the Art Mechanism of Action and Pharmacology of BoNT. 2017;32(8):1-8.
49. Arango GJ, Fernández W. Indicaciones actuales para el uso de la toxina botulínica en neurología. *Acta Neurologica Colombiana.* 2004.15:12-34
50. Albanese A, Asmus F, Bhatia KP, *et al*. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol.* 2011;18(1):5-18.
51. Pirio Richardson S, Wegele AR, Skipper B, Deligtisch A, Jinnah HA. Dystonia treatment: Patterns of medication use in an international cohort. *Neurology.* 2017;88(6):543-550.
52. Vidailhet M, Vercueil L, Houeto JL, *et al*. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. *Lancet Neurol.* 2007;6(3):223-229.
53. Krystkowiak P, Benabid A, Ph D, *et al*. *Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia.* 2005:459-467.
54. Vidailhet M, Yelnik J, Lagrange C, *et al*. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. *Lancet Neurol.* 2009;8(8):709-717.
55. Volkmann J, Wolters A, Kupsch A, *et al*. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. *Lancet Neurol.* 2012;11(12):1029-1038.
56. Gruber D, Trottenberg T, Kivi A, *et al*. Long-term effects of pallidal deep brain stimulation in tardive dystonia. *Neurology.* 2009;73(1):53-58.
57. Marks WA, Honeycutt J, Acosta F, Reed M. Deep Brain Stimulation for Pediatric Movement Disorders. *Semin Pediatr Neurol.* 2009;16(2):90-98.
58. Cersosimo MG, Raina GB, Piedimonte F, Antico J, Graff P, Micheli FE. Pallidal surgery for the treatment of primary generalized dystonia: Long-term follow-up. *Clin Neurol Neurosurg.* 2008;110(2):145-150.
59. Meoni S, Fraix V, Castrioto A, *et al*. Pallidal deep brain stimulation for dystonia: a long term study. *J Neurol Neurosurg Psychiatry.* 2017:jnnp-2016-315504.
60. Moro E, Gross RE, Krauss JK. What's new in surgical treatment for dystonia? *Mov Disord.* 2013;28(7):1013-1020.
61. Aravamuthana Bhooma R, Waugha Jeff SSS. Deep brain stimulation for monogenic dystonia. *Curr Opin Pediatr.* 2017;29(6):691-696.
62. Bronte-Stewart H, Taira T, Valldeoriola F, *et al*. Inclusion and exclusion criteria for DBS in dystonia. *Mov Disord.* 2011;26(SUPPL.1):5-16.
63. Thobois S, Taira T, Comella C, Moro E, Bressman S, Albanese A. Pre-operative evaluations for DBS in dystonia. *Mov Disord.* 2011;26(SUPPL.1):17-26.
64. Krause M, Fogel W, Tronnier V, Pohle S, Hörtnagel K, Thyen U VJ. Long-term benefit to pallidal deep brain stimulation in a case of dystonia secondary to pantothenate kinase-associated neurodegeneration. *Mov Disord.* 2006;21(12):2255-2257.
65. Patel AJ, Sarwar AI, Jankovic J VA. Bilateral pallidal deep brain stimulation for X-linked dystonia-parkinsonism. *World Neurosurg.* 2014;82:241-244.
66. Mills KA, Starr PA, Ostrem JL. Neuromodulation for Dystonia. Target and Patient Selection. *Neurosurg Clin N Am.* 2014;25(1):59-75.

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