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Review

Genetic and clinical features of primary torsion dystonia

Laurie J. Ozelius [a,*], Susan B. Bressman [b]

[a] Departments of Genetics and Genomic Sciences and Neurology, Mount Sinai School of Medicine, One Gustave L Levy Pl, Box 1498 New York, NY 10029, USA
[b] Department of Neurology, Beth Israel Medical Center, 10 Union Square East, Suite 5J, New York, NY 10003, USA

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ABSTRACT

Primary torsion dystonia (PTD) is defined as a syndrome in which dystonia is the only clinical sign (except for tremor), and there is no evidence of neuronal degeneration or an acquired cause by history or routine laboratory assessment. Seven different loci have been recognized for PTD but only two of the genes have been identified. In this review we will describe the phenotypes associated with these loci and discuss the responsible gene. This article is part of a Special Issue entitled "Advances in dystonia".

Contents

Introduction

Definition of dystonia

Dystonia refers to muscle contractions that cause sustained twisting and repetitive movements and postures, which are usually

* Corresponding author. Fax: +1 212 849 2508.
E-mail addresses: laurie.ozelius@mssm.edu (L.J. Ozelius), SBressma@chpnet.org (S.B. Bressman).

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directional in nature (Fahn, 1988). There are many causes for dystonia and various classification schemes have been employed to help organize the diverse etiologies. One classification proposes two main etiologic categories (Bressman, 2003; Elia et al., 2010): primary torsion dystonia (PTD) (previously named idiopathic torsion dystonia), and non-primary dystonia. PTD is defined as a syndrome in which dystonia is the only (except for hand tremor) clinical manifestation, and there is no evidence of neuronal degeneration or an acquired cause. Non-primary dystonia including non-degenerative "dystonia-plus" syndromes which are inherited disorders that produce clinical signs in addition to dystonia; heredodegenerative disorders which also typically include signs other than dystonia; and acquired causes. This review will focus on the PTDs.

Primary torsion dystonia (PTD)

The clinical spectrum of PTD is remarkably broad. Symptoms may begin at any age from early childhood to senescence; similarly, there is a range in the degree of muscle involvement from contractions that are limited to a single body region, such as the neck, to widespread involvement of limb, axial, and cranial muscles. Age at onset distribution for PTD is bimodal, with modes at ages 9 (early-onset) and 45 (late-onset) (Bressman et al., 1989). Moreover, there is a relationship between the age at onset of symptoms, body region first affected, and clinical progression of signs (Greene et al., 1995; O'Dwyer et al., 2005). When PTD begins in childhood or adolescence, it often starts in a leg or arm, and then progresses over 5–10 years to involve multiple body regions. When PTD begins in adult years, symptoms first involve the arm (writer's cramp), neck (cervical dystonia or torticollis), laryngeal (spasmodic dysphonia) or other cranial muscles (e.g. blepharospasm). Unlike early-onset, adult or late-onset dystonia tends to remain localized with a focal or segmental anatomic distribution. A rarer clinical phenotype, denoted in families as "mixed," starts early in life and tends to spread but cervical and cranial muscles including speech are more frequently affected compared to most early-onset primary dystonia (Tables 1 and 2).

PTD is the third most common movement disorder after Parkinson's disease and essential tremor. In Rochester, Minnesota, prevalence was 330 per million, with late-onset focal disease being 9 times more common than early-onset generalized (Nutt et al., 1988). A more recent analysis of European cases found a lower frequency of about 152 per million, and again focal cases constituted the majority (117 per million) (ESDE Collaborative Group, 2000). Both of these clinically based studies are likely underestimates of the true frequency of PTD, because a significant proportion of disease is not diagnosed (Risch et al., 1995; Muller et al., 2002).

Table 1
Classification of dystonia.

