

Clinical Presentation and Progression of Sporadic and Familial Primary Torsion Dystonia in Italy

°Anna Rita Bentivoglio, °Antonio E. Elia, †Graziella Filippini, ‡Enza Maria Valente, °Alfonso Fasano, and §Alberto Albanese

°Istituto di Neurologia, Università Cattolica del Sacro Cuore, Rome, Italy.

†Istituto Nazionale Neurologico Carlo Besta, Milan, Italy. ‡Istituto CSS Mendel, Rome, Italy.

§Istituto di Neurologia, Università Cattolica del Sacro Cuore, Rome, Italy; and Istituto Nazionale Neurologico Carlo Besta, Milan, Italy.

Dystonia is a syndrome of sustained muscle contractions, causing twisting and repetitive movements or abnormal posture. The disease is usually classified based on etiology as idiopathic (primary) or symptomatic (secondary). Primary torsion dystonia (PTD) encompasses sporadic and familial cases. Four different PTD loci and nine loci for other inherited dystonias have been identified so far. Dystonia is a clinically and genetically heterogeneous disease that is difficult to schematize based on simple phenotype-genotype correlation.

The natural history of PTD is characterized by focal onset and frequent spread to other body parts with a variable time course. In many cases, dystonia remains focal or spreads only to the adjacent musculature. Sufficient data are not available on the progression of dystonia, particularly in the European population. Moreover, few studies have focused on the clinical features of familial dystonia in large series. This chapter reviews a series of 460 PTD patients referred to the Movement Disorders Clinic of the Gemelli Hospital in Rome; we analyze the onset and progression of sporadic dystonia and describe the clinical features of familial cases.

SUBJECTS AND METHODS

The Movement Disorders Clinic was started in 1986 at the Gemelli Hospital in Rome. During an interval of 15 years, 4,581 in- or outpatients were recorded in a movement disorders registry. Patients in the registry received a clinical diagnosis of dystonia based on the observation of dystonic postures and dystonic movements occurring in combination, either at rest or following a voluntary motor task (1). The observation of sensory tricks provided an additional diagnostic criterion for a definite clinical diagnosis. Isolated head or limb tremors were not considered reliable criteria for the diagnosis. The registry included cases of PTD, of dystonia plus syndromes (2) and of secondary dystonia (e.g., due to cerebral palsy, stroke, neoplasm, drug induced, or psychogenic). The etiologic classification was based on clinical and laboratory workout including neuroimaging (3). The patients were evaluated at least twice a year by a staff neurologist, who reviewed the diagnosis and the treatment plan.

The following clinical data were retrieved from the registry: gender, ethnic origin, age, disease duration, distribution of dystonia at

onset and at the time of the last visit, disease site, and family history of movement disorders. Continuous data were expressed as mean ($\pm$ standard deviation, SD) and were compared by Student's *t*-test. Categorical data were compared by means of chi square (χ^2) test. The analysis of variance (repeated measures) was performed (4) to estimate the mean number of sites progressively involved during the follow-up in sporadic and in familial cases.

To examine the clinical features of familial dystonia, we considered the patients who reported at least one family member with dystonia. All index cases were asked for participation of their relatives in the study. Only one index subject was considered for each family. In 39 index cases, the diagnosis of familial dystonia was confirmed personally as we examined family members. Thirty-three index patients were not further investigated.

RESULTS

The Gemelli dystonia registry encompassed 593 patients (356 women and 237 men) with primary or secondary dystonia who were followed in the period 1986–2001. The patients originated mostly from Central and Southern Italy (Lazio, Campania, Apulia, and Abruzzo regions). One hundred thirty-three patients were affected by secondary dystonia, 460 (296 women and 164 men) had PTD.

The mean age at onset in PTD cases (48.3 ± 17.7 years) was higher than that of secondary cases (30.1 ± 23.0 ; $p < .001$). Perinatal cerebral injury was the commonest cause of secondary dystonia (33.3%), and treatment with neuroleptics was the second most common cause (28.0%); in 5.3% of cases a psychiatric condition not related to neuroleptic intake was associated with dystonia (obsessive-compulsive disorder, psychosis). Head trauma, brain neoplasm, thalamotomy, stroke, parkinsonism, or Fahr's disease were the causes of the remaining secondary cases.

A detailed history revealed that 380 cases were affected by sporadic PTD, whereas 80 patients reported at least one relative affected with dystonia.

