REVIEW

CME

Phenomenology and Classification of Dystonia: A Consensus Update

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ABSTRACT: This report describes the consensus outcome of an international panel consisting of investigators with years of experience in this field that reviewed the definition and classification of dystonia. Agreement was obtained based on a consensus development methodology during 3 in-person meetings and manuscript review by mail. 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. Dystonia is classified along 2 axes: clinical characteristics, including age at onset, body distribution, temporal pattern and associated features (additional movement disorders or neurological features); and etiology, which includes nervous system pathology and inheritance. The clinical characteristics fall into several specific dystonia syndromes that help to guide diagnosis and treatment. We provide here a new general definition of dystonia and propose a new classification. We encourage clinicians and researchers to use these innovative definition and classification and test them in the clinical setting on a variety of patients with dystonia. © 2013 *Movement* Disorder Society

Key Words: dystonia; classification; definition

Since its first descriptions in the late 19th century there has been continuous debate about the nosologic classification and etiology of dystonia syndromes.[1] The first account of dystonia dates back to 1911, when Oppenheim[2] reported 4 young patients. He coined the term "dystonia musculorum deformans" to indicate that "muscle tone was hypotonic at one occasion and in tonic muscle spasm at another, usually, but not exclusively, elicited upon voluntary movements." In a concurrent publication, Flatau and Sterling[3] objected to the term dystonia considering torsion spasms rather than the varying muscle tone as the clinical hallmark of the disease; they suggested the alternative name "progressive torsion spasm."

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Oppenheim's term dystonia has persisted until now, although the phenomenological description has retained some of the features reported by Flatau and Sterling.[3] Since "torsion" is considered redundant and is not always a feature of dystonia this term has been dropped from current use.

Primary focal dystonias were often categorized as cramps, task-specific or occupational spasms, or labeled psychogenic. The features of writer's cramp, in particular, were described in detail in 19th century medical monographs.[4,5] In June 1975, at the First International Dystonia Symposium, the clinical features of focal forms of dystonia, such as blepharospasm, oromandibular dystonia, torticollis, spasmodic dysphonia, and writer's cramp were reconsidered. Later, Marsden[6,7] and Sheehy and Marsden[8] proposed lumping together, under the general heading of dystonia, these focal disorders that were previously considered independent nosologic entities. In 1984, an ad hoc committee assembled by the Dystonia Medical Research Foundation provided the first consensus definition of dystonia as a syndrome consisting "of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures."[9] This definition has been so far generally retained as the classic description of dystonia. Marsden[6] noted that the term dystonia has been used to indicate either the abnormal movement, or the dystonia syndromes.

The classification of dystonia has evolved over time. Fahn and Eldridge[10] first distinguished primary dystonia (with or without a hereditary pattern) from secondary dystonia (with other hereditary neurological conditions or due to known environmental cause), and psychological forms of dystonia. Subsequently, Fahn, Marsden, and Calne proposed a classification of dystonia based on three axes: age at onset, distribution, and etiology.[9,11] Later, the etiological classification was expanded to include four subgroups of dystonia syndromes: primary, dystonia-plus, secondary, and heredodegenerative.[12] Bressman[13] further refined the etiological classification and proposed a dichotomous distinction between primary (autosomal dominant or other genetic causes), and secondary dystonia syndromes (including dystonia-plus and degenerative, complex/unknown, and acquired forms). The European Federation of Neurological Societies guidelines distinguished the etiology of dystonia syndromes as primary, heredodegenerative and secondary (or symptomatic).[14] The changing system of classifications for dystonia reflects, in part, an increased understanding of the various clinical manifestations and etiologies, but also varied opinion on the merits and criteria used for grouping certain disorders together.

During planning stages for the Fifth International Dystonia Symposium, it became increasingly clear that the currently available classifications have a number of shortcomings that have limited their clinical usefulness and prevented wide acceptance. In view of these difficulties, a Consensus Committee was established under the auspices of the Dystonia Medical Research Foundation, the Dystonia Coalition, and the European Dystonia Cooperation in Science and Technology (COST) Action.

Current Classification Schemes

The design of any classification system for dystonia depends on the goals of subdividing and grouping the many different disorders where dystonic features may occur. On the one hand there is need for a classification system that is clinically useful to aid in guiding diagnosis, diagnostic testing, and treatment. On the other hand there is a need for a classification system that organizes current knowledge regarding biological mechanisms to guide future scientific research. These 2 needs are quite distinct, making it challenging to develop a single classification system that is satisfactory for all purposes.

