SHORT REPORT

A family study on primary blepharospasm

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Background: Previous family studies provided evidence that blepharospasm (BSP) can aggregate in families but did not give accurate and reliable information on the characteristics and degree of familial clustering.

Aim: To evaluate the proportion of familial and non-familial BSP cases, the clinical expression of dystonia within families, the inheritance pattern, and the extent of penetrance.

Methods: The study was based on the examination of the first degree relatives of 56 probands with primary BSP.

Results: The 56 families produced a potential population of 436 first degree relatives of whom 296 were alive and 233 were examined. The proportion of index patients with at least one first degree relative affected by BSP, or adult onset dystonia other than BSP, was 27%. There was a remarkable degree of phenotypic variability of dystonia within families. Similar segregation ratios were calculated for probands' siblings and children. Under the assumption of autosomal dominant transmission of adult onset dystonia, penetrance was about 20%.

Conclusions: The findings of this family study are relevant for accurately counselling the families of patients with BSP and may help identify the most appropriate study design to explore genetic susceptibility in BSP.

Primary blepharospasm (BSP) is an adult onset focal dystonia characterised by involuntary contraction of the orbicularis oculi muscles.¹ Three family studies based on clinical series of patients with adult onset dystonia^{2–4} and six multigenerational adult onset dystonia families^{5–9} provided evidence that BSP can aggregate in families, but failed to give reliable information on the proportion of familial BSP cases (ranging from 12% to 29%),^{2–4} the clinical expression of dystonia within families (some studies^{3–6} reported that affected relatives tended to have the same type of dystonia as index patients, whereas others reported a more heterogeneous phenotype^{2,7–9}), the inheritance pattern, and the extent of penetrance.

In families of patients with BSP, linkage to known primary dystonia loci (DYT1, DYT6, DYT7, and DYT13) was excluded, and none of the families was large enough to allow the mapping of novel loci.^{5–7–9} Thus, valid information on the clinical expression of dystonia in the families of patients with BSP is essential for counselling families and planning the best strategy for exploring genetic susceptibility. We performed a family study based on a strict diagnostic scheme and examination of first degree relatives in a large and representative sample of patients with BSP.

SUBJECTS AND METHODS

Probands were identified from January 2002 to June 2003 among consecutive outpatients attending the neurology department of the University of Bari, Italy and living no

more than three hours' travelling distance from the centre. Because our centre serves various regions in southern Italy, this criterion ensured recruitment from a homogeneous geographical area. The local ethical committee approved our study. Inclusion criteria were a diagnosis of BSP, according to published criteria¹; age at first symptoms > 20 years¹; duration of disease greater than one year; and no other neurological abnormality except tremor associated with dystonia.¹ Exclusion criteria were features suggesting secondary dystonia—dystonia-plus and hereditary degenerative dystonia¹—and specific referral for familial dystonia.

Probands and their relatives were asked to participate in a family study on dystonia. They were told that neurological examination is the only valid means of ascertaining dystonia among relatives,¹⁰ even in apparently asymptomatic subjects. First degree relatives giving informed consent were examined at their homes by a trained physician who used a standardised protocol described elsewhere.¹⁰ Dystonia was diagnosed when slow dystonic movements and definitely abnormal postures occurred at rest or were activated by specific tasks.¹ Diagnosis of dystonia was not assigned to excessive blinking with no evidence of the Charcot's sign,¹¹ isolated apraxia of eyelid opening,¹² unusual tight hand gripping with writing or other manual activities,¹¹ shoulder elevation without significant limitation of shoulder movement,¹³ or isolated head/upper limb tremor with no signs of dystonia.¹⁴ According to the consensus statement of the Movement Disorder Society on Tremor,¹⁴ subjects presenting exclusively with persistent bilateral, largely symmetrical, postural, or kinetic tremor involving hands and forearms were given a diagnosis of essential tremor (ET).

Statistics was performed by means of the χ^2 test (Fisher's exact test for small sample sizes) and the Mann-Whitney U test. *p* Values < 0.05 were considered to be significant.

RESULTS

During the study period, 64 patients with BSP met the eligibility criteria. Of these 64 patients, 56 agreed to participate in our study, and eight did not (two patients with no living first degree relatives, four who reportedly disagreed with most relatives, and two who declined to explain the reasons for their refusal). Table 1 lists their demographic and clinical features.

The 56 families who took part in our study provided a potential population of 436 first degree relatives, of whom 296 were alive and 233 were examined. Examined relatives (133 women and 100 men; mean age, 52.5 years; age range, 20–90) and unexamined living relatives (22 women and 41 men; mean age, 51.4 years; age range, 12–81) significantly differed for sex (*p* = 0.003) but not for age (*p* = 0.64).

Dystonia was diagnosed in 18 of the 233 examined relatives from 15 families. Probands with and without affected relatives did not differ in their demographic or clinical features except for family size (mean, 10 (SD, 3.4) v

Abbreviations: BSP, blepharospasm; ET, essential tremor

Table 1 Clinical and demographic features of eligible probands with primary blepharospasm (BSP)

	Participating patients	Non-participating patients	p Value
Number of patients	56	8	
Men/women	20/36	5/3	0.29
Mean (SD) age (years)	63.9 (11.5)	65.8 (8.4)	0.62
Mean (SD) age at onset (years)	57.1 (12)	58 (9.7)	0.82
Mean (SD) years of schooling	5 (3)	5.2 (3.2)	0.86
No. of patients with eye symptoms (%)	24 (42%)	3 (37%)	0.92
No. of patients with geste antagoniste (%)	18 (32%)	2 (25%)	1.00
No. of patients with focal BSP as part of a segmental dystonia	43/13	5/3	0.66

The p values were assessed by the χ^2 test or the Mann-Whitney U test.