The 380 sporadic PTD patients had a mean age at disease onset of 49.1 ± 17.2 years. At the last available clinical examination, 234 patients presented a focal dystonia (124 cranial, 43 cervical, 21 laryngeal, 43 upper limb, and three lower limb). Segmental cases were 124, encompassing 52 patients affected by cranial-cervical dystonia, 23 by cranial-cervical and upper limb dystonia, 24 by Meige's syndrome, 17 by neck and upper limb, six by neck and trunk, two by neck and laryngeal dystonia. Multifocal dystonia occurred in seven patients and generalized dystonia in 15. There was a male-to-female ratio of 1:1.85, mainly caused by a preponderance of women with blepharospasm or cranial-cervical dystonia (M:F ratio of 1:2.6 and 1:3.7, respectively).

Of the 460 patients with PTD, 80 (17.6%) reported a family history of dystonia; eight had relatives included in the registry, and therefore, the frequency of familial cases was 15.9%. In 39 cases, familial dystonia was ascertained by direct examination of the affected relatives or indirect evidence based on medical records confirming the diagnosis. These families were studied in detail. Among the families studied, 15 presented a prevalent phenotype of focal dystonia, 16 had a segmental phenotype, and eight a generalized phenotype.

Sporadic PTD

Disease Onset

At onset, all PTD patients presented with focal symptoms, and a large variability of body districts involved. Most cases (55.3%) had cranial onset, with blepharospasm in almost all, and oromandibular dystonia in just eight. Cervical dystonia was observed in 77 patients (20.3%); 29 patients (7.6%) had spasmodic dysphonia at onset; 64 patients (16.8%) had limb onset involving one upper limb in most cases (64, 14.2%) and a lower limb in the remaining 10 (2.6%). The mean age at onset was 49.1 ± 17.2 years; age at onset varied apparently in correlation with the site of onset—

ascendec
women (dystonia
($p < .001$
groups),
with cran
Cranial,
onset w
women tl
1:2.6, 1:2
in the up
than in w
at disease

In mos
not progr
 7.2 ± 6.4
site of on
disease d
progresse
patients (
15.8 year
cal or ger
Patient
lower age
focal, seg

Featu
Focal PTD
Cranial
Blepha
Low fa
Cervical
Laryngea
Upper lim
Lower lim
Total of foca
Segmental
Meige's s
Cranial-ce
Neck and
Neck and
Neck and
Cranial-ce
Total of segi
Multifocal dy
Generalized
Total

PTD, prim

s had a mean 7.2 years. At ination, 234 ia (124 cra- upper limb, cases were affected by rianial-cervi- by Meige's limb, six by nd laryngeal occurred in stonia in 15, o of 1:1.85, ce of women rvical dysto- 3.7, respec-

, 80 (17.6%) stonia; eight registry, and al cases was onia was as- of the af- ce based on e diagnosis. etail. Among d a prevalent o had a seg- generalized

esented with ariability of ses (55.3%) spasm in al- tonia in just erved in 77 %) had spas- ents (16.8%) per limb in r limb in the age at onset et varied ap- e of onset—

ascended from lower to upper body either in women or in men. Patients with lower limb dystonia had the youngest age at disease onset ($p < .001$, when compared to the other subgroups), whereas the mean age of patients with cranial onset was the highest ($p < .001$). Cranial, cervical, laryngeal, and lower limb onset were observed more frequently in women than in men (M to F ratio 1:2.7, 1:1.8, 1:2.6, 1:4.0, respectively). Interestingly, onset in the upper limb was more frequent in men than in women (M to F ratio 2.8:1) and the age at disease onset was higher in men ($p < .05$).

Progression

In most patients (234, 61.5%) dystonia did not progress after a mean disease duration of 7.2 ± 6.4 years, but remained confined to the site of onset. In 124 patients (32.6%, mean disease duration: 10.1 ± 9.4 years) dystonia progressed to a segmental distribution; in 22 patients (5.6%, mean disease duration: 14.2 ± 15.8 years) dystonia progressed to a multifocal or generalized distribution (Table 24-1).

Patients with generalized dystonia had a lower age at disease onset than patients with focal, segmental, or multifocal distributions

(17.9 ± 16.7 , compared to 50.2 ± 17.3 years for segmental, 48.4 ± 17.7 for multifocal, and 50.4 ± 15.2 for focal cases; $p < .001$ in each case); there were no differences in age at disease onset among patients with focal, segmental, and multifocal dystonia.

