Onset and progression of primary torsion dystonia in sporadic and familial cases

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Four hundred and sixty records of patients with primary torsion dystonia (296 women and 164 men) were evaluated. The mean age at disease onset was 48.3 ± 17.7 years; 13 patients carried the DYT1 CAG deletion. The distribution of age at onset was represented by a bi-modal curve, with a nadir at 21 year separating early onset from late onset cases. In 15.9% of cases there was a positive family history of dystonia. Cranial, cervical or lower limb onset was more common amongst women (M:F ratios were 1:2.7, 1:1.9, and 1:3); by contrast, onset in the upper limb was more common in men (M:F ratio 2.2:1). As expected, disease progression was more pronounced in cases with early onset; it was reckoned that onset at or above 32 years was associated with a negligible likelihood to progress to a generalized form. The mean age at onset of familial cases was 44.8 ± 11.2 years, significantly lower than the mean age at onset of sporadic cases (53.5 ± 13.4 years). Familial cases were characterized by more sites involved throughout disease course. Familial cases had a higher tendency to progress to a segmental or generalized form than sporadic cases.

Introduction

Dystonia is a syndrome of sustained muscle contractions, causing twisting and repetitive movements or abnormal postures [1]. The etiological classification includes: primary torsion dystonia (PTD), secondary dystonia (often symptomatic of a brain injury), dystonia-plus syndromes (such as dopa-responsive dystonia or myoclonic dystonia), and heredodegenerative diseases, in which dystonia occurs as a prominent feature [2]. Primary dystonia is a clinically and genetically heterogeneous condition, age at onset is a relevant variable for the clinical presentation and the prognosis [3]. The definition of early onset dystonia is based on the identification of a threshold age to use for classifying patients. The age of 21 years has been originally set by a consensus of experts [1], but later observations have proposed to increase the threshold for this terminology up to 26 years [4]. PTD may occur sporadically or in familial aggregation; one PTD gene (named DYT1) and three different loci (named DYT6, DYT7, and DYT13) have been identified [5–7]. The natural history of PTD is characterized by focal onset and occasional spread to other body parts with a variable natural course. In adult-onset cases, dystonia usually remains restricted to a single body district or has a limited diffusion to other body regions; in patients with early onset dystonia the symptoms tend to generalize [2]. DYT1 PTD is the best characterized form of dystonia; the typical DYT1 phenotype is with early limb onset, rapidly progressive course towards generalization, and no involvement of cranial segments [8]. By contrast, limited data are available on the clinical features and the natural course of non-DYT1 dystonia, particularly in the European population.

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Subjects and methods

A movement disorders registry was started in 1986 at the Gemelli Hospital in Rome, a secondary and tertiary referral center. Patients with movement disorders were followed up at least twice a year by a staff neurologist, who reviewed the diagnosis and the treatment plan. All patients provided information on familial and personal medical history and filled in a detailed questionnaire on common motor problems observed in movement disorders. All the reportedly affected relatives of index patients were examined directly in the clinic whenever available. The patients' records were entered in the movement disorders registry. For the purpose of this study we selected from the registry only patients with a diagnosis of clinically definite or probable PTD, who were examined from January 1986 to December 2001. The diagnostic criteria have been already described [9,10]. The following clinical data were retrieved from the registry: gender, ethnic origin, age at onset, distribution of dystonia at onset and during the follow-up

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visits, and the occurrence of family history of movement disorders. Dystonia was considered familial when at least a first-, second- or third-degree family member was diagnosed as affected by PTD. The adult onset index cases of non-DYT1 families were compared with sporadic PTD patients whose records provide accurate data of spread of dystonia during the clinical follow-up. Progression of dystonia was defined as a spread of symptoms from focal to segmental, multifocal or generalized dystonia.

Genetic analysis

Blood samples were obtained by all patients who provided a written informed consent. DNA was extracted from leukocytes using standard techniques. Screening for the GAG deletion in the DYT1 gene was performed according to standard procedures [11].

Statistical analysis

Data were analysed with the use of SPSS software for Windows v. 10.1 (SPSS, Inc., Chicago, IL, USA). Results are reported as mean ± SD. A histogram of ages at onset was drawn, then the best-fit curve of the distribution of age at onset was analysed and represented in Cartesian axes. Analysis of variance was used to compare the mean ages amongst patients who had different sites of onset of dystonia. Categorical data were compared with the chi-squared test. Repeated-measures analysis of variance was performed computing the mean number of body parts progressively involved by dystonia during the natural disease course. The onset and progression of adult-onset sporadic or familial cases, who were non-carriers of DYT1 GAG deletion, were compared. The sensitivity and specificity of age at onset to assess generalization of dystonia were calculated for patients followed-up for 5 or more years. Receiver operating characteristic (ROC) curves were plotted considering different levels of age at onset (with intervals of 1 year from birth). The age level closest to 80% sensitivity and 80% specificity was defined as the best trade-off threshold for disease progression. The estimates of sensitivity and specificity were used to calculate the positive and negative predictive values of the best trade-off value of age at onset.

