Chapter 1

Development of the Concept of Dystonia as a Disease, a Syndrome and a Movement Phenomenology

Stanley Fahn

Origin of the Word 'Dystonia' and its Definition

The term dystonia was coined by Oppenheim (Oppenheim 1911; Klein & Fahn 2013) in his 1911 article describing four children with a condition not previously seen by him. Oppenheim called this syndrome by two different names: 'dystonia musculorum deformans' and 'dysbasia lordotica progressiva'. The first name relates to the spasms and to the postural deformities that develop in these children; the second name emphasises the dromedary gait and the progressive nature of the illness. Of importance, Oppenheim recognised this was an organic disorder and not one of psychogenic aetiology. Because of Oppenheim's fame worldwide as a leading neurologist, this disorder was recognised and neurologists began to use 'dystonia musculorum deformans'. Oppenheim coined the term dystonia to indicate that in this disorder there would be hypotonia on one occasion and tonic muscle spasms on another, usually but not exclusively elicited on volitional movements. Oppenheim also described twisted postures associated with muscle spasms that affected limbs and trunk; bizarre walking with bending and twisting of the torso; rapid, sometimes rhythmic jerking movements; and progression of symptoms, leading eventually to sustained fixed postural deformities. Whereas Oppenheim emphasised fluctuating muscle tone, none of the subsequent definitions of dystonia considered the presence of hypotonia very important. Rather, sustained and twisting movements were the dominant features that characterised a number of subsequent definitions of dystonia (Fahn 2011). In 1984, the Dystonia Medical Research Foundation established an ad hoc committee to develop an encompassing definition of 'dystonia' and a classification for the disorder. The committee consisted of (in alphabetical order): André Barbeau, Donald B. Calne, Stanley Fahn, C. David Marsden, John Menkes and G. Frederick Wooten. The committee met in February 1984 and proposed the following definition: 'Dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures' (Fahn et al. 1987). This definition had been uniformly accepted until supplanted by the 2013 consensus definition (Albanese et al. 2013). This newer definition expanded the previous one from a single sentence into three sentences: '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.'

The Years Before Oppenheim

There were descriptions of dystonia prior to Oppenheim's publication, but since the term *dystonia* was not yet coined, different terminologies were used. For example, the focal dystonia of writer's cramp was recognised and called Schreibkrampf (Germany), crampe des écrivains (France) and scrivener's palsy (UK) (Pearce 2005). Blepharospasm was recognised, as well as the combination of cranial and cervical dystonia (Wood 1887; Meige 1910). In 1871, Hammond (Hammond 1871) coined the term 'athetosis' (Greek for 'without fixed position') for mobile spasms. Athetosis is now recognised as either writhing movements of dystonia or as a combination of dystonia with chorea. In 1893, Gowers (Gowers 1893) called generalised dystonia *tetanoid chorea* in a patient subsequently found to have Wilson's disease. Desterac (de Toulouse 1901) called cervical dystonia *spasmodic torticollis and functional spasms.* Leszynsky (1903) called the abnormal gait of dystonia a hysterical gait. Ramsay Hunt (1908) referred to generalised dystonia as myoclonia of the trunk, but after Oppenheim's paper, recognised it as dystonia (Hunt 1916). Schwalbe, a psychiatry trainee under Ziehen, reported on the Lewin family, calling it *maladie des tics and tonic cramps with hysterical symptoms* three years before Oppenheim's paper (Schwalbe 1908; Truong & Fahn 1988). This family was subsequently reported in at least eight different articles in the literature (summarised by Eldridge 1970).

