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Primary Dystonia: Moribund or Viable?

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Introduction

Classification schemes are essential to clinicians and researchers alike; they drive diagnostic and testing algorithms and treatment approaches, and have led to major advances in understanding genetic etiologies. However, as our knowledge advances an iterative process occurs. Syndromes can now be divided into genetic etiologies; as these are interrogated, phenotypes that are different from their original clinically defined class emerge. Long laundry lists of genes and loci are produced and the lines that delineated categories may degrade. To some extent this scenario now besets the established classification scheme of dystonia. As we learn about specific etiologies, widening phenotypes, biological markers, and pathophysiology, the notion of a single or unified entity "primary dystonia" becomes less clear. This review will discuss some of the questions raised by advances in the field and their impact, if any, on the definition of primary dystonia

Changing nomenclature and the identification of dystonia causes

Primary dystonia evolved from prior classification schemes. (see Table 1), replacing the categories of idiopathic dystonia and dystonia musculorm deformans. This shift was popularly adopted during the 1980s, and 90's (Marsden 1988; Fahn S, Bressman SB, Marsden CD, 1998) a period of significant change in our knowledge about dystonia subtypes and etiologies. During these decades the first primary dystonia gene, *DYT1/TOR1A* was mapped and identified (Ozelius 1989; 1997). Concurrently, clinical genetic studies characterized the "dystonia – plus" subtypes of dopa responsive dystonia (DRD), myoclonus-dystonia (M-D), and rapid-onset dystonia-parkinsonism (RDP) (Nygaard 1988; 1993;, Ichinose 1994; Kyllerman 1990; Nygaard 1999; Dobyns 1993; Kramer 1999); this group of conditions could now be distinguished and spun off from primary dystonia. Further, family studies suggested autosomal dominant inheritance with reduced penetrance for the late-onset focal idiopathic dystonias (Waddy 1991; Defazio 1993), confirming a

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genetic susceptibility even for those with late-onset disease. Thus the adjective “idiopathic” applied in prior decades no longer seemed appropriate with the establishment of genetic etiologies.

Since the first mapping of a primary dystonia gene in 1989, five primary dystonia genes have been identified: *TOR1A* (DYT1*)*, *THAP1*(DYT6*)*, *CIZ1*, *GNAL*, and *ANO3*(DYT23) (Ozelius 1997, Fuchs 2009, Xiao 2012, Fuchs 2013, Charlesworth 2012), and loci for additional primary genes have been reported (Leube 1996; Valente 2001; Chouery 2008; Norgren 2011). The expanding list of genetic causes and loci has focused attention once again on the utility or relevance of the current classification scheme of dystonia, one that distinguishes primary from non -primary or secondary etiologies, many of which are also genetic. The confusion in sorting out etiologies of dystonia is further confounded by the nomenclature of dystonia - associated genetic loci; the list of HUGO (Human Genome Organisation) Gene Naming Committee assignations includes erroneously assigned loci, duplicated loci, and unconfirmed loci in a consecutively numbered system (Marras 2012). It also includes loci for diverse dystonia phenotypes including some, but not all, primary dystonia (DYT1, DYT6, DYT23), degenerative and non-degenerative dystonia with parkinsonism (DYT3, 5,12,16), myoclonus with dystonia (DYT11), paroxysmal dystonia. (DYT 8,9/18,10,19,20) and dystonia with (probably) associated musculoskeletal abnormalities (DYT4) (Lohmann 2013). A vetted and edited catalogue of genetic etiologies is clearly needed. But even if such a list is created, how should it organized; temporally, by the dates of gene identification, or should genetic etiologies be grouped by phenotype (Marras 2012). In trying to resolve this question one needs to determine how or if the categories of primary vs non-primary play a role. Does primary dystonia denote etiology, does it belong under the heading of “Causes of Dystonia?”.

A Historical Perspective: Can dystonia be primary if it has causes?