Results

The movement disorders registry encompassed 593 cases of dystonia (356 women and 237 men), 460 of whom were PTD cases and 133 had other forms of dystonia. All PTD patients were Caucasian, mostly originating from central and southern Italy. The

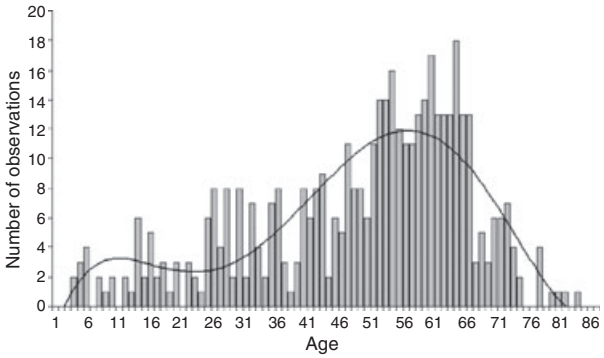

Figure 1 Frequency distribution of age at onset in 460 primary torsion dystonia cases seen at the Gemelli Hospital in Rome. The bimodal distribution observed has a nadir at 21 years that identifies two well-distinguished clusters of patients with early and late disease onset (modes at 9 and 57 years, respectively).

frequency distribution of the ages at onset is shown in Fig. 1. The best fit was obtained with a bimodal curve with modes at 9 and 57 years and nadir at 21 years. Based on this evidence, 21 years were considered as the most appropriate cut-off to distinguish early onset and late onset PTD in this series. Four hundred and sixteen (90.4%) PTD patients had clinical onset after age 21, whereas 44 patients (9.6%) had early onset. Of the 460 PTD patients, 380 (82.6) were sporadic, and 80 (17.4%) had a family history of dystonia. Eight families had more than one member included in the registry, thus the frequency of familial cases was 15.9%. In 49 families, it was possible to examine all the reportedly affected members; 39 of them were affected by dystonia (focal form in 15, segmental in 16, generalized in eight).

Clinical presentation and progression

Primary torsion dystonia was observed more frequently in women than in men (M:F = 1:1.8). In all patients onset was focal, most frequently a cranial dystonia (50.4%), followed by cervical (22.0%), upper limb (15.4%), laryngeal (8.3%) or lower limb dystonia (2.6%). Cranial onset was more frequently observed in women (M:F = 1:2.7), whereas upper limb onset prevailed in men (M:F = 2.2: 1). Patients with cranial onset had the highest mean age at disease onset (men: 53.8, women: 57.3); patients with lower limb onset had the lowest age (men: 13.3, women: 24.3). Overall, age at disease onset was lower in men than in women (44.1 and 50.6, respectively; $P < 0.001$). Cranial and laryngeal onset occurred earlier in men than in women ($P < 0.001$ and $P < 0.005$, respectively), whereas upper limb onset occurred earlier in women ($P < 0.01$; Table 1).

At the last follow-up visit, 269 patients (58.4%, mean disease duration: 12.2 ± 6.9 years) had focal dystonia,

Table 1 Mean age at onset of primary dystonia according to the site of onset and to gender

	All PTD cases		Women		Men	
Site of onset	*n*	Age	*n*	Age	*n*	Age
Cranial	238	56.3 ± 12.1[a]	174[b]	57.3 ± 11.2[a]	64	53.8 ± 14.0[a]
Blepharospasm	230	56.4 ± 11.9	170	57.2 ± 11.3	60	54.2 ± 13.3
Low face	8	54.5 ± 18.0	4	60.8 ± 9.0	4	48.3 ± 24.0
Cervical	101	41.1 ± 17.1	64	43.3 ± 17.6	37	37.4 ± 16.0
Laryngeal	38	47.7 ± 21.1	27	52.1 ± 20.3	11	36.7 ± 19.8
Upper limb	71	36.4 ± 17.3	22	28.5 ± 15.9	49[b]	39.9 ± 16.9
Lower limb	12	21.6 ± 16.3[c]	9	24.3 ± 18.0[c]	3	13.3 ± 6.1[c]
Total	460	48.3 ± 17.7	296	50.6 ± 17.3	164	44.1 ± 17.7

PTD, primary torsion dystonia.

[a]Both men and women with cranial onset had the highest age at onset ($P < 0.001$).

[b]Cranial onset was significantly more frequent in women and upper limb onset was significantly more frequent in men ($P < 0.001$).

[c]Both men and women with lower limb onset had the lowest age at onset ($P < 0.001$).

