Age at onset as a factor in determining the phenotype of primary torsion dystonia

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Abstract—*Background:* The genetic basis of most forms of primary torsion dystonia (PTD) is unknown; multiplex families are uncommon due to low penetrance. Intrafamilial, age-related, phenotypic heterogeneity was noted in 14 PTD families. The authors hypothesized that the clinical presentation of PTD was modulated by the age at onset of the dystonia, irrespective of the genotype. *Methods:* This hypothesis was addressed in a study of 14 PTD families and a meta-analysis of 83 published series of PTD. *Results:* In 12 families with adult-onset PTD, the index cases presented with cervical dystonia (CD); of the 22 affected relatives, 17 had CD, 2 had writer's cramp, 1 had blepharospasm, and 2 had spasmodic dysphonia. In the two other PTD families, the probands and all 10 symptomatic relatives had limb-onset dystonia at <20 years of age. There were differences between the median ages at onset of the different phenotypes ($p = 0.0037$). Analysis of 83 published series including 5,057 patients indicated significant differences in the mean age at onset of five phenotypes of PTD (mean age at onset; 95% CI): *DYT1* dystonia (11.3 years; 10.3 to 12.2), writer's cramp (38.4; 36.9 to 39.9), CD (40.8; 40.3 to 41.3), spasmodic dysphonia (43.0; 42.2 to 43.9), and blepharospasm–oromandibular dystonia (55.7; 55.1 to 56.4). *Conclusion:* Phenotypic variation in PTD presentation is due to the effect of age at onset modulating the expression of a genetic disorder with a caudal-to-rostral change in the site of onset.

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Despite advances in our understanding of the primary torsion dystonias (PTDs), their etiologic basis remains largely unknown. This is particularly so for the adult-onset focal and segmental forms of PTD including the most common form, cervical dystonia (CD).[1] Up to 25% of patients with adult-onset PTD may have affected relatives,[2] and it is suspected that even apparently sporadic adult-onset PTD has a genetic basis. Loci (*DYT6*, *DYT7,* and *DYT13*) have been mapped for families that include members with adult-onset PTD,[3-5] and in several families, adult-onset PTD has been excluded from linkage to these known genetic loci.[6-14] Studies of adult-onset PTD families indicate an autosomal dominant inheritance with reduced penetrance of 12 to 15%. Alternatively, penetrance may be higher in a subset of families with the remainder being nongenetic.[2,15-18]

The clinical classification of PTD by age at onset, site of onset, distribution, and progression has correlated well with the recent developments in genetic assignment of disease states.[19] The phenotype of childhood-onset dystonia beginning in a limb and spreading to other sites is highly associated with the *DYT1* mutation.[20-22] In contrast, lower limb dystonia is an infrequent manifestation of adult-onset PTD, and adult-onset PTD usually remains focal or spreads only to one contiguous body region.[23] Further, when other phenotypes such as adult-onset CD or adult-onset writer's cramp are present, they are rarely due to a *DYT1* mutation.[19,24,25]

Genetic heterogeneity for different types of dystonia, particularly CD, writer's cramp, and cranial dystonia, has been postulated. We hypothesize that the clinical phenotype of PTD is influenced by the age of an individual at the time of presentation, irrespective of the genetic etiology. To test this hypothesis, we analyzed age and site of onset in two samples: a large group of Irish families and a meta-analysis of published dystonia series.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the October 26 issue to find the title link for this article.

Methods. *Family study.* All patients with dystonia attending the clinical practices of two consultant neurologists were asked about the existence of other possibly affected family members, and family trees were constructed. Families with dystonia-plus syndromes were excluded. PTD was defined in the index cases when dystonia was the only neurologic feature other than tremor and no known secondary etiology was established. The study was approved by the Research Ethics Committee of St. Vincent's Univer-

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sity Hospital (Dublin, Ireland). In families with two or more reportedly affected members, consenting family members underwent a complete neurologic examination, part of which was videotaped according to a standardized protocol.[20] Each videotaped examination was reviewed by four consultant neurologists (two in New York and two in Dublin) experienced in the assessment of dystonia. A consensus of all four neurologists as to the presence of dystonia and the clinical phenotype was made. The clinical status of each family member in relation to the presence of dystonia was determined as belonging to one of five groups of diagnostic certainty: definite, high probable, probable, possible, and normal. For the purpose of this study, only family members who were definitely or highly probably affected were deemed to have the phenotype. Site of onset was determined by combination of patient history and neurologist review. The clinical phenotype at onset of the dystonia of each affected individual was assigned to one of the following: leg onset, writer's cramp, CD, blepharospasm/oromandibular dystonia, or spasmodic dysphonia. Patients were asked about their age at onset of symptoms; if they were unaware of their dystonia prior to examination, the age at onset was determined as the age of the individual at the time of the assessment. At least one affected member in each family was tested for the *DYT1* deletion.