Primary dystonia is an amalgam construct that evolved from etiologic – pathologic and clinical criteria, much in the tradition of “essential” tremor or “idiopathic” Parkinson disease. Exclusion criteria, including those based on pathological, historical and examination findings, have always been critical in setting primary dystonia apart from other dystonia. Oppenheim was the first to use the term dystonia (coining the disorder dystonia musculorum deformans (DMD)) in 1911 to characterize the intermittent changes in muscle tone, rhythmic jerking, and twisting contractures and postures (Oppenheim 1911). Aside from the phenomenological description, he also included important negative features: these included the lack of weakness, atrophy, sensory loss, perceptive changes, sphincter disturbance, or significant psychological abnormalities (Oppenheim 1911). These clinical exclusions were integral to his concept of dystonia as a discrete morbid entity; although in this seminal period, defined diagnostic criteria were not adopted. In the years immediately following Oppenheim’s description, reports of dystonia due to encephalitis lethargica, Wilson’s disease and birth injury emerged. Dystonia became viewed only as a hyperkinesia, symptomatic of many causes. By the late 1920’s it was concluded that dystonia “was in no way pathognomonic” (Wimmer 1929); dystonia no longer implied a specific category of disease.

Beginning with the series of papers by Herz in the 1940s (Herz 1944a; 1944b), followed by the clinical, pathologic and genetic studies of Zeman in the 1960’s (Zeman 1959; 1960; 1967) and naturalistic and family studies of Marsden and colleagues in the 1970’s (Marsden 1974; Bundey 1975) the notion of a distinct category of idiopathic dystonia that included both childhood onset generalized and adult focal forms was reborn and reinforced; ultimately it took hold as doctrine among clinicians and researchers.

Diagnostic criteria delimited an etiologic - clinical group that displayed dystonia without other neurologic abnormalities (i.e., excluding pyramidal, cerebellar, sensory or cognitive deficit); and without an apparent etiology, including historical (eg, infection, trauma or drug exposure) or structural (eg, CT or routine MRI) evidence suggesting a specific known cause (Marsden 1988). Primary dystonia was also distinguished in its temporal characteristics (it is not paroxysmal) and unlike dystonia due to dopamine deficient states, it did not respond dramatically to levodopa (Fahn 1987). Despite these defined criteria, it was clear from the start that "idiopathic" was not the best of adjectives; a specific etiology may not have been known, but Herz, Zeman, and Marsden and others either alluded to or patently argued for a genetic etiology.

Herz presciently alluded to the founder effect of DYT1, 53 years before the actual identification of the gene. Writing in 1944 (Herz 1944) he purposefully avoided discussion of the predilection of early onset dystonia to affect Ashkenazi Jews, not wanting to fuel anti-Semitism and eugenic theories. He stated "I have not elaborated on the possible prevalence of dystonia in any one group…recent experience with Rassenbiologie have been so depressing and grotesque that they do not encourage speculations". Zeman and colleagues approached the familial nature of primary dystonia in both Jews and non-Jews head on. In a series of remarkable papers they argued strongly that "idiopathic" dystonia was genetic and questioned the use of "idiopathic"(Zeman 1959). Meticulously reviewing the pedigrees of their own patients and previously reported cases, they concluded that primary dystonia was inherited in an autosomal dominant fashion with incomplete inheritance (Zeman 1959; 1960; 1967); although they conceded that many dystonia cases appeared to be sporadic and that a recessive form could not be excluded. They also argued cogently that determining the familial nature of dystonia required careful in person examination rather than family history only. This was especially important for dystonia because of its varied, and often subtle, clinical expression, including isolated writer's cramp and torticollis and other potential "formes frustes". They demonstrated how even within families there was phenotypic diversity both in age onset and body distribution. Similarly a decade later Marsden and colleagues argued for Mendelian inheritance including multiple genetic – clinical subtypes and included both childhood and adult onset phenotypes (Bundey 1975) under the category of idiopathic/primary.

Thus one could argue then that the seeds for rejecting "idiopathic" are rooted in the very notion of segregating this category of dystonia, and only bolster the move from idiopathic to primary. But is the entire concept of a coherent class of "primary" dystonia flawed? Even if we accept that the cause of all primary dystonia is no longer unknown, that at least a subset is genetic and that a genetic component likely plays a role in the rest, does current evidence support sustaining the category of primary dystonia built by Oppenheim, Zeman, Marsden and others? Do the other proposed features that characterize this category still hold? Are the exclusion criteria still valid?