7.4 (3.5) members; $p < 0.05$). Table 2 lists the clinical features of family probands and their affected relatives. Disease duration was longer than five years (six to 14 years) in nine of 13 familial probands with focal BSP. Affected relatives were assigned a diagnosis of primary dystonia because neurological examination was otherwise normal, and no causes for dystonia could be detected on interview. Only three relatives were aware of dystonia and reported interference with daily living activities. The others were unaware of being affected by a medical condition and could not report age at dystonia onset.

Four relatives (three men aged 31, 55, and 71 years, and one woman aged 77 years) had persistent bilateral, largely symmetrical, postural ($n = 2$) or kinetic tremor ($n = 2$) involving hands and forearms. The duration of the tremor ranged from seven to 12 years. There was no evidence of rest tremor, parkinsonian or cerebellar signs, or dystonia.

Segregation analysis based on all affected relatives yielded similar ratios for siblings (10 of 111; 0.09) and offspring (eight of 108 > 20 years; 0.074). Only 22% of parents were alive but none was affected on examination. Under the assumption of autosomal dominant transmission, penetrance was calculated to be approximately 20%.

DISCUSSION

In our series, 15 of 56 BSP probands had at least one living first degree relative affected by adult onset dystonia. Except for family size, familial and non-familial BSP probands did not differ in their demographic/clinical features. The expression of dystonia varied within families, with relatives

suffering from focal BSP, oromandibular, cervical, and hand dystonia, and segmental craniocervical dystonia. Compared with previous studies,^{2,3,5,6} we found a more heterogeneous phenotypic appearance of dystonia within families. Owing to the cross sectional approach, some of the variation in the clinical expression of dystonia within families might have arisen from differences in disease duration. In adult onset focal dystonia, disease expression may change over time as a consequence of the spread of dystonia to adjacent body regions.¹ Factors influencing spread include site and age of dystonia onset, and disease duration.^{1,15} Two observations lend support to the heterogeneity of the dystonia phenotype within families of BSP probands. First, the long disease duration (six to 14 years) in nine of 13 familial probands with focal BSP allowed us to predict a lack of spread with reasonable certainty because focal BSP usually spreads during the initial five years and then stabilises.¹⁵ Second, nine affected relatives presented with cervical or hand dystonia, which show a low tendency to spread.¹

The frequency of adult onset dystonia among siblings and offspring supported an autosomal dominant transmission and reduced penetrance of about 20%. This was higher than previously thought (5%).¹⁶ Owing to the cross sectional approach, we could not provide recurrence risks taking time into account. Nevertheless, empirical recurrence risks (taken directly from segregation ratios) suggested that siblings of patients with BSP may have a one in 10 chance of having dystonia.

Our study has several strengths. First, we recruited a relatively large number of patients with BSP (56), whereas previous studies included no more than 16–29. Second, the participation rate among probands and living relatives was considerably higher than in most previous family studies.^{2,4} Third, we considered both patients with focal BSP and BSP as part of segmental dystonia as valid cases, whereas two earlier studies^{2,4} included only patients with focal BSP. Fourth, we based the dystonia status on clinical examination by trained neurologists using stringent diagnostic criteria. Unlike previous studies,^{2,4} we did not use self reported family histories to identify dystonia among unexamined relatives because this method may be highly insensitive and incurs the risk of misclassifying relatives.¹⁰ Finally, we rejected subtle motor findings presenting a diagnostic challenge^{11–13} and isolated postural tremor of the hands¹⁴ as phenotypic presentations of dystonia. In our sample four relatives presented exclusively with bilateral arm tremor, fulfilling the diagnostic criteria for ET.¹⁴ On this basis, the frequency of ET-like tremor among examined relatives was not higher than the prevalence of ET in the Italian and other populations.¹⁷ Therefore, the familial coexistence of adult onset dystonia and ET-like tremor may be coincidental.

Our study may also have limitations. As a service based study, it probably overestimated familial probands. However, we corrected for bias in case selection by recruiting most consecutive patients who met the eligibility criteria during our study period. Our case population was similar to population based series,^{18,19} and is thus probably representative of primary BSP. Our estimates were based on the examination of only 54% of all relatives, which is a common problem in late onset disorders. However, the high participation rate among living relatives (87.5%), and the fact that affected relatives resembled the Italian population of adult onset dystonia patients,^{18,19} argue against a large selection bias by non-response.

In conclusion, the improved methodology of our study provided us with more accurate information on the expression of dystonia in families of patients with BSP. About one fourth of patients with BSP attending a neurological centre may have at least one affected first degree relative. The

Table 2 Demographic and clinical features of familial index patients and their affected relatives

	Family probands	Affected relatives
Number of subjects	15	18
Men/women	6/9	5/13
Mean (SD) age (years) at study	66 (7.1)	52.5 (18.5)
Median (range) duration of disease (years)	7 (1–14)*	3 (1–10)†
Type of dystonia		
Focal blepharospasm	13	5
Focal oromandibular dystonia	–	1
BSP as part of segmental craniocervical dystonia	2	3
Focal cervical dystonia	–	6
Focal hand dystonia	–	3

*Longer than 6 years in 9 patients; †including only 3 relatives. BSP, blepharospasm.

finding that familial patients generally had larger sibships indicates the need for risk factor studies focusing on family history of dystonia to adjust for sibship size to avoid confounding. The heterogeneity of the dystonia phenotype suggests that families of patients with BSP may be susceptible to the development of adult onset dystonia rather than BSP alone. If family history results from genetic factors, the probable pattern of inheritance is autosomal dominant transmission with a reduced penetrance of about 20%. Overall, this information may be relevant for counselling families of patients with BSP and identifying the most appropriate study design to explore the genetic susceptibility of the condition.

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