Published surveys of focal dystonia. All clinical surveys of PTD published in the last 25 years in the English literature were determined from a MEDLINE search and a hand search of ascertained references. The following search terms were used: primary torsion dystonia, *DYT1* dystonia, spasmodic torticollis, cervical dystonia, writer's cramp, brachial dystonia, leg dystonia, spasmodic dysphonia, laryngeal dystonia, blepharospasm, oromandibular dystonia, and Meige's syndrome. Patients in these studies were grouped into five categories: *DYT1* dystonia, writer's cramp, CD, spasmodic dysphonia, and cranial dystonia (blepharospasm, oromandibular dystonia, or both). Only surveys that included the mean age at onset and sufficient information to determine the standard deviations in the diagnostic categories were included. When a particular group of authors had published several studies on the same subjects, only the publication with the largest or larger number of study subjects was chosen. In addition, the ages at onset of a group of 122 patients with apparently sporadic CD attending the botulinum toxin clinic at St. Vincent's University Hospital were included; for convenience, these are included as if published in our analysis.

Statistical methods. Family study. The distribution of ages at onset was skewed upward by the fact that ages at onset of dystonia in asymptomatic individuals were taken as their age at time of study assessment, and therefore, the median ages at onset for each phenotypic group were determined and compared using the Kruskal–Wallis test. Analyses were performed both with and without the asymptomatic individuals.

Meta-analysis of published studies. The mean age at onset and standard errors of the mean for the relevant series of patients in each study were taken directly from the published papers or derived from the confidence limits or standard deviations. With use of a fixed effects model, a precision-weighted mean age was estimated for each of the diagnostic groups described above together with its 95% CI.[26] The significance of differences between the diagnostic groupings was determined using the heterogeneity χ^2. (A more detailed explanation of statistical methods used in the meta-analysis is included in Appendix E-1 on the *Neurology* Web site at www.neurology.org).

Results. *Family study.* Families were ascertained and investigated over a 2-year period from a reference population of 142 patients with PTD who attend our clinics. Fourteen families had PTD (see table E-1 on the *Neurology* Web site at www.neurology.org), and of these, one had dystonia due to the *DYT1* deletion. Six individuals were affected in this family, of whom four had onset in the lower limb with a median age at onset of 11.0 years (range 7 to 14 years); two individuals had upper limb onset at age 8. The *DYT1* deletion was excluded in a second family with dystonia of lower limb onset that subsequently became generalized. Lower limb dystonia at onset was symptomatic in three

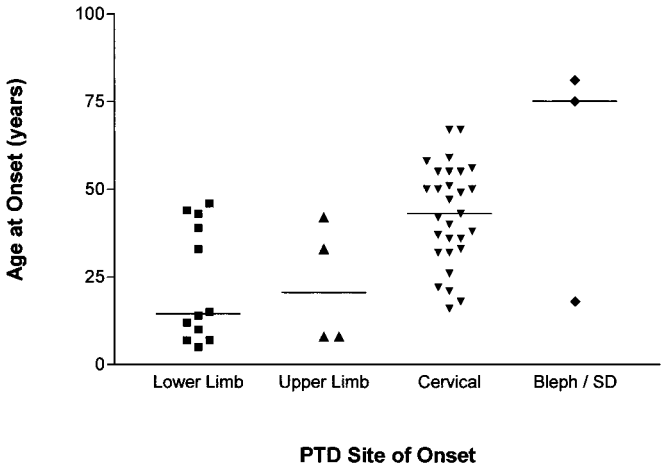

Figure 1. Scattergraph of the ages at onset of each of the 48 affected family members grouped by site of onset of dystonia. Horizontal bars indicate the medians. PTD = primary torsion dystonia; Bleph/SD = blepharospasm and spasmodic dysphonia.

affected individuals with a mean age at onset of 9 years (range 5 to 15 years). Five other asymptomatic family members with lower limb involvement were rated as being definitely affected. The mean age at time of examination of these individuals was 41 years (range 33 to 46 years).

