Dystonia – new advances in classification, genetics, pathophysiology and treatment


Dystonia is a heterogeneous movement disorder and has been defined as ‘a syndrome of sustained muscle contractions, frequently causing twisted and repetitive movements, or abnormal postures’. The classification of dystonia has developed along with increasing knowledge, and different schemes have been suggested, including age at onset, body distribution, and etiology as the main differentiating factors. A revised definition and a new classification of dystonia have now been proposed by a group of leading dystonia experts and will be referred here. The discovery of the first two gene mutations causing primary generalized dystonia (DYT1-TOR1A and DYT6-THAP1) has facilitated studies on pathogenesis and pathophysiology of primary dystonias, by comparing neurophysiology between manifesting and non-manifesting carriers, and by studying the molecular biology of the mutant gene products. During recent years, several other gene mutations causing primary dystonia, dystonia-plus, and paroxysmal dystonia disorders have been discovered. Only during the last year, by the use of whole-exome sequencing techniques, mutations in three different genes in families with predominantly cervical dystonia were found, which may lead to improved insight into the pathogenesis also of the more frequent focal dystonias. Botulinum neurotoxin (BoNT) and deep brain stimulation (DBS) have revolutionized the symptomatic treatment for dystonia during the last two decades and continue to be refined to improve efficacy and expand their indications. Unfortunately, no progress has been made in the oral medication of dystonia. Current and future new insights into pathogenetic and pathophysiological mechanisms of dystonia will hopefully lead to improvement also in this area soon.

Introduction

The term ‘dystonia’ was introduced 102 years ago by Oppenheim, who described four patients with ‘dystonia musculorum deformans’, in whom ‘muscle tone was hypotonic at one occasion, and in tonic muscle spasm at another, usually, but not exclusively, elicited upon voluntary movements’ (1). The first descriptions in the medical literature of writer’s cramp, which is a focal dystonia, were published some decades earlier (2, 3). During the first seven decades of the 20th century, focal dystonias were regarded by many neurologists to be psychogenic, but this began to change after C. David Marsden published his comprehensive paper on adult-onset torsion dystonias in 1976 (4). This was a very important contribution to the current view of dystonia as a neurological hyperkinetic movement disorder.

In 1984, a committee assembled by the Dystonia Medical Research Foundation provided the first consensus definition of dystonia as ‘a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures’ (5). This definition has been used by most clinicians and researchers since, but with the rapidly expanding spectrum of defined diseases featuring dystonia and/or dystonic tremor as the only or the main clinical sign, it has become clear that this definition has some limitations (6).
Skogseid

The classification of dystonia has developed along with increasing knowledge, and different schemes have been suggested, including age at onset, body distribution, and etiology as the main factors to differentiate between different dystonia syndromes. A group of leading experts in dystonia has now proposed both a revised definition of dystonia and a new classification (6), which may become even more widely accepted as a common definition and classification for all involved in the care of people with dystonia in the future.

The discovery in 1997 of the first gene mutation causing primary generalized dystonia (DYT1-TOR1A) (7) has facilitated studies on pathogenesis and pathophysiology of DYT1-dystonia, comparing neurophysiology between manifesting and non-manifesting carriers (8), and on the molecular biology of the mutant gene product torsinA in various animal models (9). Several other pathogenic gene mutations causing generalized forms of dystonia, including primary dystonia, dystonia-plus, and paroxysmal dystonia disorders, have been discovered since. Autosomal dominant inheritance and reduced penetrance are typical for many of these genetic dystonias, although a few recessive and X-linked disorders have also been identified (10). Although about 15–25% of patients with focal and segmental dystonia have first-degree relatives with dystonia, the search for genes or susceptibility factors explaining this has been disappointing (10). However, using the new whole-exome sequencing techniques, mutations in three different genes in families with predominantly cervical dystonia were found during the last year and may be the start of a new era of improved insight into the pathogenesis of focal dystonias, and thus of more targeted medical treatment (11). The genetic basis of metabolic or heredodegenerative disorders that often lead to dystonia has been elucidated, and neuroimaging and other laboratory techniques for diagnosing causes of secondary dystonia have improved and become more widely available. Thus, as the last two decades brought us the two revolutions in dystonia treatment, this decade may bring to light the pathogenetic basis for many of the dystonia disorders.