Can dystonia be primary if it is not "pure"?

Primary Dystonia and Tremor

A critical and continually held aspect in defining primary dystonia is the absence of neurological signs other than dystonia. Thus, it is not surprising that most families and clinical populations so defined have not demonstrated significant findings other than dystonia; further, when subtle atypical features, especially parkinsonism or myoclonus, were identified, further subclassification was created, allowing for distinct syndromes such as DRD, M-D and RDP to be clinically and genetically characterized. There is, however, an exception. Tremor is the one non-dystonic neurological feature that has crept into to "accepted" criteria for diagnosing primary dystonia, even if it does not involve a body

region affected with dystonia. The frequent occurrence of tremor in dystonia patients and family members, with or without primary dystonia, has long been recognized (Oppenheim 1911, Zeman 1959, 1960; Munchau 2001). A recent review succinctly considers the relationship between tremor and primary dystonia, especially the high rate of hand tremor in cervical dystonia, and details the complexity of the issue and need for further clarity regarding the etiologic relationship between the two types of hyperkinesias (Schiebler 2011). As alluded to above, rhythmic jerking was noted by Oppenheim, and the idea of "formes frustes" in genetic subtypes of primary dystonia is over 50 years old and included fine hand tremor (Zeman 1959). More recent studies have distinguished subgroups of patients with essential tremor and dystonia (Hedera 2010) supporting the notion of genetic susceptibilities in patients who have both dystonia and tremor.

Non- Motor Abnormalities in Identified Genetic Subtypes of Primary Dystonia

Aside from tremor, diagnosing primary dystonia has required that dystonia be the only neurological sign, that it is isolated. Yet, especially over the last 10 years there has been a renewed effort to characterize and potentially widen the clinical spectrum of primary dystonia. Using modern approaches and methodologies in genetically and clinically defined subgroups, investigators have questioned whether indeed other clinical features, particularly the rates of psychiatric abnormalities, are increased in primary dystonia.

TOR1A, the first primary dystonia gene identified, has a penetrance *of dystonia* of only 30% (Risch 1990). Once the gene was identified, gene carriers with and importantly without dystonia could be distinguished from other family members. This allowed critical questions to be directly addressed, including whether gene expression was limited to only dystonia; other phenotypes and endophenotypes could be sought. Most work has focused on using imaging to characterize distinct functional and structural imaging changes (see below); a small number of studies have depicted associated mood, learning and subtle sensory deficits.

Psychiatric interviews identified a four- fold increased risk for early-onset recurrent major depressive disorder, but not other psychiatric disorders in gene carriers (Heimann 2004, 2007); this risk was present to a similar degree in gene carriers with and without dystonia. Similarly, DYT1 gene carriers with and without dystonia demonstrated a similar degree of motor and visual sequence learning deficits, although these were not observed in DYT6 gene carriers (Carbon 2011). On the other hand neuropsychological evaluation did not find correlated abnormalities except for mild abnormalities in aspects of executive function and visuomotor construction, but only in DYT1 carriers with dystonia (Carbon 2011). Sensory abnormalities using experimental techniques have also been detected; DYT1 carriers with and without dystonia have a reduced ability to perceive visual, tactile or visuo-tactile stimuli as temporally separated (Fiorio 2007); they also are deficient in mental simulation or rotation of body movements (Fiorio 2008).