Historically, there has been broad agreement that previously proposed classifications based on age at onset and body region affected are clinically useful and should be retained. Relatively minor refinements to these axes are warranted to improve their utility and clarity. The main difficulties have related to previously proposed classifications by etiology, and many changes have been proposed for the etiological axis in recent years. These proposed changes are due in part to increased understanding of etiology, but also to differences in opinion regarding how the growing number of different etiological mechanisms should be lumped or split in relation to the varied clinical phenotypes.

The committee identified several difficulties in currently employed etiological classifications for dystonia. One of them involves terminology. The term "primary" dystonia, although historically most consistently used, carries some inherent implications. For other disorders, the term "primary" most often is used either for the first condition in some type of ordering system, to indicate the most prevalent subgroup, or to refer to the absence of other detectable abnormalities.[15] In dystonia, this term is most often used to describe phenotypes of relatively pure forms of dystonia, not associated with other neurological features and without evidence of pathological abnormalities.[9] It is widely appreciated, however, that tremor occurs in a large proportion of patients with primary dystonia and there has been increasing recognition of associated neurological or psychiatric features which indicate that the phenomenology is not purely motor.[16] Bridging terms such as "dystonia plus" were introduced to acknowledge specific syndromes in which dystonia predominates, is combined with other neurological features such as myoclonus or parkinsonism, and in which there is an absence of neuronal

degeneration. Thus the category of "primary" dystonia permits the coexistence of tremor, whereas "dystonia plus" is employed for the coexistence of parkinsonism or myoclonus.[12]

The term "secondary" dystonia also lacks clarity, as it is antithetical to primary and may indicate non-isolated dystonia, a defined pathology or more generally a known etiology. These varied meanings have led to confusion, with the term "secondary dystonia" sometimes referring to any dystonia that is not primary,[10] sometimes to any dystonia with a known cause,[13] and sometimes only to acquired dystonias.[12,14] The dichotomous usage of "primary" and "secondary"[13,17] has led to some confusion and the expression "non-primary" has been also introduced.[14]

Terms such as "heredodegenerative" that are used in existing etiological classification systems are problematic for many reasons. Some of the disorders typically put in this category are degenerative but not hereditary, such as sporadic Parkinson's disease. Other disorders are inherited, but there is no evidence for any degenerative process, such as Lesch-Nyhan disease. The "heredodegenerative" label also does not appear applicable for the large group of neurodevelopmental disorders with dystonia, such as dystonic cerebral palsy. Lumping these very different conditions together under 1 heading has limited value for understanding biological mechanisms and their potential relationships.

In addition to difficulties with varied use of terminology, a more serious problem is that the etiological classifications for dystonia are not really based on etiology. Concepts relating to "pure dystonia" and "dystonia plus" syndromes are useful for clinical application, but they are based fundamentally on phenomenology, not etiology. On the other hand, etiology provides the fundamental organizational principle for "heredodegenerative" and most "secondary" categories. However, most classification schemes qualify these groups by emphasizing that they typically include non-dystonic manifestations, again introducing phenomenology into a presumably "etiological" classification scheme. The rationale for combining phenomenology and biological mechanism in the same classification was to aid clinical recognition of dystonia syndromes and to guide diagnostic testing. However, current "etiological" classifications provide only limited guidance for recognizing syndromes.

Another more recently used scheme for organizing the inherited dystonias is based on the DYTn coding system established by the Human Genome Organisation Gene Nomenclature Committee. This system was developed to assign labels to gene loci defined by linkage analyses and is used to classify inherited dystonias in many recent reviews.[18] However, the DYTn scheme is a largely historically based list of assigned genetic loci, rather than a classification system based on biological etiology, and several serious shortcomings are recognized.[19] First, the methods used to map loci are based on statistical associations with linked genetic markers and are subject to error. For example, inaccurate family data led to assignment of DYT14 as a novel form of dopa-responsive dystonia; but subsequent studies revealed a mutation of the *GCH1* (DYT5) gene.[20] Also, loci may be named without knowledge of the causative genes, with subsequent clarification identifying a shared causative gene. Such was the case with DYT9 and DYT18; DYT18, which was assigned to GLUT1 deficiency due to mutations in the *SLC2A1* gene, was later documented to coincide with DYT9).[21] Several other DYT loci have been assigned on the basis of single families for which a causal gene has never been identified and the gene locus remains unconfirmed, raising the possibility of further corrections in the future. A second flaw with the DYTn nomenclature scheme is that it implies that disorders with a DYT assignment are dystonic disorders. This is not necessarily the case. Disorders such as myoclonus-dystonia syndrome (DYT11) are dominated by myoclonus, but have a DYT designation because there is no locus naming convention for myoclonic disorders. Other disorders, such as Lubag (DYT3) and rapid-onset dystonia-parkinsonism (DYT12), in some patients may be dominated by parkinsonism rather than dystonia. The listing of disorders together under the DYTn umbrella has uncertain value for exploring the biological bases for dystonia. A third flaw with the DYTn nomenclature system is that it implies a complete list of inherited disorders with dystonia. However, many disorders in which dystonia is both a consistent and dominant feature of the clinical phenotype were described and given locus assignments before the DYTn convention was developed. As a result, these disorders lack DYT designations. Examples of dystonic disorders without DYT loci include Wilson's disease, Lesch-Nyhan disease, glutaric aciduria, and deafness-dystonia syndrome. In view of its many limitations, the DYTn nomenclature system should not be viewed as an etiologically based classification system for the dystonias. In fact, it does little to advance the goal of creating a classification system to organize knowledge according to meaningful biological principles. For the inherited dystonias, an organizational scheme that focuses on patterns of inheritance is more useful.