Definition and classification

The new definition of dystonia, which was recently published in the journal Movement Disorders, is: “Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal, often repetitive, movements, postures or both. Dystonic movements are typically patterned, twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation’ (6). The motor phenomenology with special relevance for dystonia is further defined, including its aggravation by voluntary action and maintenance by antigravity postures, dystonic tremor, mirror dystonia, overflow, and alleviating maneuvers such as sensory tricks and gestes antagonistes. One aim of the new definition has been to exclude several conditions that also result in abnormal movements, postures or spasms, and thus mimic dystonia, the so-called pseudodystonias.

Whereas dystonia until now has been classified according to age at onset, body distribution, and etiology (primary, dystonia-plus, heredodegenerative, and secondary), the expert group now proposes to classify dystonia on the basis of two distinct axes: clinical features and etiology (6). Five descriptors are utilized to specify the clinical features axis: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and coexistence of other neurological or systemic manifestations. Age at onset is divided into infancy (0–2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–40), and late adulthood (>40 years). Body distribution is, as in earlier classifications, divided into focal, segmental, multifocal, generalized, and hemidystonia. The definition of generalized dystonia emphasizes that the trunk and two other body regions must be involved, but leg involvement is not obligatory according to this new classification. Temporal pattern distinguishes between static or progressive disease course and variability of symptoms, which could be persistent, action-specific, diurnal, or paroxysmal. Regarding the coexistence of other movement disorders, the term ‘isolated dystonia’ is used when these are not present, and the term ‘combined dystonia’ if they are. Finally, other neurological manifestations (than movement disorders) or systemic manifestations are denoted if present. The etiology axis is described by whether nervous system pathology is present or not, and whether it is inherited, acquired, or idiopathic. Under the subheading ‘nervous system pathology’, patients may have evidence of degeneration, evidence of a structural (often static) lesion, or no evidence of either of these. Inherited dystonia forms may be autosomal dominant, autosomal recessive, X-linked recessive or mitochondrial. Acquired causes may include perinatal brain injuries, infections, drugs, toxins, vascular lesions, neoplastic diseases, brain injuries (head trauma, brain surgery), or psychogenic cause.
Finally, idiopathic cases can be subdivided into sporadic or familial (6).

**Genetics and pathophysiology**

Until last year, only two primary/isolated forms of familial dystonia (DYT1 and DYT6), both with early or young adult onset had been shown to be unequivocally associated with gene mutations (7, 12). Since then, mutations in four more genes have been implicated as causes of familial, primary dystonia, of which three are segmental or focal cervical dystonia forms with adolescent to adult onset (Table 1). During recent years, several gene mutations have also been identified to explain dystonia-plus syndromes and paroxysmal dyskinesia syndromes, and those included in the DYT-designation system are shown in Table 1. In addition, five loci have been identified in single families (primary dystonia: DYT13, 17, 21, and paroxysmal dyskinesia: DYT19, 20), for which the genes have not been found. It is important to be aware, however, that there are several other inherited diseases with known genetic defects that may be clinically dominated by dystonia (with or without parkinsonism, ataxia or other cerebellar signs, myoclonus or other neurological or systemic signs), but are not included in the DYT-designation system. Examples include six disorders of dopamine synthesis (13) in addition to the DYT5a and DYT5b variants of levodopa-responsive dystonia-parkinsonism, among them sepiapterin-reductase deficiency (see paper by Koht JA et al. in this supplement). Other examples are Wilson’s disease, panthothenate-kinase-associated neodegeneration and Lesch-Nyhan’s disease, just to name a few.

