Environmental risk factors and clinical phenotype in familial and sporadic primary blepharospasm

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ABSTRACT

Background: Although environmental and genetic factors may contribute to the etiology of blepharospasm, their relative contribution in causing familial and sporadic blepharospasm is unknown.

Methods: First-degree relatives of 122 patients with primary blepharospasm were examined with a validated 2-step diagnostic procedure, including a screening questionnaire and examination of some relatives. Examiners were blinded to the questionnaire data for family history of probands. Data for demographic and clinical features, prior ophthalmologic complaints, and nondecaffeinated coffee intake were collected from probands before family investigation.

Results: Dystonia was diagnosed in 27 relatives from 23 families (20% rate of family history for dystonia). No significant differences were found between familial and sporadic cases in the frequency of coffee drinking and eye diseases or in sex, age at onset, or tendency to spread. Multivariable conditional logistic analysis testing of 67 case patients and 127 family-matched unaffected siblings yielded a significant positive association between blepharospasm and prior eye diseases (adjusted odds ratio [OR] 2.5; 95% confidence interval [CI] 1.1–6.1; $p = 0.03$) and a significant inverse association between case status and ever coffee drinking (adjusted OR 0.23; 95% CI 0.1–0.8; $p = 0.02$).

Conclusions: The new information from this large family-based study on primary blepharospasm strongly supports eye diseases and coffee as risk factors for blepharospasm. The finding that the 2 environmental exposures exerted a similar influence on familial and sporadic blepharospasm, together with the convergent phenotypic expression in familial and sporadic cases, implies that familial and sporadic blepharospasm probably share a common etiologic background. ***Neurology***® **2011;77:631–637**

GLOSSARY

BSP = primary blepharospasm; **CI** = confidence interval; **ICC** = intraclass correlation coefficient.

Primary blepharospasm (BSP), one of the most common forms of late-onset dystonia, has a prevalence of 12–133 cases per million in various populations.[1] BSP is considered a multifactorial disorder to which environmental and genetic factors both contribute.[1]

Support for an environmental contribution comes from a few case-unrelated control studies indicating an association between BSP and diseases such as dry eye, blepharitis, and keratoconjunctivitis[2,3] or suggesting that coffee might protect against BSP development.[4]

Although the genes lending risk to primary BSP are not known, support for a genetic contribution comes from studies demonstrating that BSP can aggregate in families. These mostly described a few affected relatives frequently experiencing various focal dystonias and a lack of mendelian inheritance.[5] Because the frequency of familial dystonia is established in only 11%–30% of patients,[6–13] most cases of BSP are considered sporadic.

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Despite evidence that environmental and genetic factors may contribute to BSP, current research leaves several important issues unclear. For example, information is lacking on whether environmental factors contribute differentially to familial and sporadic BSP and on whether the familial and sporadic forms differ for phenotypic features thought to reflect the etiology of the disease. Furthermore, no study has yet examined the associations of environmental factors with BSP in a family-based setting. In this study, we screened first-degree relatives of a large sample of outpatients with BSP to evaluate whether familial and sporadic BSP differ in environmental contribution and phenotypic expression.

METHODS

Probands were identified during a 9-month period among consecutive outpatients attending 9 Italian tertiary referral centers for movement disorders and living no more than 3 hours' traveling distance from the center. Institutional review boards of each center approved the study. Inclusion criteria were a diagnosis of adult-onset dystonia presenting with BSP according to published criteria,[14] age at first symptoms >20 years, duration of disease >1 year, and no other neurologic abnormality except dystonia in nearby body sites and tremor in the same body part as dystonia. Exclusion criteria were features suggesting dystonia-plus or secondary and heredodegenerative dystonia.[14]

Family study. First-degree relatives completed a self-administered diagnostic questionnaire.[15] Relatives screening positive on the questionnaire were then examined at their homes by a trained physician using a standardized protocol including triggering maneuvers for dystonic movements or postures in apparently asymptomatic subjects. Subjects screening negative on the questionnaire and reporting none or a few years (<8 years in our validation sample) of schooling were also examined.[15] Examiners did not know whether the relatives they examined screened positive or negative on the diagnostic questionnaire.

