



Influence of coffee drinking and cigarette smoking on the risk of primary late-onset blepharospasm: evidence from a multicentre case-control study

G Defazio, D Martino, G Abbruzzese, P Girlanda, M Tinazzi, G Fabbrini, C Colosimo, M S Aniello, L Avanzino, M Buccafusca, G Majorana, C Trompetto, P Livrea and A Berardelli

J. Neurol. Neurosurg. Psychiatry published online 19 Jun 2007;
doi:10.1136/jnnp.2007.119891

Updated information and services can be found at:
<http://jnnp.bmj.com/cgi/content/abstract/jnnp.2007.119891v1>

These include:

Rapid responses

You can respond to this article at:
<http://jnnp.bmj.com/cgi/eletter-submit/jnnp.2007.119891v1>

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

Online First contains unedited articles in manuscript form that have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Online First articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Online First articles must include the digital object identifier (DOIs) and date of initial publication.

To order reprints of this article go to:
<http://www.bmjjournals.com/cgi/reprintform>

To subscribe to *Journal of Neurology, Neurosurgery, and Psychiatry* go to:
<http://www.bmjjournals.com/subscriptions/>

SHORT REPORT

Influence of coffee drinking and cigarette smoking on the risk of primary late onset blepharospasm: evidence from a multicentre case control study

G Defazio, D Martino, G Abbruzzese, P Girlanda, M Tinazzi, G Fabbrini, C Colosimo, M S Aniello, L Avanzino, M Buccafusca, G Majorana, C Trompetto, P Livrea, A Berardelli

J Neurol Neurosurg Psychiatry doi: 10.1136/jnnp.2007.119891

Prior coffee and smoking habits were investigated in a multicentre case control study involving 166 patients presenting with primary late onset blepharospasm (BSP), 228 hospital control patients with primary hemifacial spasm and 187 population control subjects from five Italian centres. Information on age at disease onset, smoking and coffee drinking status at the reference age and average number of cups of coffee drunk/cigarettes smoked per day reached high and similar test-retest reproducibility in case and control patients. Unadjusted logistic regression analysis yielded a significant inverse association of prior coffee drinking and cigarette smoking with case status for the control groups. After adjustment for age, sex, referral centre, disease duration, years of schooling and ever coffee drinking/cigarette smoking, as appropriate, the smoking estimate lacked significance whereas the association of coffee intake and BSP did not (cases vs hospital control patients: OR 0.37 (95% CI 0.20 to 0.67); cases vs population control subjects: OR 0.44 (95% CI 0.23 to 0.85)). The strength of the inverse association between BSP and coffee intake tended to increase with the average number of cups drunk per day. There was a significant correlation between age of BSP onset and number of cups per day (adjusted regression coefficient 1.73; $p=0.001$) whereas no correlation was found with number of packs of cigarettes per day. Coffee drinking may be inversely associated with the development of primary BSP and this association may partly depend on the amount consumed.

The aetiology of primary blepharospasm (BSP), a common late onset dystonia,¹ probably reflects combined genetic and environmental factors.^{2,3} An exploratory case control study found a protective association between late onset dystonia and cigarette smoking.⁴ Owing to multiple testing, this study was liable to a higher risk of false results than ad hoc hypothesis testing studies. In addition, the study did not examine some potential confounders, including coffee. We therefore designed an ad hoc case control study investigating the role of lifetime coffee and cigarette habits on the risk of primary BSP.

METHODS

A total of 166 outpatients with primary BSP, diagnosed according to published criteria⁵ (131 with focal BSP and 35 with BSP as part of a segmental dystonia), were consecutively recruited at five Italian centres over a 12 month period. Cases were frequency matched on 5 year age strata, sex and referral centre to 228 outpatients with primary hemifacial spasm⁶ (hospital controls) and 187 patients' relatives (population controls), both attending the participating centres during the study period. Case and control individuals, unaware of the

study hypotheses, were asked to participate in a study on lifestyle habits approved by the ethics committee.

In each centre, a trained interviewer, not blinded to the case/control status but unaware of the study hypotheses, collected relevant demographic/clinical information. Participants were asked: "Have you ever drunk non-decaffeinated coffee or smoked cigarettes?". Subjects who responded "yes" were asked when they began and, if applicable, whether they quit smoking/drinking coffee before the reference age. This was the age of onset of dystonia or hemifacial spasm for case and hospital control patients, respectively. The reference age of the population control subjects was obtained by subtracting the average disease duration of case subjects included in the corresponding age stratum from the age of the control subject. The number of years of coffee drinking/smoking, and the average daily number of cups of coffee/packs of cigarettes (1 pack = 20 cigarettes) were also recorded. Repeatability of self reported data was checked 1 year (± 2 months) after the first interview in a random sample of case and hospital control patients. Cohen's kappa coefficients,⁷ intraclass correlation coefficients (ICCs),⁸ χ^2 test, one way ANOVA and the post hoc test, and logistic and linear regression analysis were performed by STATA8 where appropriate. A p value <0.05 was considered significant. Study power was calculated using the equation for a case control study with an unequal case/control ratio reported by Schlesselman and Stolley,⁹ assuming a 50% decrease in the risk of developing dystonia with $\alpha = 0.05$ (two sided).