Materials and Methods

An international Consensus Committee, consisting of investigators with years of experience in dystonia (A.A., K.B., M.D., S.F., H.A.J., C.K., A.E.L., and J.K.T.), was set up to review the literature and provide a consensus on classification of dystonia as well as on terminology of dystonic disorders.

The preparatory work of the group consisted of the collection and review of pertinent publications on the definition and classification of dystonia syndromes. Computerized MEDLINE searches including publications from 1966 to January 2012 were conducted using a combination of text words and Medical Subject Headings (MeSH) terms: "dystonia," "dystonic disorders," "dystonia musculorum deformans," "Meige syndrome," "torticollis," and "classification" limited to human studies. The reference lists of all known primary articles were searched for additional, relevant citations. No language restrictions were applied. A first draft of the manuscript was prepared based on the results of the literature review, data analysis, discussion, and comments from the Committee members. To reach the consensus, the draft and the preliminary conclusions were critically discussed by a first consensus group during 2 conferences held in May and October 2011. The final document was subject to review by 5 neurologists experienced in the field of dystonia, who had not attended the initial consensus (S.B.B., M.H., J.J., J.W.M., and V.F.). The resulting criticism was evaluated by the Committee and a final consensus including the complete panel was convened in 2012.

The meetings used the consensus development conference methodology to arrive at the current criteria for definition and classification.[22] Accordingly, the consensus process involves the following principles: all members (1) contribute to the discussion, (2) can state each issue in their own words, (3) have the opportunity and time to express their opinion about each issue, and (4) agree to take responsibility for the implementation of a decision. Members who do not share the majority opinion will agree to support the group decision initially on a trial basis, pending further discussion. Achieving consensus requires that all members (1) listen non-judgmentally to the opinions of other members and (2) check for understanding by summarizing what they think they hear while building on each other's thoughts and exploring minority opinions.

Results

The term dystonia is currently used to indicate at the same time a motor phenomenology encompassing specific physical signs[23] and a collection of neurological syndromes in which the phenomenology of dystonia may occur in isolation or combined with other neurological features.[24]

Definition of Dystonia

Accurate terminology is essential for unambiguous communication and sharing of knowledge. Terminology is most successful when it unequivocally captures essential and unique elements of a condition. The definition provided by the ad hoc committee of the Dystonia Medical Research Foundation in 1984[9] is still in use today, but several shortcomings have been recognized. First, the expression "sustained muscle contractions" refers to one specific manifestation of dystonia, and implies exclusion of less sustained manifestations. Muscle contractions may be continuous, forcing limbs and trunk into sustained postures, but they may also be discontinuous and irregular, such as seen in blepharospasm. Some dystonic contractions may be intermittent and seemingly rhythmical, as in the so-called dystonic tremor (Table 1). Second, the quality of "abnormal postures" is not specified in the current definition.[9] Postural changes may be spasmodic or tonic, dynamic or fixed, or any combination. Third, certain characteristic qualities of dystonia, such as the patterned and stereotypical nature of movements within an individual, the role played by movement initiation, and overflow activation of extraneous muscles, are not adequately represented by the 1984 definition.[9] Indeed, the most salient aspects of dystonia, that distinguish it from other hyperkinetic disorders, are the relation to movement and posture and the stereotyped or patterned character of the movements. The earlier definitions focused on the role of muscles, rather than the characteristics of the movement, perhaps because of the early association of dystonia and muscle tone or spasms. The current 1984 definition does not emphasize the abnormal movement pattern and overflow and does not exclude several disorders demonstrating abnormal postures that may be confused with dystonia.

In view of these limitations of the 1984 definition, the committee proposes the following revised definition:

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

In most cases, dystonia combines abnormal movements and postures. Some forms of dystonia, such as blepharospasm and laryngeal dystonia, are not associated with postures, but are characterized by focal involuntary contractions that interfere with physiological opening or closing of the eyelids or the larynx. This definition retains its roots in the phenomenology of the abnormal movements, because the pathogenesis of dystonia is not sufficiently well understood to contribute in a meaningful way to the new definition.