The Years Immediately After Oppenheim's Publication

In the same year of Oppenheim's publication, Ziehen, the psychiatrist mentor of Schwalbe (Schwalbe 1908), also described the Lewin family; he called the condition *tonic torsion neurosis* (Ziehen 1911). Two Polish neurologists, Flatau and Sterling (Flatau & Sterling 1911), described their patients later that same year and rejected the notion of varying muscle tone as the distinguishing feature of dystonia in favour of the presence of twisting muscle spasms, calling it *progressive torsion spasm*. Flatau and Sterling also mentioned heredity as a factor in the

disorder. The worldwide reputation of Oppenheim as an astute clinical neurologist helped in spreading knowledge about dystonia; immediately after his article was published, neurologists began publishing their own cases and preferred the name 'dystonia musculorum deformans' over the other offer of 'dysbasia lordotica progressiva' (Fraenkel 1912; Hunt 1916; Hallock & Frink 1917; Keschner 1918; Maas 1918; Mendel 1919; Abrahmson 1920; Frauenthal & Rosenheck 1920; Taylor 1920; Wechsler & Brock 1922). Mendel (1919) summarised all cases published up to 1919, and recognised the twisting nature of the movements and postures, suggested the term 'torsion dystonia', seeing it as a disease entity and distinguishing it from other abnormal movements (chorea, myoclonus, athetosis, hysteria).

Recognition of Secondary Dystonia, Leading to the Concept of Dystonia as a Syndrome Rather Than a Disease

In the year after Oppenheim's paper came the publication by Wilson of progressive lenticular degeneration (Wilson 1912), now known as Wilson's disease. Dystonia usually develops in this disorder. By the end of that decade came the pandemics of encephalitis lethargica, resulting often in postencephalitic parkinsonism and dystonia. In addition to these two dystonic disorders, many children with cerebral palsy manifested athetosis and dystonia. The realisation of symptomatic causes of dystonic movements and postures led to the belief by many that dystonia is a syndrome and not a specific disease entity. This concept was discussed by Wimmer at the Tenth International Neurological Reunion in Paris in 1929 (Wimmer 1929) and was widely accepted.

Resurrection of Dystonia as a Disease Entity and Not Just a Syndrome

Beginning in the 1920s and extending through the 1930s and early 1940s, dystonia was regarded as a manifestation of a number of disorders, that is, merely a clinical feature in disorders affecting the basal ganglia. Meynert (1871) first suggested that the basal ganglia were involved in disorders of abnormal movement. The concept of an *extrapyramidal system* and of *extrapyramidal diseases* was developed by Kinnier Wilson (1912, 1925). Wilson was referring to anatomical pathways related to the basal ganglia (extrapyramidal system) and the disorders that emanate from them when they are afflicted (extrapyramidal diseases). He emphasised that these disorders have three cardinal types of clinical phenomenology: variability of muscle tone (dystonia), involuntary movements and the seeming absence of true paralysis (Wilson 1925). Fahn (2011) subsequently explained the problems with using the term 'extrapyramidal'. (1) The basal ganglia have intimate connections with the pyramidal tract system and therefore the basal ganglia are not truly extrapyramidal. (2) There are other descending pathways through the spinal cord, such as vestibulospinal and reticulospinal pathways and technically these should also be called 'extrapyramidal', yet these are not related to the basal ganglia. (3) There are disorders of abnormal movement not associated with any basal ganglia pathology, such as myoclonus and ataxia, and therefore these would not fall under a term that originally referred to basal ganglia disorders. That is why Fahn coined the term *movement disorders* in 1968 to accommodate all conditions with abnormal movements (see Fahn 2011 for historical details).

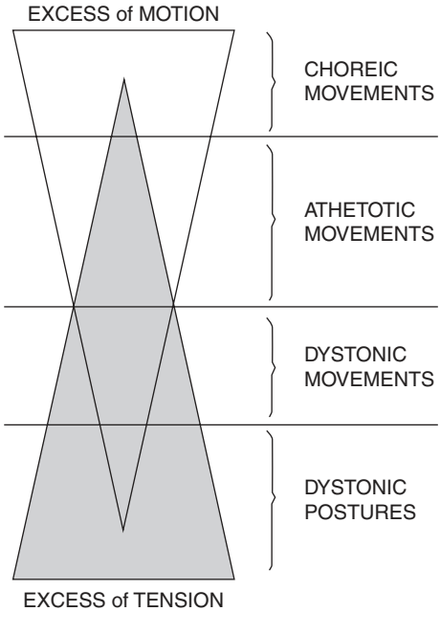

Figure 1.1 Figure from Herz (1944a) comparing excess tension and excess movement in different abnormal involuntary movements.