By age at onset
Early
Childhood
Adolescence
Late/Adult
By distribution
focal—single body region (e.g., writer's cramp, blepharospasm, torticollis, spasmodic dysphonia)
segmental—contiguous body regions (e.g., face + jaw or Meige syndrome, torticollis + writer's cramp)
multifocal—non-contiguous body regions (e.g. arm + leg which is hemidystonia if ipsilateral, blepharospasm + writer's cramp)
generalized—both legs (or one leg and the trunk) + at least one other body region—usually one or both arms
By cause
Primary (previously idiopathic)
Non-primary

Seven genes have been mapped for primary dystonia including *DYT1*, *2*, *4*, *6*, *7*, *13* and *17*, however only two of these *DYT1* (*TOR1A*), and *DYT6* (*THAP1*) have been identified. *DYT1*, *2*, *6*, *13* and *17* are associated with an early onset phenotype whereas *DYT4* and *7* are more focal in distribution (de Carvalho Aguiar and Ozelius, 2002; Chouery et al., 2008) (Table 2).

Early onset DYT1 PTD

A 3 bp (GAG) deletion in the coding region of the *TOR1A* (*DYT1*) gene located on chromosome 9 is a major cause of early onset, generalized dystonia, the most common and severe form of hereditary dystonia (Ozelius et al., 1997). The delGAG mutation removes a single in-frame amino acid (glutamic acid) from the C-terminal region (position 302 or 303) of the encoded protein, torsinA. Despite extensive screening (Ozelius et al., 1999; Leung et al., 2001; Tuffery-Giraud et al., 2001), this deletion is the only one that is clearly associated with primary dystonia to date although two other missense variations have been described involving dystonia including a p.R288Q identified in a single patient with severe fixed dystonia, facial palsy, and long tract signs, with first symptoms in infancy (Zirn et al., 2008) and a p.F205I reported in a man with orobulbar dystonia beginning in his forties with bipolar disease treated with lithium, a remote history of neuroleptic exposure and cogwheeling and action but not rest tremor in his arms (Calakos et al., 2010). Both mutations when over-expressed in cells, produced intracellular inclusions similar to those seen with the delGAG mutation (see below).

The clinical expression of DYT1 dystonia is quite variable, even within families; 70% of gene carriers have no definite signs of dystonia and among the remaining 30% dystonia ranges from mild focal dystonia, e.g. writer's cramp (Gasser et al., 1998) to life-threatening generalized dystonia ("dystonic storm") (Opal et al., 2002). There are however common DYT1 clinical characteristics that have been described across ethnic groups (Valente et al., 1998; Bressman et al., 2000; Im et al., 2004; Yeung et al., 2005; Gambarin et al., 2006; Lin et al., 2006). In the great majority of people with dystonia due to the delGAG mutation symptoms begin early with a mean age onset at 13 years (range 3 to 64 years) and all but a few cases beginning by the age of 26 years. In 90% of cases, an arm or leg is affected first. About 65% progress to a generalized or multifocal distribution, the rest having segmental (10%) or only focal (25%) involvement. Often those with focal dystonia have late-onset writer's cramp (Opal et al., 2002), and are identified through family studies. When viewed in terms of body regions ultimately involved, one or more limbs are almost always affected (over 95% have an affected arm). The trunk and neck may also be affected (about 25–35%) and they may be the regions producing the greatest disability (Chinnery et al., 2002); spread to cranial muscles is less common (<15–20%).

DYT1 dystonia is inherited in an autosomal dominant manner with reduced penetrance (30%) (Risch et al., 1990). If symptoms do not occur prior to 26 years of age in carriers, they usually remain unaffected for the rest of their lives. However, with the identification of the disease gene, we now know that unaffected *TOR1A* mutant gene carriers have endophenotypes in the absences of overt motor signs of dystonia expanding the notion of penetrance and phenotype. Comparing non-manifesting family members to their non-carrier family members as well as those manifesting dystonia, it was found that both manifesting and non-manifesting gene carriers had the same increased risk for early onset recurrent major depression when compared to their non-carrier related family members (Heiman et al., 2004) but no differences in OCD frequency (Heiman et al., 2007).

Other DYT1 endophenotypes have been investigated using various imaging and neurophysiological approaches with the goal of illuminating pathophysiologic mechanisms that take a gene carrier from "non-manifesting" to manifesting. Non-manifesting gene carriers show deficits in specific motor sequence learning paradigms