Non- Motor Abnormalities in Adult and Focal Subtypes of Primary Dystonia

Non-dystonia clinical and subclinical signs also have been investigated, and identified, in subtypes of adult-onset primary dystonia. Psychiatric symptoms have long been noted among adult focal dystonia patients (Jahanshahi 1991; Lauterbach 1992), although many older studies had methodological weaknesses (Kuyper 2011; Stamelou 2012). In a more recent study of 86 focal dystonia patients (most with cervical dystonia), psychiatric disorders were systematically assessed and a 4.5 higher lifetime rate of any psychiatric disorder was found compared to population controls (Lencer 2009). Highest rates were identified for social phobia, agoraphobia, panic disorder, OCD, alcohol abuse and drug dependence. Mood disorders were moderately increased, and most (except social phobia) preceded dystonia. Another recent study of focal dystonia patients, and both healthy and disease controls

(hemifacial spasm) also identified a higher rate of psychiatric disorders in dystonia patients, with psychiatric diagnoses preceding dystonia in almost 70% (Fabbrinni 2010). In this study, depressive disorders, and not OCD or anxiety, were the specific abnormalities identified; further these were restricted to patients with cervical dystonia and blepharospasm, and were not observed in those with spasmodic dysphonia or brachial dystonia. Other studies using healthy and disease control groups, however, do find an increased risk of OCD,, although depressive symptoms and anxiety were common (Voon 2010; Barahona-Corea 2011; Mula 2012).

Sensory abnormalities have also been a subject of investigation in primary adult - onset focal dystonia patients. Clinically evident sensory abnormalities are not associated with the focal dystonias, and when present trigger consideration of other diagnoses; however, the prominent presence of pain (especially in cervical dystonia) and efficacy of sensory tricks or “geste antgoniste” have long suggested sensory processing impairments (Hallett 1995). Dysfunction of sensory integration in contributing to primary dystonia pathogenesis was reinforced when enlarged and overlapping sensory receptive fields were identified in a primate model of focal dystonia (Byl 1996) and confirmed in human focal dystonia (Bara-Jimenez 1998; Elbert 1998; Nelson 2009). Like DYT1 dystonia, higher temporal discrimination thresholds (TDT) have been reported in adult – onset primary dystonia (Tinazzi 1999, 2002; Fiori 2003;2008; Bradley 2012); but unlike DYT1 and DYT6, dystonia, spatial discrimination is also abnormal (Bara-Jimenez 2000; Sanger 2001; Molloy 2003; Deik 2012). Moreover, the TDT has been proposed as an endophenotype or biomarker of genetic susceptibility in relatives of adult onset primary dystonia patients (Bradley 2010; Kimmich 2011). Other experimental sensory abnormalities that have been described include impaired illusion of movement induced by vibration regardless of affected body part (Grunewald 1997; Rome 1999) and mental rotation of body parts (Fiorio 2006; 2007).

In summary, there is growing evidence that primary dystonia may include a limited spectrum of non-motor features, especially sensory and psychiatric abnormalities. Although the identified sensory impairments are not detected on routine clinical examination, their presence has provided insight into underlying pathogenic mechanisms involving sensory systems and integration into motor planning and execution. For a subset of primary dystonia psychiatric features also appear to represent an expression of the underlying dystonia diathesis. As in other movement disorders, such a Parkinson’s disease, increased attention to psychiatric symptoms is generating a needed focus on this important aspect of the disorder, one that may significantly impact quality of life (Slawek 2007; Ben Shlomo 2002). This focus includes clinical practice recommendations (i.e, screening for psychiatric symptoms) and future research avenues such as assessing treatment efficacy and investigating the pathogenic relationship between motor and psychiatric expression.

Then, accepting that primary dystonia may include non-motor features is the concept of a distinct category of primary dystonia now somehow nullified? Like non-primary dystonias, primary dystonia includes other signs; and so, shouldn’t it be dismantled and somehow incorporated into the long list of secondary dystonias? The suggested answer can be taken from our views on essential tremor and Parkinson’s disease. Both of these “movement disorders” have survived despite the identification of a number of associated, non- motor clinical features, features that may be present but are not necessary for diagnosis. Similarly, the associated disturbances identified in primary dystonia are not inconsistent with current established exclusion criteria (Marsden 1988).

Can dystonia be primary if structural lesions are identified?