Several conditions resulting in abnormal movements, postures, or spasm, which are not associated with the specific phenomenology of dystonia have been recognized. The revised definition attempts to exclude these conditions that may mimic dystonia, which are also

TABLE 1. Motor phenomenology relevant to dystonia

Voluntary action	Purposeful, anticipated, goal-directed movement produced by will. Dystonia is typically influenced by voluntary movement or voluntarily maintained posture, as in antigravity support.
Dystonic tremor	A spontaneous oscillatory, rhythmical, although often inconstant, patterned movement produced by contractions of dystonic muscles often exacerbated by an attempt to maintain primary (normal) posture. The dystonic tremor may not be relieved by allowing the abnormal dystonic posture to fully develop without resistance ("null point"). Dystonic tremor may be difficult to distinguish from essential-type tremor.[39,45]
Overflow	Motor overflow commonly found in dystonia is unintentional muscle contraction which accompanies, but is anatomically distinct from the primary dystonic movement.[46,47] It commonly occurs at the peak of dystonic movements.
Mirror dystonia	Mirror dystonia is a unilateral posture or movement that is the same or similar in character to a dystonic feature that can be elicited, usually in the more severely affected side, when contralateral movements or actions are performed.[47]
Alleviating maneuvers (sensory tricks or gestes antagonistes)	Voluntary actions that specifically correct the abnormal posture or alleviate the dystonic movements. These are usually simple movements ("gestes") involving, or directed to, the body region affected by dystonia,[23] but not consisting in a forceful opposition to the phenomenology of dystonia.

called "pseudodystonias."[12] In general, the pseudodystonias have a known or presumed cause that is thought to differ from the causes of the broader dystonia group. The most common examples are listed in Table 2. In the future, it may be possible to revise the definition of dystonia further by incorporating aspects of pathogenesis that exclude the pseudodystonias. There was some debate about whether psychogenic dystonia should be listed under pseudo or acquired forms. The panel finally reached consensus to classify psychogenic dystonia as acquired (Table 3).

Classification

The design of any classification system depends on the goals of subdividing and grouping the many different disorders where dystonic movements may occur. The most clinically useful exercises must address the needs of organizing diagnostic testing, determining prognosis, and guiding therapy. As discussed previously, dystonia syndromes are currently classified along 3 main axes: etiology, age at onset and body distribution.[25] We propose here a revision of this classification scheme that identifies two distinct axes: clinical features and etiology. A combination of these two sets of descriptors is considered to provide meaningful information on any dystonia patient and serve as a basis for the development of research and treatment strategies (Table 3).

Axis I. Clinical Characteristics

Clinical Characteristics of Dystonia.
The clinical characteristics describe the phenomenology of dystonia in a given patient. Five descriptors are utilized to specify clinical characteristics: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations. This structure is also useful for prognostic purposes and for identifying management strategies.

Age at Onset

Classification by age is clinically important for both diagnostic testing and prognostic value. Dystonia that begins in childhood is more likely to have a discoverable cause, and more likely to progress from focal to generalized.

Despite general agreement regarding the importance of age, several shortcomings relating to current conventions have been recognized. Until now, dystonia syndromes have been dichotomously classified as having onset in childhood or adulthood. The most often suggested age for discriminating these groups is 26 years, which is not consonant with ages typically used to separate children from adults. This age threshold was based on a bimodal distribution in age at onset of a New York sample of patients with "idiopathic torsion dystonia" and utilized for DYT1 gene mapping, and subsequently found useful in formulating DYT1 testing guidelines.[26] There is little evidence that a single age cutoff can be generalized to all dystonia populations. In fact, there is evidence that it cannot. For example, dystonia that emerges during the first year of life has a very high probability of being due to an

TABLE 2. List of pseudodystonias (imitators of dystonia)

Dystonic (tonic) tics
Head tilt (vestibulopathy, trochlear nerve palsy)
Bent spine, camptocormia, scoliosis
Atlanto axial and shoulder subluxation
Arnold-Chiari malformation
Soft tissue neck mass
Congenital muscular torticollis
Congenital Klippel-Feil syndrome
Satoyoshi syndrome
Dupuytren's contractures
Trigger digits
Neuromuscular causes (Isaacs syndrome, etc.)
Spasms (hypocalcemia, hypomagnesemia, alkalosis)
Orthopedic and rheumatological causes
Sandifer syndrome
Deafferentiation (pseudoathetosis)