With this background of dystonia being regarded solely as a syndrome as its place in neurology at that time, Ernst Herz published a massive review of dystonia in a trilogy of back-go-back papers (Herz 1944a, 1944b, 1944c) describing his observations of dystonia, analysis of motion pictures of abnormal movement disorders and review of the literature. Among other contributions in these papers, Herz showed EMG samples of dystonic movements repeatedly showing simultaneous firing of agonist and antagonist muscles, whereas he demonstrated that in chorea there is only contractions of agonist muscles. Herz also compared dystonic movements and postures with athetosis and chorea by explaining their relationships to excess tension and excess movement (Figure 1.1). Herz concluded that in addition to dystonia being a manifestation of some disorders, and thus a syndrome, it can also be a specific disease entity. He said the diagnosis of 'dystonia' as a disease entity should be made only in cases with the following characteristics: (a) selective systemic symptoms in the form of dystonic movements and postures; and (b) gradual development, without recognisable aetiologic factors at the onset.

Herz emphasised that dystonic movements are slow, long-sustained turning movements; but he also mentioned the presence of rapid spasms sometimes seen in this disorder, calling them myoclonia and tic twitchings. For the more regular, rhythmic movements sometimes seen, he used the term *myorhythmia*. Today, myorhythmia has been used differently by different

authors. Monrad-Krohn and Refsum (1958) and Masucci et al. (1984) used the term *myorhythmia* to label what is today called rhythmic myoclonias such as palatal myoclonus. But this use seems to have been abandoned today. Perhaps the most recent use of the term myorhythmia is for the slow-moving, repetitive, synchronous, rhythmic contractions in ocular, facial, masticatory and other muscles in Whipple disease, which have been called *oculofaciomasticatory myorhythmia* (Schwartz et al. 1986; Hausser-Hauw 1988; Tison et al. 1992).

The Definition of Dystonia Continued to Change Even After Herz's Contribution

Following Herz's massive review of dystonia in 1944 (Herz 1944a, 1944b, 1944c), neurologists accepted that dystonia can be a disease entity as well as a feature in several syndromes. But over time, different definitions for dystonia as an abnormal movement emerged. Denny-Brown, a respected neurologist and neurophysiologist, suggested dystonia should be applied to any posture with a fixed or relatively fixed attitude (Denny-Brown 1965). The problem with this definition is that it is too broad and could be applied to the fixed postures seen after hemiplegic strokes, for example. That is probably why Denny-Brown's definition never caught on. At the time the first international symposium on dystonia was convened in New York in 1975, Fahn and Eldridge proposed dystonic movements to be sustained, involuntary, twisting movements which could be fast or slow (Fahn & Eldridge 1976). These authors were troubled by the confusion caused by the term dystonia being used for both the movement phenomenology and the syndromes or disorders producing dystonic movements. Fahn and Eldridge therefore suggested that the term 'torsion dystonia' be used as the name for the disease entity, and 'dystonia' for the abnormal movements. But this separation never caught on and dystonia continued to be used for the movements and for the disease and syndrome.

At that first international symposium in 1975 another major advance was immediately accepted. This was C. David Marsden's analysis that dystonia does not need to be applied to just those people with generalised dystonia, but can be equally applied to focal and segmental dystonias (Marsden 1976). Marsden discussed in particular blepharospasm, oromandibular dystonia, writer's cramp, torticollis and axial dystonia. Prior to this paper, it was common to consider the focal and segmental dystonias as formes fruste, as was done in the epidemiology studies of Zeman and Dycken (Zeman & Dyken 1967). This symposium also contributed the publication by Lillian Lee and colleagues (1976) of X-linked recessive dystonia-parkinsonism found on the Island of Panay in the Philippines and the first English presentations of dopa-responsive dystonia by Masaya Segawa and colleagues (1976). At the symposium, Allen and Knopp (1976) presented a Caucasian family with this form of autosomal dominant dystonia.