When patients were compared on the basis of the body area affected at onset, it was observed that clinical progression occurred in a higher percentage of patients with lower limb onset (75%), than of those with cervical (48.0%), cranial (40.4%), laryngeal (27.6%), or upper limb onset (20.3%). No gender-related difference occurred in the progression of dystonia.

The progression rate varied in relation to the site affected at disease onset. In the majority of patients with cranial onset in whom spread of dystonia occurred, the disease progressed to cranial-cervical involvement or to Meige's syndrome, with very few cases of generalization. Cervical (and laryngeal) dystonia progressed to cranial-cervical or cervical-brachial segmental dystonia; generalization occurred in 9% of patients with cervical onset and in no patient with laryngeal onset. In 11 out of 54 patients with upper limb onset, dystonia progressed to other sites, mostly to a

TABLE 24-1. Presentation of dystonia at the last examination in sporadic cases

Features of dystonia	Number	M/F	Age at onset	Disease duration
Focal PTD				
Cranial	124	35/89	57.4 ± 9.4	6.6 ± 5.6
Blepharospasm	122	34/88	57.3 ± 9.4	6.7 ± 5.6
Low face	2	1/1	47.5 ± 24.7	1.0 ± 0.0
Cervical	43	17/26	42.0 ± 14.5	9.5 ± 8.0
Laryngeal	21	7/14	55.0 ± 17.4	5.9 ± 6.1
Upper limb	43	34/9	38.0 ± 15.9	7.7 ± 6.6
Lower limb	3	1/2	33.3 ± 22.0	3.3 ± 4.2
Total of focal forms	234	94/140	50.4 ± 15.2	7.2 ± 6.4
Segmental PTDs				
Meige's syndrome	24	8/16	57.9 ± 9.2	8.8 ± 7.3
Cranial-cervical	52	11/41	53.1 ± 15.3	9.2 ± 8.8
Neck and upper limb	17	8/9	37.9 ± 21.5	15.8 ± 11.6
Neck and trunk	6	1/5	40.8 ± 18.5	5.3 ± 2.8
Neck and laryngeal	2	0/2	51.0 ± 12.7	6.0 ± 0.0
Cranial-cervical and upper limb	23	4/19	47.3 ± 19.9	11.2 ± 11.3
Total of segmental forms	124	32/92	50.2 ± 17.3	10.1 ± 9.4
Multifocal dystonia	7	1/6	48.4 ± 17.7	5.7 ± 4.7
Generalized dystonia	15	6/9	17.9 ± 16.7	18.3 ± 17.7
Total	380	133/247	49.1 ± 17.2	8.6 ± 8.5

PTD, primary torsion dystonia

cervical or cranial-cervical involvement. Seven out of 10 patients with onset in the lower limb had a clinical progression, which led to a generalized form in all.

Duration of clinical history was directly related to the spread of symptoms ($p < .001$), thus revealing that dystonia is a progressive disease. The most relevant clinical progression occurred during the first 5 years; after that period the disease was more stable (Fig. 24-1).

Primary Torsion Dystonia Families

The frequency of familial inheritance in the registry was estimated to be 15.9%. This was calculated by considering that eight patients, out of 80 who had at least one relative with dystonia, were already on record. Thirty-nine PTD families were studied; in 15 the prevalent phenotype was focal, in 16 segmental, and in eight generalized. Age at onset was

adult (>21 years) in 34 families; onset was early (≤ 21 years) in three families; in two families age at onset was variable.

In nine families the prevalent phenotype was cranial-cervical dystonia with occasional generalization, two families had cranial-cervical dystonia with upper limb involvement, and three had a cranial-cervical form. Cervical dystonia was the prevalent phenotype in seven families (with occasional lower limb involvement in four of them). Cranial dystonia (blepharospasm, with or without lower cranial involvement) was the most common presentation in five families; focal laryngeal dystonia occurred in three families, and isolated writer's cramp in two. Generalized dystonia occurred in eight families (in two of them with rapid movements resembling myoclonic dystonia); two non-Jewish families and one Sephardi Jewish family had the *DYT1* mutation; some family members of the non-Jewish