TABLE 3. Proposed classification of dystonia

- Axis I. Clinical characteristics
  - Clinical characteristics of dystonia
    - Age at onset
      - Infancy (birth to 2 years)
      - Childhood (3–12 years)
      - Adolescence (13–20 years)
      - Early adulthood (21–40 years)
      - Late adulthood (>40 years)
    - Body distribution
      - Focal
      - Segmental
      - Multifocal
      - Generalized (with or without leg involvement)
      - Hemidystonia
    - Temporal pattern
      - Disease course
        - Static
        - Progressive
      - Variability
        - Persistent
        - Action-specific
        - Diurnal
        - Paroxysmal
  - Associated features
    - Isolated dystonia or combined with another movement disorder
      - Isolated dystonia
      - Combined dystonia
    - Occurrence of other neurological or systemic manifestations
      - List of co-occurring neurological manifestations
- Axis II. Etiology
  - Nervous system pathology
    - Evidence of degeneration
    - Evidence of structural (often static) lesions
    - No evidence of degeneration or structural lesion
  - Inherited or acquired
    - Inherited
      - Autosomal dominant
      - Autosomal recessive
      - X-linked recessive
      - Mitochondrial
    - Acquired
      - Perinatal brain injury
      - Infection
      - Drug
      - Toxic
      - Vascular
      - Neoplastic
      - Brain injury
      - Psychogenic
    - Idiopathic
      - Sporadic
      - Familial

inherited metabolic disorder with specific diagnostic implications and grave prognostic consequences.[27] On the other hand dystonia that emerges between 2 and 6 years of age might be more consistent with dystonic cerebral palsy, especially if it follows a period of developmental motor delay. Other dystonia syndromes, such as dopa-responsive dystonia, tend to emerge between 6 and 14 years of age. Finally, sporadic focal dystonia usually emerges after 50 years of age. If a major goal of classification by age is to aid diagnostic testing and determining prognosis, more refined age categories that focus on the most likely disorders occurring in each age group are needed.

In earlier classifications, more age groups had been considered, such as childhood (0–12 years), adolescent (12–20), and adult onset (>20).[11] In order to keep consistency with terminology used for several other neurological disorders, we propose a similar scheme distinguishing the following age at onset:

- Infancy (birth to 2 years);
- Childhood (3–12 years);
- Adolescence (13–20 years);
- Early adulthood (21–40 years);
- Late adulthood (>40 years).

Body Distribution

Classification by body region affected is clinically important because of implications for diagnosis and therapy. For example, the diagnostic considerations in adult-onset focal dystonia are very different from those in young-onset generalized dystonia. The treatment of choice for focal and segmental dystonias involves botulinum neurotoxins, while for generalized dystonias more often involves medications or surgery. Describing the body distribution has a relevant clinical value, including the possibility to evaluate spread of motor symptoms over time.

Body regions involved by dystonia are the upper or lower cranial region, the cervical region, the larynx, the trunk, the upper limbs, or the lower limbs. These different territories may be involved individually or in different combinations. The body distribution may change over time, typically with progression to the involvement of previously uninvolved sites. Spread of dystonia can be monitored by repeated assessments in cases where spatial progression occurs.[28]

We propose to use the following definitions:

- Focal. Only one body region is affected. Typical examples of focal forms are blepharospasm, oromandibular dystonia, cervical dystonia, laryngeal dystonia, and writer's cramp. Cervical dystonia, is considered a form of focal dystonia, although by convention the shoulder can be included as well as the neck.
- Segmental. Two or more contiguous body regions are affected. Typical examples of segmental forms are: cranial dystonia (blepharospasm with lower facial and jaw or tongue involvement) or bibrachial dystonia.
- Multifocal. Two noncontiguous or more (contiguous or not) body regions are involved.
- Generalized. The trunk and at least 2 other sites are involved. Generalized forms with leg involvement are distinguished from those without leg involvement.

- Hemidystonia. More body regions restricted to one body side are involved. Typical examples of hemidystonia are due to acquired brain lesions in the contralateral hemisphere.

These definitions correspond, for the most part, with current usage, except for generalized dystonia where involvement of the trunk is considered the key feature for classification and leg involvement is annotated as an additional feature.

Temporal Pattern

Dystonia phenomenology can evolve with disease progression or display momentary or daily variability in relation to voluntary actions, external triggers, compensatory phenomena, alleviating maneuvers (gestes antagonistes) or psychological state. The temporal pattern is an important clinical characteristic that facilitates diagnosis and treatment choices. Important temporal characteristics are related to disease course and distinguish static from progressive forms. This terminology is particularly used by pediatric neurologists, but it also suits adult cases. In addition, diurnal variability provides descriptors on the occurrence of dystonia through the day. Variability allows separating dystonia that consistently occurs under the same conditions, be it task-specific, action-specific, or spontaneous, from variable forms of dystonia (diurnal and paroxysmal). Paroxysmal dystonia should be distinguished from dystonia always triggered by the same activity or action (ie, task-specific dystonia). In paroxysmal dystonia, the same trigger on different occasions might or might not induce an attack, whereas in action dystonia (including task-specific) the same motor activity will predictably induce dystonia. Paroxysmal dystonia typically lasts after the trigger has ended, while action (or task-specific) dystonia is no longer evident when the inducing action is completed.