The year after this international symposium, the first research-oriented foundation involved specifically with dystonia was established by the husband-and-wife team of Sam and Frances Belzberg from Vancouver, British Columbia in Canada, calling it the Dystonia Medical Research Foundation (DMRF). With an influx of funds from the Belzbergs, research grants were awarded to investigators with excellent grant applications. Two of the early concerns of the foundation were to have a uniformly accepted definition and classification of dystonia. As described above in the opening paragraph, an ad hoc committee was formed and it came up with the definition of 'Dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures' (Fahn et al. 1987). This definition lasted until it was expanded in 2013 to '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', also presented in the opening paragraph above.

Classification Schemes for Dystonia

As the definition of dystonia has changed over time, the classification of dystonias has evolved as well. At the first international symposium on dystonia in 1975, Fahn and Eldridge (Fahn & Eldridge 1976) presented a classification based on aetiology, dividing the dystonias into idiopathic (familial and sporadic), secondary (heredodegenerative and environmental) and psychological (considered rare at that time). At the same symposium, Marsden et al. (1976) proposed a classification based on bodily distribution (focal, segmental and generalised). The ad hoc committee on definition and classification of dystonia formed by the DMRF met in 1984 (see above paragraph) and recommended a classification that included age at onset (because prognosis of dystonia was highly dependent on this factor), bodily distribution (expanded on the formulation of Marsden and colleagues (1976)) and aetiology. The triple parallel classification scheme was published by Fahn et al. a few years later (Fahn et al. 1987).

This parallel classification approach has been maintained but tweaked in subsequent attempts to improve the classification of dystonia. Fahn et al. (1998) added a new aetiologic category, dystonia-plus, to distinguish these non-degenerative dystonias that have an additional movement disorder component (e.g. parkinsonism and myoclonus) from primary dystonias (which are pure dystonia with the exception that tremor can be present). The dystonia-plus disorders include myoclonus-dystonia and dopa-responsive dystonia, among others. In 2011, a fifth aetiologic category was included to incorporate the dystonias seen as a component of other well-recognised movement disorders, such as Parkinson's disease, progressive supranuclear palsy, corticobasalganglionic degeneration, tics and the paroxysmal dyskinesias (Fahn et al. 2011).

The classification of dystonia received a major overhaul by the consensus committee in 2013 (Albanese et al. 2013), which classified dystonia into two major axes: Clinical Features and Aetiology. But the classification scheme is more complicated than just two major axes because there are five individual parallel classifications within Clinical Features and two parallel

classifications within Aetiology, namely (1) neuropathology and (2) listing whether the disorder is inherited, acquired or idiopathic. Thus, there are actually seven parallel sections in this new classification scheme. Although more detailed than all previous classifications, the latest one avoids ambiguity and overlap when all seven categories are utilised (Albanese et al. 2013).

Other Developments in Dystonia

Over the 100 years since Oppenheim coined the term dystonia, there have been countless research studies that have shed light on epidemiology, pathology and genetics of dystonia. Each of these topics is too huge to cover in this chapter. Advances in therapy, particularly the application of botulinum toxin and the development of deep brain stimulation with specific targets to reduce dystonia, have been momentous and have provided much benefit for people with dystonia. Much remains to be done, however, and judging by past developments, the future holds great promise for exciting new advances in understanding and treating dystonia.

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Section I

Basics

Section I Basics

Chapter 2

Classification of Dystonia

Alberto Albanese and Stefania Lalli

There has long been a need to update the classification of dystonia. This movement disorder has historically been considered at the same time a symptom and collection of syndromes. Knowledge about dystonias has greatly developed since the seminal description of *Dystonia musculorum deformans* by Oppenheim (Oppenheim 1911). In recent years, the phenomenology of dystonia has been defined and several new genetic forms have been described. The traditional concept of 'primary dystonia' encompassing both phenomenological and aetiological definitions was no longer tenable. In 2013 a new classification of dystonia was released after a two-year work based on consensus of dystonia experts (Albanese et al. 2013). We describe here the mainstay of the new classification and provide some critical comments for its implementation.