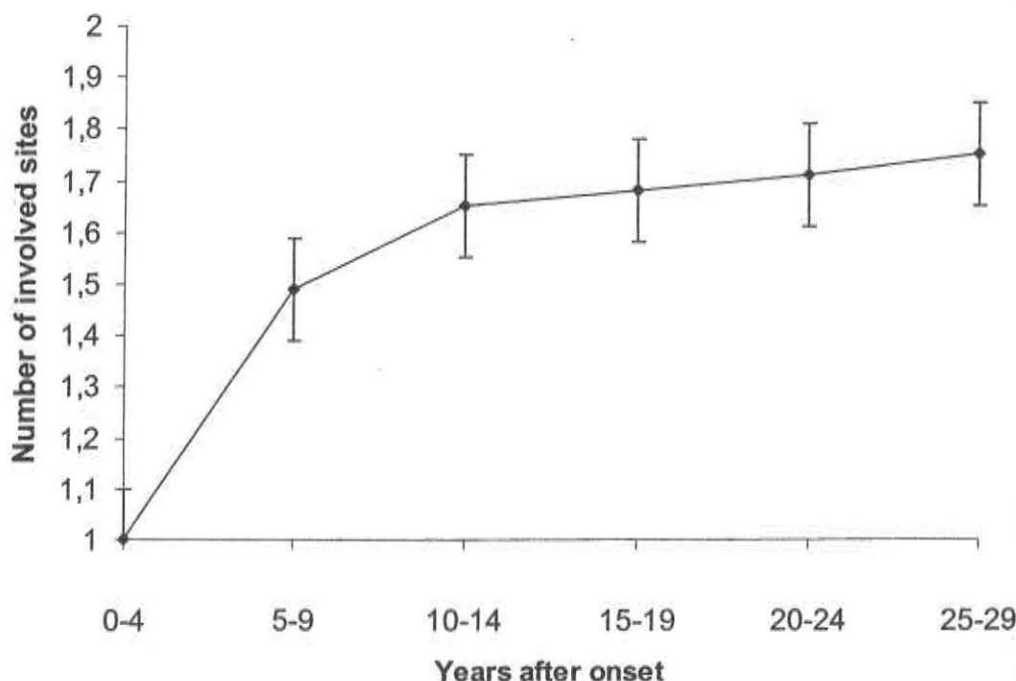


FIG. 24-1. Clinical progression of dystonia in a population of 380 patients with sporadic primary torsion dystonia (PTD), who were followed up after disease onset. Number of involved sites is shown as average $\pm$ standard error of the mean.

families pro-
tured. We di-
focal oron
lower limb

We scree-
deletion on
carried the
them were
were memb-
tients (two
out of 140 v
GAG delet-
DYT1 cases
ers. *DYT1* p-
 23.3 ± 19.7
of 17.4 ± 17
of 1.2:1. All
in five cases

Among fa-
unaffected g-
ically defini-
(5). She was
affected by
Two other v-
sented with
and mild pr-
progressed to
ing the upper
mained conf

TABLE 24-2

Genetic
characterization

DYT1+
DYT1-

DYT13+

lies; onset was families; in two ble.

lent phenotype with occasional ; had cranial- limb involve- l-cervical form. alent phenotype onal lower limb Cranial dystonia out lower cranial mmon presenta- ryngeal dystonia s, and isolated ralized dystonia two of them with myoclonic dys- families and one the *DYT1* muta- of the non-Jewish

families presented with atypical clinical features. We did not observe any familial case of focal oromandibular dystonia or isolated lower limb dystonia.

Genetic Data

We screened 163 subjects for the GAG deletion on the *DYT1* gene; 13 of them (8%) carried the mutation (Table 24-2). Three of them were affected by sporadic PTD and ten were members of three families. Three patients (two familial PTD and one sporadic), out of 140 with adult onset, carried the *DYT1* GAG deletion. Overall, we identified 11 *DYT1* cases of PTD and two unaffected carriers. *DYT1* patients had a mean age at onset of 23.3 ± 19.7 years, and mean disease duration of 17.4 ± 17.4 years. Men-to-women ratio was of 1.2:1. All cases presented with limb onset; in five cases onset was in a lower limb.

Among familial *DYT1* cases there was an unaffected gene carrier who presented a clinically definite form of psychogenic dystonia (5). She was the mother of a 21-year-old man affected by classic generalized *DYT1* PTD. Two other women in the same family presented with early-onset upper limb dystonia and mild progression: in one case dystonia progressed to a segmental distribution involving the upper body; in the other, dystonia remained confined to the upper limb. A typical

form of *DYT1* PTD affected four patients with early onset in a lower limb and rapid generalization.