The disease course can be either static or progressive.

The variability can have 4 different patterns:

- Persistent. Dystonia that persists to approximately the same extent throughout the day.
- Action-specific. Dystonia that occurs only during a particular activity or task.
- Diurnal fluctuations. Dystonia fluctuates during the day, with recognizable circadian variations in occurrence, severity and phenomenology.
- Paroxysmal. Sudden self-limited episodes of dystonia usually induced by a trigger with return to preexisting neurological state.

Associated Features.

Isolated Dystonia or Combined with Another Movement Disorder

Dystonia may occur in isolation or in combination with other movement disorders. The resulting syndromes may give rise to recognizable associations, such as isolated dystonia or dystonia with myoclonus, parkinsonism, or other movement disorders, etc. The term "primary" was introduced to "define syndromes in which dystonia is the sole phenotypic manifestation (with or without dystonic tremor)."[12,25] As noted above, this term is problematic. In order to provide unambiguous meaning, the following clinical descriptive terminology seems preferable:

- Isolated dystonia. Dystonia is the only motor feature, with the exception of tremor.
- Combined dystonia. Dystonia is combined with other movement disorders (such as myoclonus, parkinsonism, etc.).

Isolated dystonia encompasses many cases previously described as "pure" or "primary," whereas most patients previously classified under "dystonia plus" or "heredodegenerative" would now be classified as having combined dystonia. Unlike previous classifications, in the new classification the term isolated or combined refers to the phenomenology, and does not carry implications about the underlying etiology. In combined forms dystonia does not necessarily have to be the predominant movement disorder and may not be the prominent motor phenomenology (eg, foot dystonia in Parkinson disease, mild dystonic features in myoclonus dystonia).

Occurrence of Other Neurological or Systemic Manifestations

The presence or absence of other neurologic or systemic features is a vital component for characterizing dystonia syndromes. Non-motor features have been recently described in cases of dystonia with different etiologies,[16,29] cognitive decline is typically observed in degenerative or progressive dystonia syndromes. Wilson disease is a disorder where dystonia is typically combined with other neurological or psychiatric symptoms and liver disease.[30] The broad neurological spectrum evolves over time, with frequent revisions as new information is gained.

Recognition of Dystonia Syndromes

Classification along the first axis is primarily aimed to facilitate clinical recognition, diagnosis, and treatment. Once a patient is classified according to this axis, the identification of the clinical characteristics of dystonia and of the associated features defines the syndromic pattern and helps clinical orientation among the diverse presentation and associations of dystonia.

Dystonia syndromes have a remarkable degree of phenotypic variability with frequent overlap among different syndromes. There is no pathognomonic presentation that allows for reliable clinical-etiological correlations, either for genetic or for environmental

forms. Some characteristic and more common syndromic patterns that are encountered in clinical practice are briefly described here as examples. The consideration of these types of dystonia syndromes has been a common clinical approach used to assist in the etiological diagnosis of dystonia. Usage of the phenomenological classification described in the first axis will help recognize and assemble dystonia syndromes into these diagnostically useful phenomenological categories.

Early-Onset Generalized Isolated Dystonia. Dystonia beginning in childhood often progresses to generalized involvement, sometimes quite rapidly. These cases may be familial or sporadic, genetically defined or without known cause. Dystonia associated with the DYT1 gene encoding the protein TorsinA is the best characterized and the best studied etiology. DYT1 dystonia is transmitted as an autosomal-dominant trait with a penetrance of about 30%. A second identified gene, THAP1, causes DYT6 dystonia, an autosomal dominant syndrome of isolated dystonia with about 60% penetrance.[24] Similar presentations can also be found in sporadic or familial cases of yet undefined etiology.[31]

Focal or Segmental Isolated Dystonia with Onset in Adulthood. Cervical dystonia, blepharospasm, and writer's cramp are the most common forms of focal dystonia, usually with onset in the fifth decade.[32] Variable involvement of cervical muscles results in abnormal head, neck, and shoulder positions, most frequently involving horizontal turning (torticollis) and dystonic head tremor.[33] Blepharospasm is caused by dystonic contractions of the orbicularis oculi often accompanied by contractions of the procerus and corrugator muscles.[34] Onset is usually insidious, with eye irritation or dryness followed by excessive blinking, especially in bright light. Oromandibular dystonia affects the jaw muscles, with prominent jaw opening or closing.[14] There is often additional involvement of the tongue, facial, and pharyngeal muscles. Laryngeal dystonia (also known as "spasmodic dysphonia") is a task-specific form that affects the voice by causing either adduction or abduction of the muscles responsible for phonation.[35] Writer's cramp is a task-specific dystonia, with onset typically between the ages of 30 and 50 years. The syndromes of late adult-onset focal isolated dystonia are usually sporadic without identifiable cause, and rarely progress to generalized dystonia, but can extend to contiguous body regions.