In the remaining 12 PTD families, the phenotype was one of adult-onset focal dystonia. The proband in each of these 12 families presented with CD, reflecting a bias in ascertainment of our cases from adult neurology clinics where CD is treated. In four probands, subsequent segmental spread to cranial, laryngeal, or upper limb involvement had occurred. The median age at onset of dystonia in the 12 probands was 42 years (range 16 to 67 years). In these 12 families, 126 first- and second-degree relatives were examined and 22 were rated as affected; CD was seen in 17 of these, with a median age at onset of 49 years (range 21 to 67 years). In four of these individuals, progression to segmental cervical and upper limb involvement was seen. Of the remaining five affected relatives, two had writer's cramp (onsets at 33 and 42 years), one had blepharospasm (onset at 75 years), and two had spasmodic dysphonia (onsets at 81 and 18 years). Three affected relatives in these families were asymptomatic with CD (age 33 years), upper limb dystonia (age 42 years), and blepharospasm (age 75 years).

The median age at onset for the affected family members with leg-onset dystonia was 14.5 years, for upper limb onset 20.5, for CD 43 years, and for cranial (blepharospasm/oromandibular dystonia and spasmodic dysphonia) 75 years. The corresponding mean ages at onset were 22.9, 22.8, 42.8, and 58 years. The median ages at onset for each site of onset showed a significant somatotopic caudal-to-cranial increase (figure 1) ($p = 0.0037$, Kruskal–Wallis test). When the eight asymptomatic affected individuals are excluded from the analysis, the mean ages at onset for the remaining affected family members with leg onset were 10 years, for upper limb onset 16.3 years, for CD 43.1 years, and for cranial dystonia 49.5 years. The corresponding median ages at onset were 10, 8, 45, and 49.5 years ($p = 0.0002$, Kruskal–Wallis test).

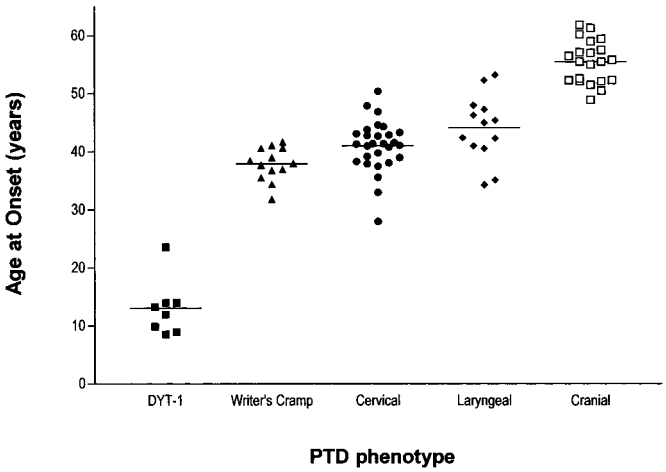

Figure 2. Scattergraph of the mean ages at onset from all the 83 series of primary torsion dystonia (PTD) grouped by site of onset. DYT-1 = DYT1 *dystonia; cervical = cervical dystonia; laryngeal = spasmodic dysphonia; cranial = oromandibular dystonia and/or blepharospasm.*

Published studies. Fifty-five studies met inclusion criteria, and these contained a total of 83 series: 8 *DYT1* dystonia, 13 writer's cramp, 28 CD, 13 spasmodic dysphonia, and 21 blepharospasm/oromandibular dystonia. When series were stratified by gender, each gender was counted as a single series in the meta-analysis. (See table E-2 for patient numbers and mean ages at onset with the standard error of mean for each study grouped by clinical presentation, along with full references for the articles used in the meta-analysis.) Graphic representation of the mean age at onset quoted in each study grouped by clinical presentation indicates the tendency to increasing age at onset with a caudal-to-rostral gradient in clinical presentation (figure 2).

When the mean age at onset was calculated for each clinical category, the grouped means with their 95% CI show clear separation demonstrating the caudal-to-rostral gradient (table). The differences between the precision-weighted mean ages at onset are clearly most marked between the *DYT1* group and all the others (with >25 years' difference between those with *DYT1* dystonia and those with writer's cramp). The other marked difference in mean age at onset is between the blepharospasm/oromandibular dystonia and spasmodic dysphonia groups with >12 years' difference between these. The three groups most closely related in age at onset (writer's cramp, CD, and spasmodic dysphonia) do clearly separate in that the 95% confidence limits for their mean ages at onset do not overlap.