Primary Dystonia and Neuropathology

Unlike Parkinson's disease, specific pathology has never been a diagnostic feature of primary dystonia. Indeed, the lack of obvious neuropathology and neurodegeneration has been a feature distinguishing primary dystonia from other etiologies. Similarly, imaging is used in the clinical setting to exclude structural abnormalities suggesting non-primary diagnoses, such as stroke and neurodegeneration with brain iron accumulation. However, any conclusion about the neuropathology of primary dystonia is mitigated by the paucity of studies, including detailed quantitative analyses. Etiologic heterogeneity further limits any attempt to draw conclusions when combining cases. But even considering the limited state of knowledge, there is some evidence suggesting that genetic and clinical subtypes may demonstrate morphologic abnormalities.

Among the positive pathological reports, neuronal loss in brainstem nuclei has been reported in several cases with Meige (Zweig 1988; Mark 1988, Kulisevsky 1988), and two cases of spasmodic dysphonia (Simonyan 2010). Two recent comprehensive reviews of primary dystonia pathology (Standaert 2011; Paudel 2012) discuss this in further detail, and note that while brainstem changes are present in a minority of cases, they stress the inadequate number of studies, with the majority demonstrating *no* abnormalities.

With identification of primary dystonia genes it has become possible to specify genetic cases; to date only DYT1/TOR1A has been investigated. Initial studies included assessing torsinA localization (Walker 2002; Rostasy 2003). They did not identify abnormalities in brain localization of torsinA or other evidence of other associated pathology, although one study noted apparent differences from controls in the size and density of substantia nigra dopamine neurons. This finding however was based on subjective rating and not rigorous quantitative methodology. In the pursuit for other CNS evidence explaining clinical phenomenology, other studies have assessed neurochemistry and identified subtle differences in dopamine content in the rostral putamen (Furukawa 2000) and dopamine turnover (Augood 2002).

In 2004 the notion that primary dystonia was a "functional" disorder that lacked any structural alteration was challenged in a study of four confirmed DYT1 cases (McNaught 2004). Using highly sensitive antibodies, ubiquitin and torsinA- positive inclusions were identified within neurons in the brainstem, including the pedunculopontine tegmental nucleus, the cuneiform nucleus, and periaqueductal gray matter. This DYT1 associated finding awaits replication, although it does not appear to be present in adult onset primary dystonia, as an analysis of 6 adult-onset primary cases did not demonstrate similar inclusions or other pathology (Holton 2008).

In the absence of critical post mortem material, investigation of animal models could potentially shed light on underlying structural changes. In one DYT1 knock-in mouse model ubiquitin- and torsinA-containing aggregates in neurons of the pontine nuclei were identified (Dang 2005). These mice also demonstrated a reduction in the length of primary dendrites and a decrease in the number of spines on the distal dendrites of Purkinje cells (Zhang 2011). This morphological abnormality also was present in mice with a knock out of the DYT1 gene in purkinje cells only. (Zhang 2011). A recent study of using a DYT1 knock-in mouse model identified subtle microstructural abnormalities in the striatum consistent with the altered basal ganglia signaling (Song 2013).

Primary Dystonia and Imaging

Diffusion tensor imaging (DTI) studies have been performed in various primary dystonia populations; these include patients with writer's cramp and cervical dystonia (Colosimo 2005; Fabbrini 2008; Delmaire 2009) and DYT1 and DYT6 gene carriers (Argyelan 2009; Carbon 2009). These studies identified various abnormalities in fiber tracks connecting the basal ganglia, cerebellum, thalamus and cortex. There have also been several studies using MRI and voxel based morphometry in primary dystonia populations, including DYT1 and focal cervical and hand dystonia patients; diverse and not always consistent abnormalities were identified in the putamen, thalamus cerebellum and sensorimotor cortex (see Zoons for review)

Although the lack of detailed neuropathological analyses in any one genetic or phenotypic subtype certainly limits what can be surmised, there is at least some evidence suggesting morphological abnormalities in some primary dystonia subtypes, even if overt cell loss or neurodegeneration is for the most part lacking. Animal and imaging studies also support subtle structural alterations especially involving the basal ganglia and cerebello-thalamo-cortical tracts. Does this, then, demonstrate yet again that criteria for primary dystonia no longer hold and the construct should be dismantled? As with the previous arguments regarding primary dystonia causality and purity of phenotype, the answer lay in determining whether the findings substantively alter the meaning and utility of this construct. Primary dystonia criteria require that imaging and neuropathology not demonstrate structural or other abnormalities indicating a non-primary etiology and that by definition remains intact; further, based on available information, there is little evidence for significant cell loss or neurodegeneration.