The diagnosis of dystonia among relatives required the presence of slow dystonic movements and definitely abnormal postures appearing at rest or activated by specific tasks. Interobserver agreement on the diagnosis of dystonia at different body sites was evaluated by k statistics using video recordings from 20 patients with late-onset dystonia, 10 patients with movement disorders other than dystonia, and 10 healthy control subjects. According to the Landis classification, substantial (k index between 0.6 and 0.8) to almost perfect (k >0.8) interobserver agreement was obtained for the diagnosis of BSP (k = 0.81), oromandibular dystonia (k = 0.71), cervical dystonia (k = 0.82), laryngeal dystonia (k = 0.73), and hand dystonia (k = 0.75).

Familial vs sporadic BSP. Probands with a positive family history of dystonia and their relatives with BSP were compared with the probands with sporadic BSP. Secondary analysis was done, excluding the relatives with BSP from the familial group. A structured interview was used to collect data about age, sex, years of schooling, age at the onset of dystonia, duration of disease, and time to spread of dystonia from the eyelids to other body sites. In a test-retest repeatability study, a sample of 38 patients with BSP showed high repeatability in recalling age at BSP onset 6 months after the first interview (intraclass correlation coefficient [ICC] = 0.87; $p < 0.0001$). Although information on date of spread (approximated to 1 year) was supported by information from medical records when available, in about one-half of the patients, the date of spread was ascertained by our own observation at follow-up visits.

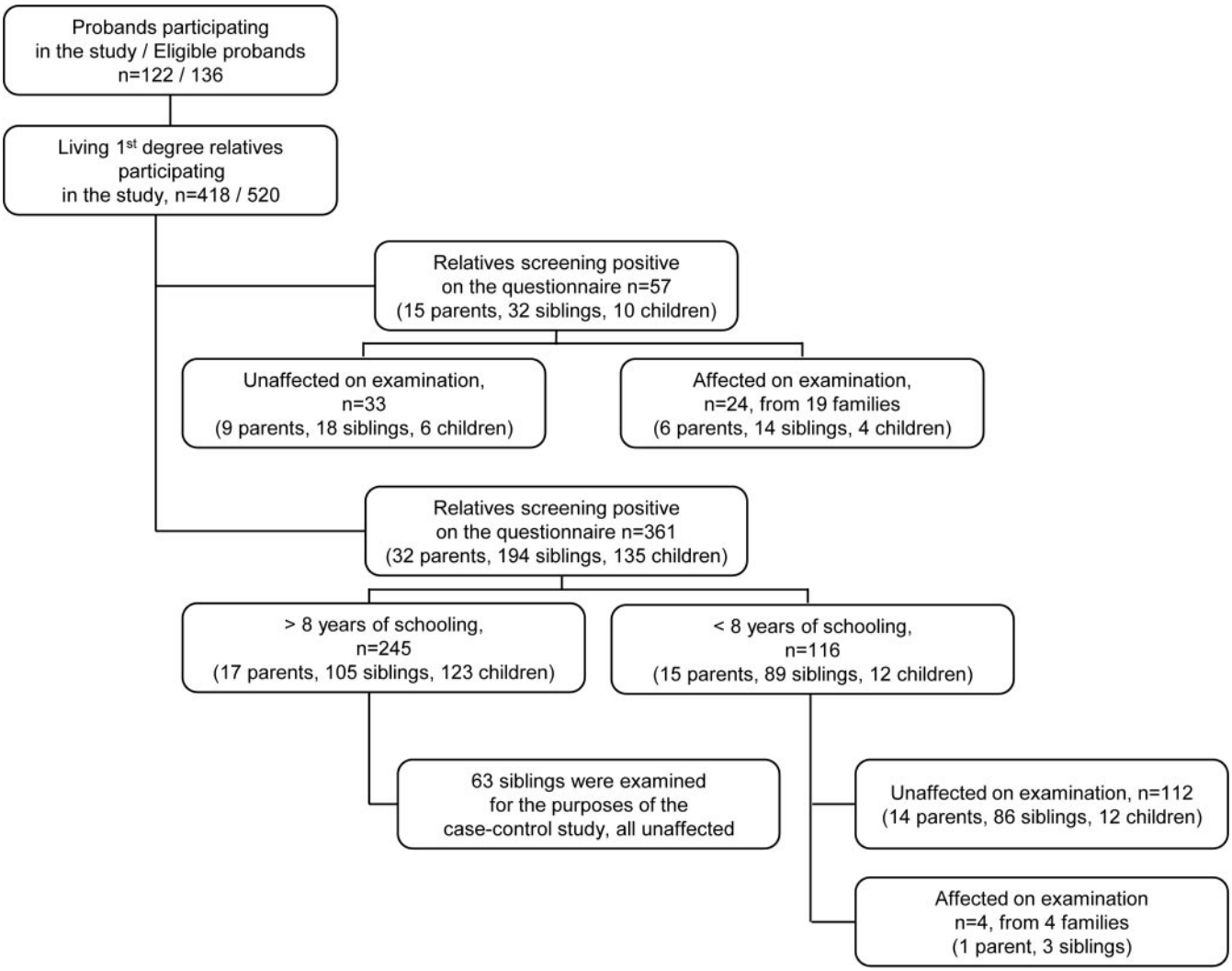
Ophthalmologic complaints were assessed with a previously validated questionnaire yielding high sensitivity and specificity in detecting diseases of the anterior ocular segment.[3] The questionnaire assessed whether subjects ever felt their eyes were dry, ever had a gritty, sandy, or burning sensation, or ever had red eyes. If the answer to any of these questions was yes, the interviewer recorded the year at onset of the eye problem. Risk factor analysis included only eye disease starting before the reference age, the age at BSP onset for probands, and the youngest age at onset of BSP symptoms in the family for unaffected siblings.