Four *DYT1* carriers with generalized dystonia had limb onset and spread to cervical muscles (in one case there was also laryngeal and oromandibular involvement). The mean age at disease onset was 10.0 ± 5.4 years. One *DYT1* carrier presented dystonia of the right shoulder at age 42; progression included scoliosis and action-induced tremor of the right hand. Two years later she presented tremor in the left hand, 20 years after the onset she also presented head tremor.

In four families that were large enough for linkage studies, linkage to the *DYT6* and *DYT7* loci was excluded.

The set of families with cervical dystonia and occasional generalization included a large family with 11 affected members linked to a novel PTD locus (*DYT13*) located on chromosome 1p36.13-36.32 (6). The prevalent phenotype revealed focal or segmental dystonia with prominent involvement of the cranial-cervical region and the upper limbs (7). The age at onset in the affected subjects was variable, ranging from 5 to 45 years. No anticipation (of age at onset and severity) was documented among generations. Onset occurred either in the cranial-cervical region (in six patients) or in the upper limb (in two patients), and was apparently segmental (both upper

TABLE 24-2. Genetic classification of primary torsion dystonia (PTD) patients and families (not considering dystonia plus syndromes)

Genetic characterization	No. of patients (no. of families)	Clinical features	Age at onset
<i>DYT1</i> +	10 (3)	Limb onset and rapid generalization	Juvenile
<i>DYT1</i> -	4 (2)	Blepharospasm	Adult
	2 (1)	Cranial-cervical	Juvenile
	6 (3)	Cranial-cervical	Adult
	2 (1)	Cranial-cervical or upper limb	Adult
	3 (1)	Cranial-cervical or generalized	Juvenile
	15 (4)	Cranial-cervical or generalized	Adult
	2 (1)	Cervical	Juvenile
	3 (1)	Cervical or generalized	Adult
	4 (2)	Upper limb	Adult
	2 (1)	Generalized	Juvenile
	4 (1)	Myoclonic	Juvenile
<i>DYT13</i> +	11 (1)	Cervical or generalized	Variable

sporadic primary tor-
volved sites is shown

limbs) in one. Progression was mild and the disease course was relatively benign in all the affected individuals. All the patients with long disease duration had a spread of symptoms to other body regions; in two patients the disease progressed to generalization, but their functional impairment remained mild. The estimated penetrance of the *DYT13* gene in this family was 58%.

DISCUSSION

The present series includes 460 PTD patients referred to the Gemelli Movement Disorders Clinic during a 15-year interval (1986–2001). Population data are influenced by several conditions: the center is a referral clinic for adult cases from central and southern Italy; children are not referred routinely, and this may bias the estimated prevalence of both early-onset PTD and secondary dystonias (particularly those secondary to birth injury). In the present series, early-onset cases accounted for 10.2% of the total and secondary dystonias for 22.4%. This is at odds with earlier series collected in other movement disorders centers where patients with early onset were approximately 20% of the total (8,9). This may indicate between-center differences in the catchment areas or in the availability of pediatric neurologists. Another difference is in the population collected by different centers; North American series encompass many Ashkenazi Jewish patients, who are poorly represented in European registries. Genetic heterogeneity between this and other series provides an intriguing glimpse on differences in populations.

Most patients with sporadic PTD in the present series (61.6%) had a final phenotype of focal dystonia, 32.6% had a segmental form, 1.8% were multifocal, and 3.9% had generalization. This is in agreement with data indicating that most patients with adult-onset PTD have focal dystonia, whereas segmental or multifocal dystonia represent altogether 22% of cases (10). According to the prevalence data estimated by an earlier study, patients with focal dystonia are ten times more

numerous than those with generalized forms (11). Considering focal PTD, most patients in this series were affected by blepharospasm or by cervical dystonia. This is consistent with the results of several studies indicating that blepharospasm is more frequent in southern Italy (12) than in the United States, Japan, or northern Europe, where cervical dystonia is the most common focal dystonia (11,13,14). Interestingly, an epidemiologic study performed in Segovia, Spain, found that blepharospasm was the commonest focal dystonia, thus providing a parallel between the two Mediterranean countries (15). Nevertheless, the relative frequency of blepharospasm and of cervical dystonia may be overestimated in the Gemelli series because patients affected by these focal forms were referred specifically for botulinum toxin treatment. This is probably a common bias in all clinical series collected during the last 15 years that attempt to deduce prevalence of dystonia on the basis of patient series collected at movement disorders clinics.