Conclusion: Primary dystonia is a viable research and clinical construct

Through systematic application of the the construct of primary dystonia, much has been learned over the last half century about its clinical, etiologic and pathophysiological aspects, although even more remains to be determined. The heterogeneity that was evident to Zeman and Marsden has been partially clarified and also amplified. The identification of genetic causes, such as mutations in *DYT1* and *THAP1*, although accounting for only a small proportion of all primary dystonia (Defazio 2010), has illuminated how single etiologies can be expressed in broad and overlapping primary dystonia phenotypes; phenotypes that include essentially the entire primary dystonia clinical spectrum, motor and non - motor (Bressman 2000, 2009; Xiromerisiou 2012).

But does the science of recent years upend the definition of primary dystonia? There are psychiatric features and experimental sensory abnormalities that occur in *some* primary dystonia patients that may be etiologically related. Neuropathological studies are inconclusive, and microstructural abnormalities have been detected using specialized MRI techniques. These findings probably require that we more carefully word exclusionary criteria. Perhaps rather then simply excluding all neurological signs they should explicitly state: except for tremor, there are no other motor abnormalities, and no evidence of cognitive decline or sensory loss by routine clinical examination. The other exclusion criteria still hold; i.e., without an apparent acquired etiology such as infection, trauma or drug exposure or structural lesion on routine imaging.

Primary dystonia as a clinical construct has proven to be an incredibly durable, reliable, and effective research and clinical tool. Still, does its prior utility justify continued use? To date, there is no data assessing or comparing algorithms for diagnosing or treating dystonia. Yet, even, as we dissect the heterogeneity of dystonia (including primary dystonia), we need overarching guidelines that direct us first to group phenomena based on their shared

characteristics.. So, without other clearly better ways to categorize, a pragmatic approach is for neurologists and others to continue current practice and employ primary dystonia criteria. This is a critical element, along with consideration of a patient's age onset and distribution of dystonia, in clinical thinking. Surgical and medical trials, genetic research studies, and diagnostic testing guidelines rely on currently established criteria. Future study, including much needed pathologic analysis, may change this approach; but for now there is no evidence it needs to be abandoned. Quite the contrary: research investigation remains focused on characterizing etiologies and investigating shared and differing pathophysiologic mechanisms of primary dystonia. Understanding the mechanisms underlying writer's cramp or torticollis due to *TOR1A, THAP1, CIZ1, ANO3, GNAL* and as yet unidentified etiologies is not that different from understanding how mutations in *LRRK2, alpha synuclein,* and *GBA* cause Parkinson's disease; how their mechanisms differ and how they converge. But in order to get to this level of investigation a meaningful pragmatic approach to classification is needed, and for the present, primary dystonia fulfills this need.

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Table 1
Shift in Classification Schema for Dystonia

Classification Changes are noted in bold.

1987: Fahn, Marsden, Calne[1]	**1998: Fahn, Bressman, Marsden[2]**	**2011: Albanese/EFNS[3]**
1. By **Cause**	1. By **Etiology**	1. By Cause (Etiology)
a. Idiopathic	**a. Primary**	**a. Primary**
sporadic	familial	**Primary "pure"**
familial	sporadic	**Primary plus**
b. Symptomatic	**b. Dystonia-plus syndromes**	**Primary paroxysmal**
	c. Secondary	**b.** Heredodegenerative
	d. Heredodegenerative disease	**c.** Secondary
2. By Age at Onset	By Age at Onset	**a. Early-onset** (≤20–30 years)
a. Childhood	**a.** Childhood	**b. Late-onset**
b. Adolescent	**b.** Adolescent	
c. Adult	**c.** Adult	
3. By Distribution	By Distribution	
a. Focal	**a.** Focal	
b. Segmental	**b.** Segmental	
c. Multifocal	**c.** Multifocal	
d. Generalized	**d.** Generalized	
e. Hemidystonia	**e.** Hemidystonia	

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