Nondecaffeinated coffee intake was assessed as reported[4] by asking the subject "Have you ever drunk nondecaffeinated coffee?" Participants who responded yes were asked whether they began and, if applicable, quit drinking coffee before the reference age. According to the status at the reference age, participants were classified as never drinkers, ex-drinkers, or current drinkers. In a test-retest repeatability study, self-reported data on coffee drinking status at the reference age showed high repeatability (ICC = 0.85; $p < 0.0001$), whereas repeatability was <0.80 for the average number of cups per day (ICC = 0.67; $p < 0.05$) and years of coffee drinking (ICC = 0.57; $p < 0.05$). To check for possible confounding, we assessed cigarette smoking in the same way as coffee drinking. Information on clinical features and environmental exposures from probands was obtained before family data were collected.

Family-based case-control study. We selected sibships containing a BSP proband or a relative with BSP and at least one unaffected control sibling who was older than the age at onset of BSP in his or her affected sibling. Unaffected siblings who had not been examined with the 2-step procedure underwent clinical examination to be sure that they were really unaffected. In selected sibships, environmental risk factors were assessed as detailed in the preceding section by a trained physician for each center. Assessors were not blinded to the affected/unaffected status because it is difficult to blind a patient with dystonia from a healthy subject, but the assessors were unaware of the study hypothesis.

Statistical analysis. Data are means ± SD unless otherwise specified. Differences between groups were examined using the χ^2 test and Mann-Whitney U test. Linear regression models (adjusted by age, sex, education, referral, and ever smoking) were used to test the relationship of age at BSP onset (continuous variable) to environmental factors and family history of dystonia. Cox proportional hazards regression models with the endpoint time to spread were used to estimate the relationship between spread and family history of dystonia. Patients without spread were included in the survival function for the entire length of time they participated in the study, and their data were censored beyond that time. Statistical power was assessed according to Parmar and Machin.[16] Conditional logistic regression models with unequal case/control ratios were used to assess the relationships of prior eye diseases and coffee intake to case or control status. Coffee intake was also analyzed, stopping the onset of exposure 10 years before the reported onset of disease. Case probands and unaf-

Figure 1 Family study procedure



fected control siblings were matched by family to account for familial correlations in the data. Sex was analyzed as a categorical variable and age and years of schooling as continuous variables; p values <0.05 were considered statistically significant. Data were analyzed with the Stata 11 package.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Board of the University of Bari (IRB no. 1274/CE) in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. Informed consent was obtained for all participants before inclusion in the study.