Dystonia-Parkinsonism. A number of disorders, many of which are inherited, combine dystonia and parkinsonian features, sometimes accompanied by pyramidal tract involvement or other neurological deficits. Non-motor features, including cognitive decline, are not infrequent.[36,37] Dystonia-parkinsonism syndromes encompass more common conditions as well as rarer forms.[36–38] Of notable interest are: dopa-responsive dystonia (DRD), Wilson's disease, Parkin-, PINK1-, and DJ-1-associated parkinsonism (PARK2, 6, and 7), X-linked dystonia-parkinsonism/Lubag (DYT3), rapid-onset dystonia-parkinsonism (DYT12), and neurodegeneration with brain iron accumulation (NBIA, including PANK2- and PLA2G6-associated neurodegeneration, neuroferritinopathy, and others). Various dominantly, recessively and X-linked inherited genes underlying dystonia-parkinsonism have recently been and continue to be identified, which have been enumerated either as DYTn or PARKn.

Myoclonus Dystonia. Rapid jerky movements may occur in dystonia patients.[39] Particularly when affecting a limb, these can be mistaken for distinct myoclonic jerks due to various causes. The term "myoclonic dystonia" is used to refer to this myoclonic-like appearance of fast dystonic movements. Patients with "myoclonus dystonia" (DYT11) present a combination of dystonia and myoclonus; this disorder is probably the same as "essential myoclonus" since many of these patients have subtle additional dystonia or some individuals have pure myoclonus while others in the same family have both myoclonus and dystonia[40]; in many cases, myoclonic jerks can be distinguished from fast "jerky" dystonic movements based on clinical and electrophysiological features.[41]

Axis II. Etiology

The second axis addresses etiology. This is an evolving area, to be updated regularly as new information is obtained. The etiology of many forms of dystonia is still not fully understood. At the present time, two complementary characteristics may be useful for classification: identifiable anatomical changes and pattern of inheritance. Anatomical causes can be investigated using brain imaging or by pathology. Inheritance differentiates inherited from acquired conditions by means of metabolic, genetic, or other tests. These two characteristics, anatomical change and pattern of inheritance, should not be considered mutually exclusive means for etiological classification. For example, brain imaging can be helpful for both purposes, as MRI examination can reveal a perinatal lesion indicating acquired dystonia.

The term "primary" is currently used as an etiological descriptor for genetic or idiopathic cases in which dystonia is isolated and there is no consistent pathologic change.[12] This dual meaning does not help clarity and use of the term primary is currently discouraged. In the present classification, the two components of the etiological axis are considered separately.

Nervous System Pathology. Autopsy studies of what previously was called "primary dystonia" have indicated that there are no obvious degenerative changes or other structural defects. However, the numbers of brains studied, and the methods used to study them, so far are insufficient to exclude subtle cell loss or minor structural defects. Recent human neuroimaging studies have consistently revealed subtle abnormalities in several brain regions in syndromes of isolated dystonia involving the basal ganglia, cerebellum, cortex, brainstem, and thalamus. These studies reveal changes in the volume or integrity of both gray and white matter and suggest that some underlying structural defect may exist. Furthermore, autopsy studies of isolated generalized DYT1 dystonia have indicated some such changes: one autopsy study described inclusion bodies in the brainstem, while another described enlarged dopamine neurons in the midbrain.[42] These findings require confirmation. Studies in animal models of DYT1 dystonia have also shown histopathological abnormalities, such as abnormal dendritic structure of cerebellar Purkinje neurons or enlarged midbrain dopamine neurons. These recent scientific findings raise questions regarding the criteria used to define neuropathological defects, which may not require frank neuronal degeneration, but instead may involve dystrophic cells, axonal or dendritic loss, synapse loss, pathological inclusions, or merely alteration of axonal or dendritic branch structure and complexity.

Evidence of degeneration, either at the gross, microscopic, or molecular level, provides a useful means to discriminate subgroups of dystonia into degenerative and nondegenerative forms:

- Degeneration (progressive structural abnormality, such as neuronal loss);
- Static lesions (non-progressive neurodevelopmental anomalies or acquired lesions);
- No evidence of degeneration or structural lesion.