The present study confirms that generalized dystonia presents at an earlier age at onset than focal or segmental forms (16) and that the age at onset is inversely related to the diffusion of dystonia (9). In the present series, the mean age at onset was 17.9 ± 16.7 years for generalized dystonia, 50.2 ± 17.3 for segmental, and 50.4 ± 15.2 for focal dystonia. The present series also indicates sex-related differences in age at disease onset: in patients with cranial, cervical, or laryngeal dystonia age at onset was higher in women than in men, while in patients with upper limb dystonia age at onset was higher in men. This observation is in keeping with earlier reports (13,17,18) and points to a role of sex hormones in the pathophysiology of dystonia (19,20).

Significant differences were observed when patients with focal onset were categorized by their age at onset, in keeping with the observation that the mean age at onset increases as the site of onset ascends in the body (9). In patients with cranial dystonia, a progression to other body areas occurred in

40.4% report affect Amer obser in 73% In the dysto other laryng have only onset (22), (9). A cerne Geme previc adult- (9), a Jewis due to preser with v who c tion.

The of dys estima ous st rence tients. incide atives rospas of pop has be an ep (26).

The Gemel patient for the GAG dyston radic p vation export ing pr

eralized forms most patients in blepharospasm or consistent with indicating that ent in southern states, Japan, or focal dystonia is onia (11,13,14). gic study per- and that blepha- focal dystonia, between the two). Nevertheless, pharospasm and overestimated in atients affected referred specifi- atment. This is all clinical series ears that attempt onia on the basis movement disor-

ns that general- earlier age at on- forms (16) and ely related to the he present series, 7.9 ± 16.7 years 2 ± 17.3 for seg- r focal dystonia. cates sex-related onset: in patients ryngeal dystonia women than in upper limb dysto- in men. This ob- h earlier reports role of sex hor- logy of dystonia

were observed set were catego- keeping with the age at onset in- st ascends in the rcranial dystonia, a areas occurred in

40.4% of cases; this figure is similar to that reported in another series of Italian patients affected by blepharospasm (21). In the North American population, however, it has been observed that a spread of symptoms occurred in 73% of 107 patients with cranial onset (9). In the present series, cervical and laryngeal dystonia have a higher rate of progression to other body areas (cervical dystonia: 48.0%; laryngeal dystonia: 27.6%). Previous studies have found that spread of disease occurs in only 22% of non-Jewish patients with adult onset (9), in 31.9% of cervical dystonia cases (22), and only in 14% of laryngeal PTD cases (9). As far as upper limb dystonia is concerned, the rate of progression observed in the Gemelli registry (20.4%) is lower than that of previous studies reporting figures of 41% for adult-onset cases, 72% for early-onset cases (9), and 60% for *DYT1* negative Ashkenazi Jewish patients (23). This discrepancy may be due to the higher age at onset of patients in the present series that encompasses many patients with writer's cramp or occupational dystonia, who do not have progression to generalization.

The frequency of cases with family history of dystonia among our PTD population was estimated to be 15.9%, in keeping with previous studies, which estimated familial occurrence between 18% (24) and 23% (25) of patients. The latter study reported that the incidence of dystonia among first-degree relatives of patients with torticollis and blepharospasm is higher than expected on the basis of population data. Furthermore, familiarity has been considered a risk factor for PTD in an epidemiologic study performed in Italy (26).

The analysis of familial cases of the Gemelli registry showed that among 140 PTD patients with adult onset who were screened for the *DYT1* mutation, three had the *DYT1* GAG deletion. In two patients with familial dystonia, the age at onset was 50; in the sporadic patient, age at onset was 42. This observation provides caveats on the possibility of exporting to the European population the testing proposed for North American patients

seeking genetic testing for the *DYT1* mutation (27). Further comparisons should probably account for differences in genetic backgrounds between North America and Europe.