RESULTS

Family study. During the study period, 136 patients presenting with BSP (96 with focal BSP) met the eligibility criteria, and 122 (91%) agreed to participate in the study. There were 35 men and 87 women aged 67.3 ± 10.5 years. Age at BSP onset was 57.2 ± 10.6 years.

Participating patients provided a population of 520 living first-degree relatives, of whom 418 (80%) (47 parents, 226 siblings, and 145 children) underwent screening for dystonia. The screening procedure (figure 1) identified 27 relatives with dystonia (12 men and 15 women; age at dystonia onset 51 ± 11.7 years) from 23 of 122 families (18.8%). No causes of secondary dystonia were found in the affected relatives who had focal BSP (n = 16), BSP as part of a segmental dystonia (n = 2), cervical dystonia (n = 6), and hand dystonia (n = 3).

Familial and sporadic BSP. Patients who had a positive family history of dystonia (23 probands and 18 relatives affected by BSP), and the 99 probands who did not, had comparable age, sex, education, and age at BSP onset (table 1). The study had an estimated 90% chance of detecting a 5-year difference in age at BSP onset between familial and sporadic BSP groups with $\alpha = 0.05$ (2-sided). Likewise, the crude frequency of spread was similar in familial and sporadic cases, and multivariable Cox analysis confirmed that the likelihood of BSP spread was no greater in either

Table 1 Demographic and clinical features and frequency of prior eye diseases and coffee drinking in patients who had a positive family history of dystonia and those who did not

	Positive family history	Negative family history	*p* Values
No. patients	41	99	
Mean age, y, mean ± SD	65.8 ± 10.7	67.5 ± 10.8	0.4
Sex, M/F	14/27	27/72	0.5
Schooling, y, mean ± SD	6.5 ± 4.6	6.9 ± 4.1	0.6
Age at onset of blepharospasm, y, mean ± SD	57.1 ± 13.4	56.8 ± 9.8	0.9
Blepharospasm as part of a segmental dystonia, n (%)	16 (39)	36 (36)	0.9
Prior eye disease, n (%)	14 (39)	36 (34)	0.9
Ever coffee drinking, n (%)	30 (72)	69 (69)	0.8

of the 2 groups (adjusted hazard ratio 0.97, 95% confidence interval [CI] 0.45–2.1; $p = 0.9$). The study had an 82% chance of detecting a 2-fold difference in the risk of spread between familial and sporadic BSP with $\alpha = 0.05$ (2-sided). Overall, similar findings were obtained by excluding the 18 BSP relatives and analyzing the 23 BSP probands with a family history of dystonia alone (data not shown).