159 (34.5%, mean disease duration: 14.6 ± 9.4 years) had segmental dystonia and 32 (6.9%, mean disease duration: 25.5 ± 16.7 years) had a multifocal or generalized form. Progression occurred in a larger number of patients with early onset (75%) than in those with late onset (38%; $P < 0.0001$). As expected, early onset cases had a significantly longer disease duration ($P < 0.001$). Four hundred and forty-three patients, who had been followed-up for at least 5 years, were analysed to determine the predictive accuracy of age at onset towards generalization of dystonia. The best trade-off threshold was 32 years, yielding a sensitivity of 83% (20 of 24 patients with generalization were detected) and a specificity of 83% (349 of 419 cases without generalization were detected). The negative predictive value was 99%, indicating a negligible probability that patients with onset ≥32 years would progress to generalization.

DYT1 and non-DYT1 patients

Two hundred and forty-three patients were tested for the DYT1 GAG deletion. This mutation was found in 13 cases (5.4%), three of whom were sporadic. The remaining 10 DYT1-positive patients belonged to three families. The DYT1 GAG deletion was excluded in 23 index cases from a total of 39 familial index cases. The DYT1 mutation was found in seven of 17 patients with generalized dystonia (41%). All the DYT1-positive patients with generalized dystonia had limb onset: the upper limb in one case, the lower limb in six cases. The mean age at onset in DYT1 patients was 17.4 ± 13.7 years. The DYT1-positive cases presented generalized dystonia within a mean time of 5.6 ± 5.1 years from onset. DYT1-negative patients with generalized dystonia were 10: five of them had limb onset (the upper limb in two and the lower limb in three), three of them had cervical onset, in one onset was with laryngeal dystonia and in one with blepharospasm. Non-DYT1 patients had a mean age at onset of 23.9 ± 15.8 years (not significantly different from DYT1-positive cases) and a milder (although not statistically different) progression than DYT1-positive patients; generalization occurred on average 7.5 ± 5.8 years after onset.

The records of 58 sporadic adult-onset patients who were non-carriers of DYT1 mutation were considered appropriate for analysis of progression of dystonia; they were compared with those of 18 adult-onset probands who were non-carriers of DYT1 GAG deletion (Table 2).

Familial cases had lower mean age at disease onset (44.8 ± 11.2 years) than sporadic patients (53.5 ± 13.4; $P < 0.001$). The mean follow-up period was 15.3 ± 7.9 years for sporadic and 13.8 ± 11.2 for familial cases. Spread of dystonia to at least a second body site occurred more frequently in familial cases (77%) than in sporadic (46%; $P < 0.05$). Spread of symptoms occurred either in sporadic or in familial cases during the natural disease course, the number of sites involved by disease progression was significantly higher in familial cases ($P < 0.05$). The spread of symptoms was directly related to the duration of illness either in sporadic or in familial cases ($P < 0.001$) however, in sporadic cases the most relevant spread occurred during the first 10 years; in familial patients, instead, progressive spread of dystonia occurred throughout the disease course ($P < 0.05$).

Discussion

In the present study, prediction of progression to a generalized dystonia was specifically addressed. The data show that 32 years is the best threshold to predict

Site of onset	Sporadic dystonia			Familial dystonia		
	n	M/F	Age	*n*	M/F	Age
Cranial	37	10/27	58.2 ± 9.5	8	3/5	51.6 ± 9.10
Cervical	9	6/3	46.3 ± 13.4	6	2/4	37.0 ± 8.5
Laryngeal	3	1/2	50.7 ± 21.6	1	0/1	53
Upper limb	9	7/2	42.2 ± 16.2	3	2/1	39.3 ± 12.2
Lower limb	0	–	–	0	–	–
Total	58	24/34	53.5 ± 13.4	18	7/11	44.8 ± 11.2[a]

[a]Significantly different from mean age at onset of sporadic patients ($P = 0.0098$).

Table 2 Mean age at disease onset in cases with sporadic adult onset dystonia and in cases with adult onset familial dystonia who were non-carriers of DYT1 GAG deletion. Only the proband has been analysed in each dystonia family

generalization in a patient with dystonia. Patients aged 32 years or more at disease onset have a negligible probability to generalize, whereas generalization occurs in a sizable proportion of patients with onset before that age.

Hospital series have repeatedly reported that the frequency distribution of age at onset in dystonia is bimodal. Age-at-onset ranks stratify around two modes that are well divided by a single nadir, thus identifying two seemingly separate clusters of patients. The threshold separating these two clusters has been set variably in different series, based on the observed nadir (ranging from 15 to 35 years; Table 3). However, the prospective value of such retrospective clustering of patients, towards the prediction of the likelihood that dystonia may generalize in a single individual, has not been ascertained. A bimodal distribution of frequencies has also been observed in the present series; the modes are at 9 and 57 years and the nadir separating the two clusters of retrospective observations is at 21 years. Therefore, the present observation is in keeping with most of the previous studies, which have measured age intervals for the nadir encompassing approximately 21 years of age (Table 3). This confirms that the terminology used to distinguish early onset and late onset dystonia should use a threshold age of 21 years, as originally proposed by a consensus committee [1].