Although the estimated frequency of DYT1-dystonia is only 1/160000 worldwide, it is the most common form of early-onset primary/isolated dystonia (14). Nearly all cases carry the same mutation, a recurrent GAG deletion in exon 5 of the TOR1A (TorsinA) gene (7), inherited as an AD trait. But clinical dystonia develops in only 20–30% of mutation carriers, and this low penetrance is associated with the presence of the p.D216H polymorphism (15). In the typical DYT1-phenotype, dystonia starts in a limb during childhood and often spreads within a few years to the other limbs and trunk to become generalized, with the cranial-cervical region usually spared. Interestingly, the dystonia may, however, remain segmental or be purely focal and show adult onset (16), and clinical manifestations can show a variable phenotype within the same family (17, 18). Mutant TorsinA has been found to be abnormally located within cell compartments and to exhibit aberrant interaction with other proteins. The results are thought to be synaptic vesicle recycling defects and altered development of neuronal connections (9).

In contrast to DYT1-dystonia, DYT6-dystonia is characterized by onset in cranial-cervical and laryngeal areas, but also tends to generalize and most often has a juvenile onset. Penetrance is about 60%. Mutations in the THAP1 (thanatos-associated-protein-1) gene were initially identified in Amish–Mennonite families (12), but by 2011, about 60 familial and sporadic cases had been reported worldwide (19). Concomitantly, a more

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**Table 1** Dystonia syndromes with known gene mutations included in the DYT designation system

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>DYT no.</th>
<th>Inheritance pattern</th>
<th>Clinical description</th>
<th>Chromosome</th>
<th>Mutated gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/Isolated dystonia</td>
<td>DYT1</td>
<td>AD</td>
<td>EO, extremities &gt; frequent generalization</td>
<td>9q34</td>
<td>TOR1A</td>
</tr>
<tr>
<td></td>
<td>DYT4</td>
<td>AD</td>
<td>YO, larynx &gt; Occasional generalization</td>
<td>19p13.12-13</td>
<td>TUBB4a</td>
</tr>
<tr>
<td></td>
<td>DYT6</td>
<td>AD</td>
<td>YO/AD &gt; Gen./Seg. Larynx</td>
<td>8p11.21</td>
<td>THAP1</td>
</tr>
<tr>
<td></td>
<td>DYT23</td>
<td>AD</td>
<td>AO, Cervical dystonia (CD)</td>
<td>9q34</td>
<td>CIZ1</td>
</tr>
<tr>
<td></td>
<td>DYT24</td>
<td>AD</td>
<td>AO, Tremulous CD, +/- brachial, larynx</td>
<td>11p14.2</td>
<td>ANO3</td>
</tr>
<tr>
<td></td>
<td>DYT25</td>
<td>AD</td>
<td>AO, CD, +/- face, larynx, legs</td>
<td>18p11</td>
<td>GNAL</td>
</tr>
<tr>
<td>Dystonia-Plus/Dystonia combined with other movement disorders</td>
<td>DYT5a</td>
<td>AD</td>
<td>Dopa-responsive dystonia</td>
<td>14q22.1-2</td>
<td>GTPCH1</td>
</tr>
<tr>
<td></td>
<td>DYT5b</td>
<td>AR</td>
<td>Dopa-responsive dystonia</td>
<td>11p15.5</td>
<td>TH</td>
</tr>
<tr>
<td></td>
<td>DYT11</td>
<td>AD</td>
<td>Myoclonus-dystonia</td>
<td>7q21.3</td>
<td>SGC</td>
</tr>
<tr>
<td></td>
<td>DYT12</td>
<td>AD</td>
<td>Rapid-onset dystonia-parkinsonism</td>
<td>19q13.2</td>
<td>ATP1A3</td>
</tr>
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<td></td>
<td>DYT16</td>
<td>AR</td>
<td>Early-onset dystonia-parkinsonism</td>
<td>2p13.1</td>
<td>PRKRA</td>
</tr>
<tr>
<td></td>
<td>DYT3</td>
<td>X-linked</td>
<td>Dystonia-parkinsonism</td>
<td>Xp13.1</td>
<td>TAF1</td>
</tr>
<tr>
<td>Paroxysmal [P] Dyskinetic syndromes</td>
<td>DYT8</td>
<td>AD</td>
<td>P Non-Kinesiogenic Dyskinesia</td>
<td>2p35</td>
<td>MR1</td>
</tr>
<tr>
<td></td>
<td>DYT9/</td>
<td>AD</td>
<td>P Dyskinesia w/episodic ataxia + spasticity</td>
<td>1p34.2</td>
<td>SLC2A1</td>
</tr>
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<td></td>
<td>DYT18</td>
<td>AD</td>
<td>P Exercise-induced Dyskinesia</td>
<td>1p34.2</td>
<td>SLC2A1</td>
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<tr>
<td></td>
<td>DYT10</td>
<td>AD</td>
<td>P Kinesiogenic Dyskinesia (PKD)</td>
<td>16p11.2</td>
<td>PRRT2</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; EO, early onset; YO, young onset; AO, adult onset.
heterogenic phenotype was described, including onset in adults or in a limb, and lack of generalization (20). In sharp contrast to DYT1-dystonia, almost every case of DYT6-dystonia bears a unique mutation, requiring direct sequencing of the entire THAP1 coding region for molecular diagnosis.