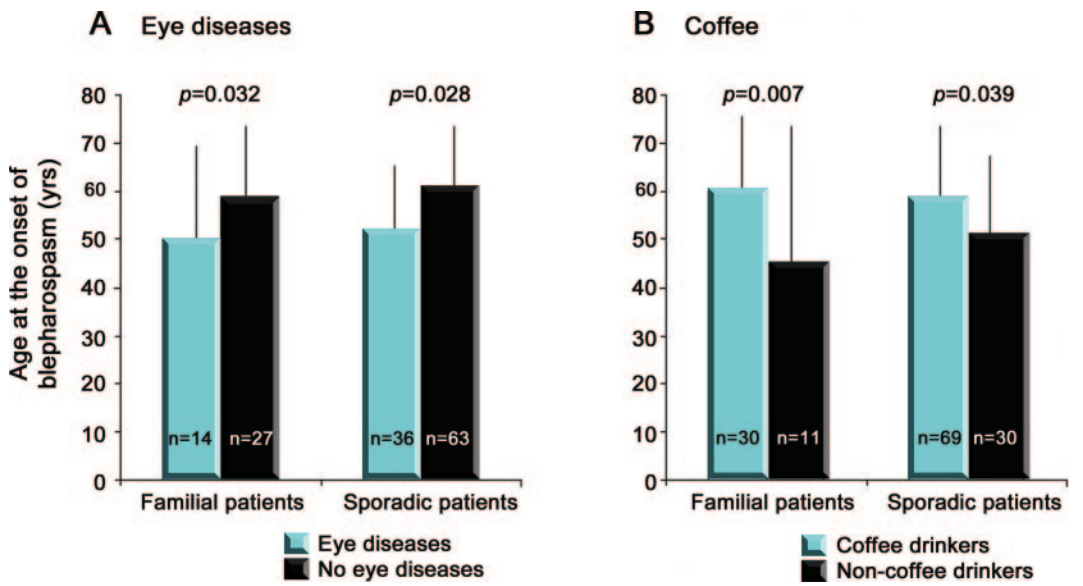
Ocular symptoms suggesting dry eye, blepharitis, or keratoconjunctivitis were reported before dystonia onset by 50 of 140 patients with BSP. Mean time elapsing between onset of eye symptoms and onset of BSP was 1.8 ± 0.7 years. In 32 of 50 patients (64%), the diagnosis was confirmed by an ophthalmologist, and in 14 of 50 patients, ocular symptoms went into remission after BSP onset. Ocular symptoms were seen at a similar frequency in patients with familial and sporadic BSP (14 or 41 vs 36 of 99; $p = 0.9$).

Of the 140 patients with BSP, 99 were ever coffee drinkers at BSP onset, of whom 14 were ex-drinkers. Patients with familial and sporadic BSP included similar percentages of ever coffee drinkers (30 of 41 vs 69 of 99; $p = 0.8$) and ex-drinkers (6 of 41 vs 8 of 99; $p = 0.4$).

Multivariable linear regression analysis yielded a significant relationship between age at BSP onset and eye diseases and coffee intake, so that the presence of eye diseases was associated with a 3.4-year reduction in age at BSP onset (adjusted regression coefficient −3.4; 95% CI −7.4 to −0.98; $p = 0.045$) and coffee was associated with a 5.7-year increase in age at onset (adjusted regression coefficient 5.7; 95% CI 0.89 to 10.5; $p = 0.02$). No relationship was found between age at BSP onset and family history of dystonia (adjusted regression coefficient −0.79; 95% CI −5.9 to −4.3; $p = 0.76$). No significant interaction terms were calculated between eye diseases and family history of dystonia ($p = 0.35$) and coffee and family history of dystonia ($p = 0.27$). In both familial and sporadic cases, patients who reported prior eye diseases consistently had a lower age at BSP onset than those who did not (figure 2A), whereas patients who drank coffee had a higher age at BSP onset than those who did not (figure 2B).

Eye diseases and coffee were not associated with differences in sex distribution or tendency to spread in patients with familial and sporadic cases,

Figure 2 Effect of prior eye diseases (A) and coffee drinking (B) on age at the onset of blepharospasm (mean ± SD years) in patients with familial and sporadic blepharospasm



The number of patients in each group is indicated in the graphs.

Table 2 Conditional logistic regression analysis for 67 case patients with blepharospasm vs their 127 unaffected control relatives

Variable	Case patients (n = 67)	Unaffected siblings (n = 127)	Odds ratio[a] (95% confidence interval); p value	
			Univariable analysis	Multivariable analysis
Eye diseases	20	25	1.9 (0.9–4.2); 0.09	2.6 (1.1–5.9); 0.03
Ever coffee drinkers	54	113	0.24 (0.1–0.59); 0.002	0.19 (0.1–0.53); 0.001

[a] Adjusted by age, sex, education, referral, ever smoking, and family history of dystonia.

but the comparisons lacked statistical power (data not shown).