The comparison of the natural history in familial and sporadic cases showed that spread of symptoms occurred in both groups over time. Progression after 5, 10, 15, 20 or 25 years was more pronounced in familial PTD cases than in sporadic ones. Earlier evidence showed that most cases of either early onset or late onset dystonia present 'maximum progression of disability within the first 5–10 years after the onset of the illness' [12], or in the first 5 years after onset [3,13]. In the present series, this observation is confirmed for sporadic cases, but not for familial cases that show

Table 3 Retrospective series reporting the frequency distribution of age at disease onset in dystonia

Recruiting centers	Patients	Age at onset		Modes	Onset <21 (% cases)	Nadir	Reference
		Years	Distribution				
National Hospital (London)	72	1–59	Bimodal	0–10 and 41–50	66	21–30	[22]
St Barnabas Hospital (New York)	226	NA (mostly juvenile)	Bimodal	9 and 16–20	82	15	[34]
Columbia University (New York)	560	NA	Bimodal (for segmental dystonia)	6–10 for generalized dystonia and 50–60 for focal and segmental	27	~25	[23]
Columbia University (New York)	178	NA	Bimodal	9 and 55	NA	27	[35]
Institute of Psychiatry, King's College Hospital, National Hospital, Hospital for sick children (London)	107	4–67	Bimodal	5–10 and 45–50	65	30–35	[17]
Columbia University (New York)	160	4–74	Bimodal	0–10 and 31–40	58	21–30	[8]
Gemelli Hospital (Rome)	460	1–83	Bimodal	9 and 57	9.6	21	Present series

AJ, Ashkenazi Jewish; NJ, non-Jewish; J, Jewish; NA, not available.

constant progression even after several (up to 30) years of follow-up. A comparison of the spread of symptoms between sporadic and familial dystonia has been previously performed only in a North American study on early onset PTD, where no differences were found between the two groups [3]. The present report suggests that, in the Italian population, a more severe progression can be appreciated also several years after onset in familial dystonia cases. This is probably because of a specific genetic background. In keeping with this, it has been observed that dystonia can spread to new body parts even 30 years after onset in an Italian family with DYT13 dystonia [14].

In the present series, familial cases had earlier age at onset than sporadic patients, a difference mainly because of a lower age of patients with cervical onset. Some earlier studies failed to observe differences in the age at onset between familial and sporadic focal [15,16] or non-focal dystonias [17], whereas others are in keeping with the present observation [18,19]. Our series does not support, instead, differences in age at onset in upper limb dystonia; this confirms a previous study showing no differences in age at onset between familial and sporadic cases with writer's cramp [20].

In the present cohort primary cases accounted for 77.6% of the total population of dystonia patients, in keeping with earlier observations performed in other centers [21]. The clinical features of PTD patients in this series confirms that generalized dystonia has early onset and often starts in a lower limb. In addition, it has been observed that spread of symptoms occurs in a much larger number of patients with early onset than with late onset, confirming that age at disease onset is the most important prognostic factor [3,22,23]. The highest age at disease onset in this series was observed in patients with cranial presentation, whereas patients with onset in lower limbs had the lowest age. The frequency of familial cases observed in the present series is also in keeping with earlier reports [24,25], although it may be somewhat underestimated because of the low sensitivity provided by family history taking [26]. Indeed, other series describing a higher frequencies of familial occurrences have been reported [15–17].

The present registry revealed gender-related differences of age at disease onset in PTD subgroups classified by the site of onset. In PTD cases with cranial or laryngeal onset men were affected at a younger age than women; by contrast, in cases with upper limb onset age at onset was lower in women than in men. In addition, gender-related differences in the prevalence of PTD subgroups were observed. Cranial, cervical or laryngeal onset occurred more frequently in women than in men; upper limb onset was more frequent in men. These observations are in keeping with previous reports form England [27,28] and suggest that these clinical features are shared by other patients particularly amongst European population. These gender-related variations support the possibility that sex hormones play a role in the pathophysiology of dystonia [29,30].

A remarkable higher incidence of blepharospasm compared with other focal forms of dystonia has been reported in Italy, Spain and Japan [25,31–33]. The present series had no epidemiological objectives and may have been biased in part by referrals for botulinum toxin treatment; notwithstanding, it is interesting to remark that our patients with blepharospasm outnumbered those with other focal forms of dystonia.

In summary, the clinical features of sporadic dystonia cases appear remarkably heterogeneous in different series, with a number of consistent core features. This suggests that some still unmapped genes interact with an assortment of environmental factor to produce the varied clinical spectrum of sporadic dystonia.

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