Discussion. Our analysis of published clinical series of sporadic PTD and the family study shows that the mean ages at onset of the various phenotypes differ significantly. With increasing age, there is a caudal-to-rostral shift of the site of onset in the order: leg-onset dystonia, writer's cramp, CD, spasmodic dysphonia, and blepharospasm/oromandibular dystonia. A caudal-to-rostral gradient with age is present in *DYT1* dystonia where the typical phenotype is that of leg or brachial onset before age 26.[19] Analysis of the age at onset by site of onset of 43 Ashkenazi Jewish probands[21] shows that the mean age at onset in the leg (17 patients) was 8.1 years (95% CI 7.2 to 8.9), in the arm (22 patients) 11.5 years (9.6 to 13.3), in the neck (3 patients) 20.7 years (11.3 to 30.1), and in the larynx (1 patient) 18 years (Kruskal–Wallis, $p = 0.0005$). Our study demonstrates that this relationship extends beyond *DYT1* and is present in dystonia of presumed genetically heterogeneous etiology, with wider variability in expression than *DYT1*. The phenotypic heterogeneity in 4 of the 12 adult-onset PTD families indicates that the same genetic disorder within a family may cause widely differing clinical manifestations. Intrafamilial phenotypic heterogeneity was also noted in an Italian pedigree in which all known genetic loci had been excluded; of six affected members, three had CD, two blepharospasm, and one an occupational upper limb dystonia.[14] Other reported pedigrees have demonstrated intrafamilial heterogeneity.[6,8,11,12] Therefore, although the causative gene presumably plays a role in age at onset, with *DYT1* predicting early-onset disease and *DYT6* adolescent/young-adult-onset disease,[4] our data suggest that age at onset itself is a predictor of phenotype. It is associated with site of onset in dystonia of presumed multiple different genetic etiologies.

Dystonia may develop in another body part in 30%

Table *Results of analysis of studies* grouped by clinical category with number of patients, precision-weighted mean age at onset, and 95% CI for each group*

Dystonia phenotype	No. of studies†	Total no. of patients	Mean age at onset, y	95% CI, y
DYT1	8	149	11.25	10.28 to 12.22
Writer's cramp	13	280	38.4	36.91 to 39.89
Cervical dystonia	28	2673	40.75	40.26 to 41.25
Spasmodic dysphonia	13	921	43.0	42.15 to 43.86
Blepharospasm/OMD	21	1034	55.73	55.05 to 56.40

$\chi^2 = 5474.06$, $df = 4$, $p < 0.0001$.
* See table E-2 on the *Neurology* Web site.
† A study may refer to a subgroup of patients in a particular publication.
OMD = oromandibular dystonia.

of adult-onset focal PTD cases. This segmental spread affects adjacent muscles earlier than more distal ones, further supporting a relationship between time and somatotopic involvement. In an Italian study, 55 of 159 patients presenting with blepharospasm experienced progression; spread to the jaw developed within an average of 1.3 years, the larynx in 2.1 years, the neck in 2.2 years, and the arms in 4.3 years.[27]

The pathophysiologic basis of the age at onset/site of onset relationship in PTD is not known. A hypothesis could be proposed that normal progressive age-related change in the putamen renders putaminal neurons vulnerable in a somatopic manner to the expression of a genetic disorder. Dystonia can be caused by lesions of the putamen,[28-31] and putaminal abnormalities have been detected by transcranial sonography in PTD.[32] Somatotopy has been demonstrated in the human putamen; two functional MRI studies have demonstrated an overlapping but distinct representation for the foot, hand, and face in the putamen.[33,34] There were some differences between the two studies, but the somatotopic distribution was similar: The foot was dorsal, lateral, and rostral to the hand, and the face was ventral and medial to the hand. Normal age-related accumulation of iron in the brain has been demonstrated by a number of techniques, and studies suggest that the putamen is particularly affected.[35-37] Putaminal neurons may be thus exposed to increased oxidative stress due to hydroxyl radical production caused by the reaction of transitional metal ions with hydrogen peroxide. The accumulation of iron in the putamen follows a posterolateral-to-anteromedial gradient,[38] which is similar to the foot–hand–face putaminal somatotopy and may, in part, be responsible for the observed effect of age on the clinical presentation of PTD, although such a role remains speculative. Understanding the somatotopic relationship may lend insight into pathophysiologic mechanisms influencing the development and spread of dystonia.

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