Recently, through the use of whole-exome sequencing in combination with linkage analysis, four new genes have been found that are strongly implicated as causative of primary/isolated segmental/focal dystonia, mainly affecting the upper body, particularly the cervical and laryngeal region, and with very little tendency to generalize. Mutations in the TUBB4a gene were found in a large English–Australian family that has the fully penetrant adductor spasmodic dysphonia (DYT4-dystonia) with juvenile to adult onset, occasional generalization, and sometimes alcohol benefit (21, 22). Three different genes have been found in families with mainly adolescent to adult onset of cervical focal or segmental dystonia (involvement of larynx or arm, Table 1). First, a missense mutation in the CIZ1 gene was reported in a large family with adult onset CD, but in only 2 of 308 sporadic cases (23). The protein encoded by CIZ1 is a nuclear protein involved in DNA synthesis and cell-cycle control. Mutations in a second gene, ANO3, were identified as the cause of an autosomal dominant cranio-cervical-brachial dystonia (24), and five novel variants were found when the whole gene was screened in a cohort of 188 individuals with cervical dystonia. Interestingly, patients with mutations in ANO3 often had dystonic tremor, affecting the head, voice or upper limbs, and some patients with isolated upper limb tremor had been misdiagnosed as having essential tremor. Age at onset ranged from early childhood to 40 years of age (24). As with CIZ1, the dystonia never became generalized. ANO3 is most highly expressed in the striatum and is thought to encode a calcium-activated chloride channel (24) that is believed to be involved in modulating neuronal excitability. Finally, in 2013, two groups reported that mutations in the GNAL gene could cause adult onset primary dystonia (25, 26) with a strong predilection for the cervical region. Cervical dystonia was observed in 93% and spread to other sites in half of cases (25). According to the report of the first group, six of 39 families screened (15%) had mutations in this gene, but the second group found only three patients with mutations among 760 persons screened (26). GNAL encodes the stimulatory subunit of a G-protein that is involved in dopamine signaling (27) and is expressed in medium spiny neurons in the striatum. Here, it is thought to link D1 and adenosine A2 receptors, and thus may interfere with postsynaptic dopamine and/or adenosine signaling.

A comprehensive account of the pathophysiology of dystonia is far beyond the scope of this review. A general overview of the mechanisms that have been implicated is illustrated in Fig. 1. As can be seen, the pathophysiological picture appears multifaceted and impacts a broad spectrum of neurophysiological processes. Extensive structural and functional imaging studies have been performed on manifesting and non-manifesting carriers of DYT1- and DYT6-mutations, and were recently reviewed. The results suggest that primary dystonia can be viewed as a neurodevelopmental circuit disorder, involving the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways (28). Aberrant plasticity in various forms of primary dystonia has been reported from several groups. One of them recently reported an interesting comparison between primary and secondary dystonia regarding this and found normal motor cortex plasticity in secondary dystonia as opposed to primary dystonia (29), thus demonstrating that abnormally enhanced cortical plasticity is not required for clinical expression of dystonia.