Family-based case-control study. Sixty-seven sibships were selected, thus allowing the comparison of 67 patients with BSP and 127 unaffected siblings. The 2 groups had similar age (66.7 ± 11.7 vs 64.8 ± 14.1 years; $p = 0.2$), sex (63 women and 34 men vs 104 women and 69 men; $p = 0.5$), and years of schooling (6.4 ± 2.7 vs 5.9 ± 3.2 years; $p = 0.45$). Patients with BSP who participated in the case-control study and those who did not had comparable frequency of family history of dystonia (11 of 67 vs 12 of 55; $p = 0.6$) and other clinical features (data not shown).

Prior ocular symptoms were reported by 20 of 67 case patients and 25 of 127 control siblings ($p = 0.002$). Case patients included fewer ever coffee drinkers than control siblings (54 of 67 vs 113 of 127, $p = 0.012$), whereas case and control groups included similar percentages of ever smokers (18 of 67 vs 45 of 127; $p = 0.7$). Multivariable conditional logistic regression analysis (table 2) showed that prior eye diseases were more frequent and ever coffee drinking was less frequent in patients with BSP than in control relatives. Both associations were independent of age, sex, years of schooling, referral, ever smoking, and family history of dystonia (table 2). The interaction terms between eye diseases/coffee and family history of dystonia did not reach significance. Stratification by family history of dystonia yielded small groups, and the interaction analysis lacked power (data not shown). Similar results were obtained when coffee exposure was stopped 10 years before the reported onset of disease (adjusted odds ratio 0.2; 95% CI 0.1 to 0.8; $p = 0.02$).

DISCUSSION What distinguishes this study from others is that instead of conducting a conventional family-based study to identify patients with a family history of dystonia and affected relatives and comparing their clinical phenotypes, we also assessed the potential environmental risk factors for BSP suggested by previous case-unrelated control studies in a family-based setting. Because affected and unaffected family members are more likely than unrelated case-control sets to be overmatched for environmental exposures and lifestyles, the comparison between case patients and age-matched unaffected relatives may obscure weak associations between environmental factors and the disease and give support to influential associations. The opposite influence exerted by eye diseases and coffee on age at BSP onset, together with the associations of BSP with prior eye diseases and coffee drinking (but not with cigarette smoking) we observed by comparing patients with BSP and unaffected siblings, suggests that the association of BSP with these environmental exposures is presumably unaffected by confounding familial influences. This finding strongly supports eye diseases and coffee as risk modifiers for BSP.

A further new finding in this family-based study concerns the overlapping phenotypic clinical features, probably reflecting the etiology of BSP (age at onset, sex distribution, and tendency to spread) in familial and sporadic BSP. Previous family studies could not address this issue or provided unreliable data on age at onset of familial and sporadic late-onset dystonia, probably owing to various design flaws. Among these were the small size of the enrolled samples, a limitation that might have diminished measurement accuracy[6,7,12,13]; the ascertainment of family history of dystonia by proband interview,[8–11] a method that yields lower diagnostic sensitivity and specificity in detecting affected relatives than directly examining at risk relatives[17]; and, finally, assigning in some studies a diagnosis of dystonia to relatives with subtle motor signs without definite signs of dystonia.[8,13]

The convergent phenotypic expression may imply that familial and sporadic BSP share a common etiologic background. This implication receives support also from the comparable frequency and the similar influence exerted by eye diseases and coffee on age at BSP onset in familial and sporadic cases. Our data are not sufficient to determine whether the phenotypic similarities between familial and sporadic BSP are also the expression of a similar genetic burden. In keeping with our hypothesis that familial BSP etiologically resembles sporadic BSP is the observation that in DYT1 dystonia, another form of primary dystonia, patients with familial and sporadic cases share the causative mutation in the *DYT1* gene and also major clinical features.[18–20]