REFERENCES

1. Fahn S, Eldridge R. Definition of dystonia and classification of the dystonic states. *Adv Neurol* 1976;14:1-5.
2. Fahn S, Bressman S, Marsden CD. Classification of dystonia. *Adv Neurol* 1998;78:1-10.
3. Bressman SB. Dystonia. *Curr Opin Neurol* 1998;11:363-372.
4. Diggle PJ, Liang KY, Zeger SL. *The analysis of longitudinal data*. New York: Oxford University Press, 1994.
5. Bentivoglio AR, Loi M, Valente EM, et al. Phenotypic variability of *DYT1*-PTD: does the clinical spectrum include psychogenic dystonia? *Mov Disord* 2002;17:1058-1063.
6. Valente EM, Bentivoglio AR, Cassetta E, et al. *DYT13*, a novel primary torsion dystonia locus, maps to chromosome 1p36.13-36.32 in an Italian family with cranial-cervical or upper limb onset. *Ann Neurol* 2001;49:362-366.
7. Bentivoglio AR, Del Grosso N, Albanese A, et al. Non-*DYT1* dystonia in a large Italian family. *J Neurol Neurosurg Psychiatry* 1997;62:357-360.
8. Bressman SB, Fahn S. Childhood dystonia. In: Watts RL, Koller WC, eds. *Movement disorders*. New York: McGraw-Hill, 1997:419-429.
9. Greene P, Kang UJ, Fahn S. Spread of symptoms in idiopathic torsion dystonia. *Mov Disord* 1995;10:143-152.
10. The Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group. A prevalence study of primary dystonia in eight European countries. *J Neurol* 2000;247:787-792.
11. Nutt JG, Muentner MD, Aronson A, et al. Epidemiology of focal and generalized dystonia in Rochester, Minnesota. *Mov Disord* 1988;3:188-194.
12. Defazio G, Livrea P. Epidemiology of primary blepharospasm. *Mov Disord* 2002;17:7-12.
13. Duffey POE, Butler AG, Hawthorne MR, et al. The epidemiology of the primary dystonias in the north of England. *Adv Neurol* 1998;78:121-125.
14. Nakashima K, Kusumi M, Inoue Y, et al. Prevalence of focal dystonias in the Western area of Tottori prefecture in Japan. *Mov Disord* 1995;10:440-443.
15. Sempere AP, Duarte J, Coria F, et al. Prevalence of idiopathic focal dystonia in the province of Segovia, Spain. *J Neurol* 1994;241:S124.
16. Fahn S. Concept and classification of dystonia. *Adv Neurol* 1988;50:1-8.
17. Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group. Sex-related influences on the frequency and age of onset of primary dystonia. *Neurology* 1999;53:1871-1873.
18. Soland VL, Bhatia KP, Marsden CD. Sex prevalence of focal dystonias. *J Neurol Neurosurg Psychiatry* 1996;60:204-205.
19. Kompoliti K. Estrogen and movement disorders. *Clin Neuropharmacol* 1999;22(318):326.
20. Loscher W, Blanke T, Richter A, et al. Gonadal sex hor-

- mones and dystonia: experimental studies in genetically dystonic hamsters. *Mov Disord* 1995;10:92-102.
21. Defazio G, Berardelli A, Abbruzzese G, et al. Risk factors for spread of primary adult onset blepharospasm: a multicentre investigation of the Italian movement disorders study group. *J Neurol Neurosurg Psychiatry* 1999; 67:613-619.
 22. Jahanshahi M, Marion MH, Marsden CD. Natural history of adult-onset idiopathic torticollis. *Arch Neurol* 1990;47:548-552.
 23. Bressman SB, de Leon D, Kramer PL, et al. Dystonia in Ashkenazi Jews: clinical characterization of a founder mutation. *Ann Neurol* 1994;36:771-777.
 24. Leube B, Kessler KR, Goecke T, et al. Frequency of familial inheritance among 488 index patients with idiopathic focal dystonia and clinical variability in a large family. *Mov Disord* 1997;12:1000-1006.
 25. Stojanovic M, Cvetkovic D, Kostic VS. A genetic study of idiopathic focal dystonias. *J Neurol* 1995;242: 508-511.
 26. Defazio G, Berardelli A, Abbruzzese G, et al. Possible risk factors for primary adult onset dystonia: a case-control investigation by the Italian Movement Disorders Study Group. *J Neurol Neurosurg Psychiatry* 1998;64: 25-32.
 27. Bressman SB, Sabatti C, Raymond D, et al. The DYT1 phenotype and guidelines for diagnostic testing. *Neurology* 2000;54:1746-1752.

Cog

*Arl

One mig
tion and
logic dis
as focal
investiga
potential
ognized t
nition, th
behavior
and moti
controls
These th
lying net
relates.

There
tion:

1. Rece
ties 1
grate
2. Men
form
3. Thin
nizat
4. Expr
mear
comi

Althou
cognition
function,
that are c
with the