Historical View

The classification of dystonia syndromes has evolved over time, partly reflecting increased understanding of the various aetiologies and clinical presentations, and also varied opinions on the criteria used for grouping disorders together.

Since its first descriptions in the late nineteenth century there has been continuous debate about the nosologic classification and aetiology of dystonia syndromes. Although the first account of dystonia probably dates back to Gowers, it was Oppenheim who drew international attention to this new entity, by reporting four young patients (Oppenheim 1911). 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 June 1975, at the First International Dystonia Symposium, David Marsden proposed lumping together under the general heading of dystonia the focal forms of dystonia, already known as blepharospasm, Meige syndrome, torticollis and writer's cramp (Marsden 1976). In 1984, an ad hoc committee convened by the Dystonia Medical Research Foundation provided the first consensus definition of dystonia as follows: 'a syndrome consisting of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures' (Fahn et al. 1987). This definition has been generally retained as the first general description for dystonia.

The classification of dystonia has evolved over time. Fahn and Eldridge (1976) 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 aetiology (Fahn et al. 1987). The aetiological classification was later refined with the proposal of a dichotomous distinction between primary and secondary forms (Bressman 2004). The European Federation of Neurological Societies guidelines further distinguished the aetiology of dystonia syndromes as primary, heredodegenerative and secondary (or symptomatic) (Albanese et al. 2011).

While these clinical classifications were developed, a parallel classification system was developed based on discovery of new dystonia loci or genes, that were named DYTn (currently from DYT1 to DYT27) and listed in genetic databases (Klein 2014). The DYTn listing cannot be considered a classification system for dystonia, as it does not contain a comprehensive assemblage of all dystonia forms and is not helpful for clinical assessment.

Unsettled Issues With Earlier Classifications of Dystonia

The term 'primary' dystonia, although historically consistently used, carried some inherent implications. In dystonia, this term was most often used to describe phenotypes of relatively pure forms of dystonia, not associated with other neurological features and without evidence of pathological abnormalities. However, tremor occurs in a large proportion of patients with primary dystonia and there has been increasing recognition of associated neurological or psychiatric features indicating that the phenomenology is not purely motor. Bridging terms such as 'dystonia-plus' were introduced to acknowledge specific syndromes where dystonia predominated, combined with other neurological features, such as myoclonus or parkinsonism, in the absence of neuronal degeneration. Thus the category of 'primary' dystonia indicated at the same time isolated dystonia and no appreciable degeneration, whereas 'dystonia-plus' was employed for the coexistence of non-dystonic features (e.g. parkinsonism) and a degenerative nature of the condition.

The term 'secondary' dystonia also lacked clarity, as it was antithetical to primary and indicated non-isolated dystonia, a defined pathology or more generally a known aetiology. These

varied meanings led to inconsistencies, with the term 'secondary dystonia' sometimes referring to any dystonia that is not primary, sometimes to any dystonia with a known cause, and sometimes only to acquired dystonias. Terms such as 'heredodegenerative' used in existing aetiological classification systems were problematic for many reasons. Some of the disorders typically positioned in this category were degenerative but not hereditary, such as sporadic Parkinson's disease. Other disorders were inherited, but there was no evidence for any degenerative process, such as Lesch–Nyhan disease. The 'heredodegenerative' label also did not appear applicable for the large group of neurodevelopmental disorders with dystonia, such as dystonic cerebral palsy.

The DYTn scheme was based historically on a sequentially numbered list of assigned genetic loci, rather than a classification system with an aetiological meaning. A further flaw with the DYTn nomenclature scheme was that it implied that disorders with a DYTn assignment were dystonic in nature. This is not necessarily the case. Disorders such as myoclonus-dystonia (DYT11) may be dominated by myoclonus, and have a DYTn designation because there is no locus naming convention for genetic myoclonus. Other disorders, such as Lubag (DYT3) and rapid-onset dystonia-parkinsonism (DYT12), in some patients may be dominated by parkinsonism rather than dystonia. The heterogeneous listing under the DYTn umbrella has uncertain value for exploring the biological bases for dystonia. Moreover, many disorders where 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 DYTn designations. Examples of dystonic disorders laying outside the DYTn listing include Wilson's disease, Lesch–Nyhan disease, glutaric aciduria and deafness-dystonia syndrome.