Inherited or Acquired.

1. Inherited (dystonia forms of proven genetic origin). The DYT classification is retained here as a useful list for designating subtypes, but not as a classification system.
    - Autosomal dominant. Several autosomal dominant forms are listed under this heading, such as DYT1 (OMIM #128100), DYT5 (#128230), DYT6 (#602629), DYT11 (#159900), rapid-onset dystonia-parkinsonism (DYT12, #128235), neuroferritinopathy (NBIA3, #606159), dentatorubral-pallidoluysian atrophy (#125370), and Huntington disease (#143100).
    - Autosomal recessive. The list of autosomal recessive forms of inherited dystonia is continuously growing. Notable forms encompass Wilson disease (OMIM #277900), PKAN (NBIA1, #234200), PLAN (NBIA2, #256600), and type 2 juvenile Parkinson disease (PARK2, #600116), as well as numerous metabolic disorders.
    - X-linked recessive. Inherited dystonia with X-linked transmission encompass forms such as Lubag (DYT3, OMIM #314250), Lesch-Nyhan syndrome (#300322), and Mohr-Tranebjaerg syndrome (#304700).
    - Mitochondrial. Mitochondrial forms, such as Leigh syndrome (OMIM #256000) or Leber optic atrophy and dystonia (#500001), also give rise to inherited dystonias.
2. Acquired (dystonia due to a known specific cause).
    - Perinatal brain injury: dystonic cerebral palsy, delayed-onset dystonia;
    - Infection: viral encephalitis, encephalitis lethargica, subacute sclerosing panencephalitis, human immunodeficiency virus (HIV) infection, other (tuberculosis, syphilis, etc.);
    - Drug: levodopa and dopamine agonists, neuroleptics (dopamine receptor blocking drugs), anticonvulsants, and calcium channel blockers;
    - Toxic: manganese, cobalt, carbon disulfide, cyanide, methanol, disulfiram, and 3-nitropropionic acid;
    - Vascular: ischemia, hemorrhage, and arteriovenous malformation (including aneurysm);
    - Neoplastic: brain tumor, and paraneoplastic encephalitis;
    - Brain injury: head trauma, brain surgery (including stereotactic ablations), and electrical injury;
    - Psychogenic (functional).
3. Idiopathic (unknown cause).
    - Sporadic;
    - Familial.

Many cases of focal or segmental isolated dystonia with onset in adulthood fall in this category. The most common forms of focal dystonia can have sporadic or familial occurrence. Idiopathic forms may be reclassified as inherited, as new dystonia genes are recognized.[43,44]

Conclusion and Outlook

We propose here a new classification of dystonia that takes into account inconsistencies of previous classification schemes and updates the 1984 definition of dystonia.[9] This new scheme, based on a consensus opinion, is to a large extent compatible with previous classifications and resolves several inconsistencies in previous terminology. The main innovations provided by this proposal are an updated definition of dystonia and an updated classification that distinguishes clinical characteristics

from etiology. We believe that ambiguity of previous terminology will now be reduced. We have also revised all definitions in order to facilitate a more consistent implementation of the new classification.

Notwithstanding the systematic revision of the definition and classification, some issues were resolved only in part. First, the differentiation of pseudodystonia from dystonia needs further verification. The new definition should facilitate distinguishing true dystonia from look-alikes: once it is implemented in clinical practice, several pseudo-dystonias will be recognized to be different from true dystonia. Still, it may be possible that for the remaining forms better differentiation methods are required. Another, partially related, issue was where to place psychogenic dystonia in the etiologic categorization. In the consensus classification this is listed among acquired forms, although the panel debated the alternative to consider psychogenic dystonia as a pseudodystonia. Finally, another debated point was how to better characterize the presence of microscopic changes such as cell loss and degeneration. The development of molecular neuropathology will lead to the identification of more subtle features of neurodegenerative processes that may require improving the definition of neurodegeneration.

The loss of the traditional terms (such as "primary," "plus," "heredodegenerative," etc.) will inevitably lead to some discomfort. However, keeping these older terms for the sake of comfort will lead to a situation in which clinicians are left behind speaking an archaic language, while the scientific community making the inroads into advancing our knowledge moves on and adopts a language more suited for its purposes. Such a dichotomous split would create an unfortunate barrier between clinical practice and scientific discovery. We believe that changes in terminology will facilitate communication and will foster future research in the field of dystonia.

In the future, the etiological axis will essentially be a database. The features discussed in the clinical axis and other essential pieces of information will form the basis for a manual for the clinician. We encourage clinicians and researchers to use and test this new definition and classification scheme, and we also encourage the incorporation of the new terminology into clinical rating scales. ■

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