A retrospective study may be subject to bias that our study design and procedures avoided or minimized. First, recruiting consecutive patients in a multicenter setting gave a case series resembling the general population of cases in Italy,[1] thus minimizing a selection bias due to recruitment from tertiary referral centers. Second, we applied stringent criteria for diagnosing dystonia among relatives, and the satisfying levels of interobserver agreement on the diag-

nosis of dystonia at different body sites also minimized an observer bias from misclassifying affected or unaffected relatives. The 20% frequency of familial dystonia found in this study is consistently within the range of estimates from the most valid surveys.[6,7,12,13] The heterogeneity of dystonia among relatives of patients with BSP is also consistent with prior studies.[21] Third, in the present and previous studies,[22] we showed that self-reported age at dystonia onset may be reliably determined from retrospective reports in primary late-onset dystonia. Fourth, we assessed environmental risk factors suggested by previous case-unrelated control studies even though we cannot exclude the possibility that other unknown environmental factors differentially contribute to familial and sporadic BSP. Fifth, recall bias could have been a concern in unaffected siblings given that case patients might be more aware of possible risk factors for disease. This bias might have affected the association with eye diseases rather than the inverse association with coffee drinking. The frequency of ophthalmologic complaints preceding BSP in our sample was close to the frequency of the exposure in the general population of BSP, and the association of eye diseases and BSP was independent of education, an important determinant of a subject's awareness of the disease and likelihood of seeking medical attention. The high frequency of coffee intake in our sample reflects the common coffee drinking habit among people living in Italy. We also consider bias caused by the assessors being unblinded to the case or control status unlikely insofar as the assessors were unaware of the study hypothesis. Finally, the analysis of coffee drinking would have been more informative if coffee intake had been assessed quantitatively to check for a dose-response effect. Owing to the few ex–coffee drinkers, however, this group could not be analyzed separately, and the reliability of retrospective assessed quantitative measures of exposure (cups per day and years of coffee intake) was poor. Although patients with BSP might have avoided coffee drinking because this habit can intensify involuntary spasms, stopping the onset of exposure 10 years before the reported onset of disease left the results unchanged, thus going against a cause-and-effect bias.

Overall, the new information from the largest family study conducted on BSP so far shows that familial and sporadic BSP share the phenotypic presentation. This finding, together with the similar influence exerted by eye diseases and coffee on age at BSP onset in familial and sporadic groups, implies that familial and sporadic BSP probably share a common etiologic background. Our study also strengthens eye diseases and coffee as risk-modifying factors for BSP regardless of familial influences. Candidate gene studies should therefore include these exposures as covariates.

AUTHOR CONTRIBUTIONS

Dr. Defazio: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision, and obtaining funding. Dr. Abbruzzese: drafting/revising the manuscript, study concept or design, and analysis or interpretation of data. Dr. Aniello: drafting/revising the manuscript and acquisition of data. Dr. Bloise: drafting/revising the manuscript and acquisition of data. Dr. Crisci: analysis or interpretation of data and acquisition of data. Dr. Eleopra: drafting/revising the manuscript and analysis or interpretation of data. Dr. Fabbrini: drafting/revising the manuscript and analysis or interpretation of data. Dr. Girlanda: drafting/revising the manuscript, study concept or design, and analysis or interpretation of data. Dr. Liguori: drafting/revising the manuscript and analysis or interpretation of data. Dr. Macerollo: drafting/revising the manuscript and acquisition of data. Dr. Marinelli: drafting/revising the manuscript, contribution of vital reagents/tools/patients, and acquisition of data. Dr. Martino: drafting/revising the manuscript, analysis or interpretation of data, and acquisition of data. Dr. Morgante: drafting/revising the manuscript and acquisition of data. Dr. Santoro: drafting/revising the manuscript, study concept or design, and analysis or interpretation of data. Dr. Tinazzi: drafting/revising the manuscript and analysis or interpretation of data. Dr. Berardelli: drafting/revising the manuscript, study concept or design, and analysis or interpretation of data.

DISCLOSURE

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