New Definition and Current Classification

In May 2011 an international Consensus Committee was set up to provide a consensus on classification of dystonia as well as on terminology of dystonic disorders. Dystonia is now 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, twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

This definition improves and expands the previous definition by summarising the relevant features of dystonia, particularly the combination of dystonic postures and dystonic movements, the tremulous nature of dystonic movements and the specific relationship of dystonia with voluntary movement. 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 characterised by focal involuntary contractions that interfere with physiological opening or closing of the eyelids or the larynx.

The revised definition attempts to exclude such conditions that may mimic dystonia, which are also called 'pseudodystonias' (Fahn et al. 1998). In general, the pseudodystonias have a known or presumed cause that is thought to differ from the causes of the broader dystonia group. Some typical examples are: dystonic (tonic) tics, head tilt (vestibulopathy, trochlear nerve palsy), bent spine, camptocormia, scoliosis, atlanto-axial and shoulder subluxation, Arnold-Chiari malformation, congenital muscular torticollis, congenital Klippel-Feil syndrome and Sandifer syndrome (Albanese et al. 2013).

The new classification of dystonia has greatly innovated clinical usage. Two axes have been identified. Axis I depicts clinical features and provides a synthetic snapshot of the patient's clinical condition at a given moment. Axis II identifies aetiology based on anatomical alterations, or identified abnormalities.

Axis I: Clinical Features

This axis describes the patient's phenomenology at a given moment (Figure 2.1). Five descriptors are utilised in this axis: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations (Table 2.1).

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 to progress from focal to generalised. The new classification defines five age periods, from paediatric to adult: infancy (birth to two years); childhood (3–12 years); adolescence (13–20 years); early adulthood (21–40 years); late adulthood (40 years and older). Age at onset may give important clues to the underlying aetiology. Dystonia that emerges during the first year of life has a very high probability of being due to an inherited metabolic disorder with specific diagnostic implications and grave prognostic consequences. On the other hand, dystonia that emerges at 2–6 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 at 6–14 years of age. Finally, sporadic focal dystonia usually emerges after 50 years of age. In such context, several age categories focused on the most likely disorders occurring in each age group were proposed.

Body Distribution

Classification by body region 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 generalised dystonia. Body regions involved by dystonia are the upper or lower cranial region, the cervical region, the larynx, the trunk, the upper or lower limbs. These different territories may be involved individually or in different combinations. The treatment of choice for focal and segmental dystonias involves botulinum neurotoxins, while for generalised dystonias more often involves

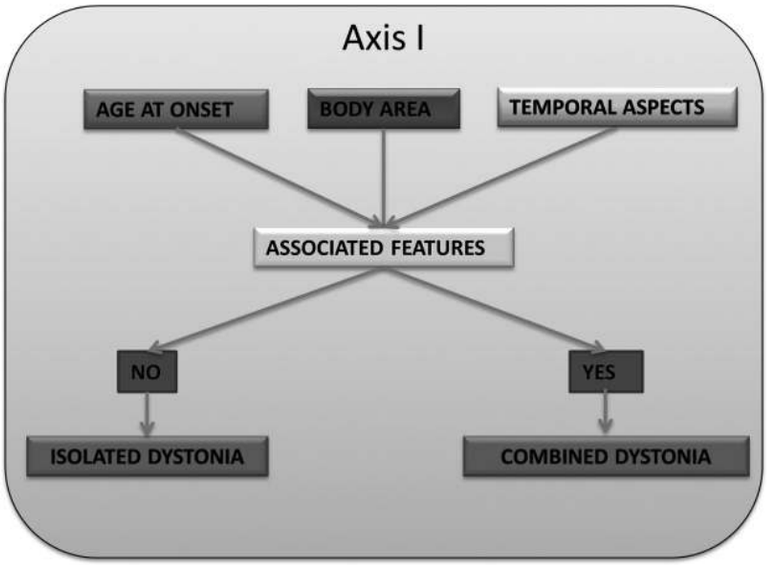

Figure 2.1 Axis I guides on the recognition of the phenomenology of dystonia and of the prevalent phenotypical pattern driving the search of a specific aetiology.