Treatment

Firstly, it is important not to overlook treatable causes of dystonia, such as monoamine transmitter deficiency disorders and Wilson’s disease. In the various subtypes of monoamine transmitter deficit disorders and Wilson’s disease. In the various subtypes of monoamine transmitter
Dysport declined well below the initial titer in 31 patients or even higher doses after 1 year), NABTs inco-BoNTA (200 Mouse Units every 3 months TA, and who were switched to treatment with (NABTs) after treatment with abo- or ona-BoNTA and that dystonia patients that develop NABTs to either of the latter should be switched to inco-BoNTA rather than to rima-BoNTB. So far, all the BoNT-producing companies still recommend no less than 12 weeks interval between treatments, but this may change if any of the companies provide studies showing that more frequent injections of their drug do not increase immunogenicity. Long-term treatment with BoNT in CD is associated with a good health-related quality of life in the majority of patients (32, 33), and the proportion of patients that experiences this might be even higher if shorter intervals between treatments could be recommended. EMG or ultrasound guidance can also improve efficacy of BoNT injections in selected cases, particularly in hand dystonias.

Deep brain stimulation (DBS) in the postero-ventro-lateral part of the internal globus pallidus (GPI-DBS) has been established as an effective treatment for primary generalized dystonia, through the pioneer open Montpellier study (34), the first single-blinded French study (35), and the randomized, sham-stimulation-controlled German study, in which our center participated (36). This study showed significant improvement in quality of life already after 3–6 months of GPI-DBS (36, 37). All of these groups have during recent years also published long-term outcomes in their patients. At 3 years follow-up, mean improvement in the motor part of the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) was 58% in the French study (38) and 61% in the German study (39), thus a further significant improvement compared with results at the 6 months follow-up. In the German study, 5 years follow-up data were also available and showed a sustained efficacy, both in the generalized and segmental dystonia group (39). The Montpellier group have observed worsening of dystonia after many years of very effective bilateral GPI-stimulation in some of their primary generalized dystonia patients and have shown that implanting a second pair of electrodes (on average 4.5 years after the first pair) can improve outcome in some of these patients (40).

Several open and a few blindly evaluated patient series of GPI-DBS in primary focal or
segmental cervical dystonia have shown that this treatment can be very effective also in this dystonia subgroup. In our own patient series (41), median improvement in the severity score of the TWSTRS (Toronto Western Spasmodic Torticollis Rating Scale) showed a median improvement of 70% at median follow-up of 21 (12–48) months (n = 8), and the Toronto group (42) have recently reported blinded evaluations at mean 7.7 years showing a 54% (SD 27%) improvement (n = 10). Thus, severe and medically intractable primary CD should be evaluated for GPI-DBS.

GPI-DBS has also been used with good benefit in myoclonus–dystonia and in patients with drug (neuroleptic)-induced tardive dystonia. Functionally important benefit from GPI-DBS has also been observed in other forms of secondary dystonia, such as dyskinetic cerebral palsy (43), PKAN, Lesch–Nyhan syndrome, and in some other secondary dystonia syndromes. Beneficial effect for dystonia has also been reported for DBS in other targets, such as the subthalamic nucleus, the zona incerta (for dystonic tremor), and ventral thalamic nuclei, such as the ventral–oralis nuclei for task-specific hand dystonia. These targets have much less robust scientific basis than GPI-DBS in dystonia, however.

Unfortunately, no progress has been made in the oral medication of dystonia during the last decades. It is hoped that current and future insights into pathogenetic and pathophysiological mechanisms will lead to more progress in this area within the near future, as well-tolerated oral medications that provide a significant benefit to dystonia patients are desperately needed.

Future dystonia research should aim to define the causal links between underlying genetic defects and the different pathophysiological processes implicated in dystonia, with the ultimate aim to develop treatments that target selectively the most pivotal mechanisms in each case. In current clinical practice, however, diagnosing dystonia and selecting the right treatment still relies heavily on the clinical knowledge and skills of the doctor who encounter the patient. Although the treatment options for most patients are still symptomatic, they can be very effective in experienced hands, and thanks to this, many patients can enjoy a good quality of life living with their dystonia.

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References