medications or surgery. Describing the body distribution has a relevant clinical value, including the possibility to evaluate spread of motor symptoms over time. The body distribution may change over time, typically with progression to the involvement of previously uninvolved sites.

Distribution is focal when 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.

In segmental distribution 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 bi-brachial dystonia.

Distribution is multifocal when two non-contiguous or more (contiguous or not) body regions are involved.

In generalised distribution the trunk and at least two other sites are involved. Generalised forms with leg involvement are distinguished from those without leg involvement.

In patients with 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.

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 manoeuvres (gestes antagonistes) or psychological state. 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 (i.e. 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. Disease course can be either static or progressive.

The variability can have four 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 recognisable circadian variations in occurrence, severity and phenomenology. Paroxysmal: sudden self-limited episodes of dystonia usually induced by a trigger with return to pre-existing neurological state.

Associated Features

Current terminology classifies conditions where dystonia is the sole motor feature (apart from tremor) as 'isolated dystonia', while 'combined dystonia' refers to dystonias with other accompanying movement disorders.

Isolated or Combined Dystonia

Dystonia may occur in isolation or in combination with other movement disorders. The resulting syndromes may give rise to recognisable associations, such as isolated dystonia or dystonia with myoclonus, parkinsonism or other movement disorders, 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 aetiology.

Table 2.1 Classification of dystonia

Axis I	
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 Generalised (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	
Aetiology	
• 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

Occurrence of Other Neurological or Systemic Manifestations

The presence or absence of other neurologic or systemic features is a vital component for characterising dystonia syndromes. A full history and examination are required to determine whether there are non-motor components of the syndrome. Of particular importance are ophthalmological symptoms or signs, which may suggest specific disorders. The presence of visual symptoms and dystonia mandate a formal ophthalmological examination to look for evidence of optic nerve or retinal abnormalities that are characteristic of some inherited metabolic diseases. Corneal abnormalities, in particular Kayser–Fleischer rings characteristic of Wilson's disease, can also be present. The presence of a supranuclear gaze palsy, whether vertical, horizontal or both, can be a useful clue.

Central nervous system involvement in addition to motor features such as cognitive impairment, psychiatric symptoms or epilepsy might drive towards specific diagnosis.

Axis II: Aetiology

The second axis addresses aetiology. This is an evolving area, to be updated regularly as new information is obtained. The aetiology of many forms of dystonia is still not fully understood. 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.

Nervous System Pathology

Evidence of degeneration, either at the gross, microscopic or molecular level, provides a useful means to discriminate subgroups of dystonia into degenerative and non-degenerative forms. Degeneration is defined as a progressive structural abnormality, such as neuronal loss. Static lesions are non-progressive neurodevelopmental anomalies or acquired lesions. Alternatively, there may be no evidence of degeneration or structural lesion.

Inherited or Acquired Dystonia

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. With the advances in genetic technologies such as exome and whole-genome sequencing, new genes underlying dystonia will be discovered and idiopathic dystonia types will be reclassified in inherited forms once new genes are recognised. A general overview of some phenotypes and genotypes underlying 'isolated' and 'combined' inherited dystonia syndromes is summarised in Figure 2.2.

Acquired Dystonia due to a known specific cause, such as perinatal brain injury, infection, drugs, toxic substances, vascular causes, neoplasms, brain injury, psychogenic or functional origin.

Idiopathic Unknown cause (sporadic or familial). Many cases of focal or segmental isolated dystonia with onset in adulthood fall into this category.