RESULTS

Test-retest study

The sample included 33 cases and 34 hospital control patients, comparable with the overall sample for age, sex, education and disease duration (not shown). Case and control subjects showed high (>0.80)¹⁰ and comparable repeatability in recalling age of disease onset (cases, ICC = 0.93, $p<0.0001$; control patients, ICC = 0.87, $p<0.0001$), coffee status (cases, $k = 0.89$, $p<0.0001$; control patients, $k = 0.87$, $p<0.0001$) and smoking status (cases, $k = 0.90$, $p<0.0001$; control patients, $k = 0.93$, $p<0.0001$) at the reference age as well as the average number of cups/day (cases, ICC = 0.89, $p<0.0001$; control patients, ICC = 0.85, $p<0.0001$) and packs/day (cases, ICC = 0.95, $p<0.0001$; control patients, ICC = 0.92, $p<0.0001$). Repeatability consistently differed or was <0.80 for years of cigarette smoking (cases, ICC = 0.90, $p<0.0001$; control patients, ICC = 0.67, $p<0.05$) and years of coffee drinking (cases, ICC = 0.57, $p<0.05$; control patients, ICC = 0.44, $p<0.05$). These variables were therefore excluded from data analysis.

Abbreviations: BSP, blepharospasm; ICC, intraclass correlation coefficient; PD, Parkinson's disease

Table 1 Results of univariable and multivariable logistic regression analysis on ever coffee drinking and ever cigarette smoking

	Case subjects (missing data)	Control subjects (missing data)	Univariable model OR (95% CI), p value	Multivariable model OR (95% CI), p value
Cases (n = 166) vs hospital control patients (n = 228)				
Ever coffee drinking	122 (5)	199 (5)	0.38 (0.22 to 0.66), 0.001	0.37 (0.20 to 0.67) 0.001
Ever cigarette smoking	52 (3)	110 (2)	0.51 (0.33 to 0.77), 0.002	0.64 (0.38 to 1.2) 0.2
Cases (n = 166) vs population control subjects (n = 187)				
Ever coffee drinking	122 (5)	166 (0)	0.38 (0.21 to 0.69), 0.002	0.44 (0.23 to 0.85) 0.015
Ever cigarette smoking	52 (3)	82 (0)	0.59 (0.38 to 0.94), 0.03	0.77 (0.44 to 1.34) 0.36

The multivariable model included age, sex, duration of disease, referral centre, years of schooling, ever coffee drinking and ever cigarette smoking. Case and control subjects for whom information was missing (in parenthesis) were excluded from the analysis.

Case control study

In the whole sample, participation rate was 100% among cases and hospital control subjects, and 94% among population controls. Cases and the hospital and population control groups had similar ages (mean 66.4 (SD 9.2) vs 64.9 (12.1) vs 66.7 (10) years; one way ANOVA: $p = 0.16$), sex distributions (53 men/113 women vs 90 men/138 women vs 58 men/129 women; χ^2 test, $p = 0.14$) and disease durations (mean 8.7 (SD 6.7) vs 8.8 (6.5) years; $p = 1.0$) but cases were less educated than hospital and population controls (mean years of schooling 6.2 (SD 3.8) vs 7.4 (4.3) vs 8.2 (4.9) years; one way ANOVA: $p < 0.001$) and included fewer coffee drinkers and cigarette smokers (table 1).

Four per cent of cases, 4% of the hospital control group and 5% of the population control group were past coffee drinkers ($p = 0.96$); 15% of cases, 22% of the hospital control group and 17% of the population control group were past smokers ($p = 0.2$). Stratifying cases by disease duration showed no increase in the relative frequency of the exposures across strata as disease duration increased (not shown).

Univariable logistic regression analysis, referred to the reference age, yielded a significant inverse association of ever coffee drinking and cigarette smoking to BSP (table 1). Multivariable analysis (including smoking, coffee drinking, age, sex, referral

centre, disease duration and years of schooling) confirmed the inverse association with coffee but there was a lack of association with smoking (table 1). Similar results were obtained for current coffee drinking/smoking alone (not shown). Study power estimates for ever smoking were 91% and 88% for the hospital and population control groups, respectively. There was no significant interaction between coffee drinking and cigarette smoking (not shown). Logistic regression analysis, referred to 10 years before disease onset, gave similar results. As illustrative examples, the adjusted OR in the cases versus the hospital control group were 0.40 (95% CI 0.22 to 0.71) for ever coffee drinking and 0.66 (95% CI 0.39 to 1.2) for ever smoking.

Cases reported a significantly lower mean number of cups of coffee/day than hospital and population controls (1.8 (SD 0.91) vs 2.32 (1.37) vs 2.44 (1.22); one way ANOVA: $p < 0.0001$). In contrast, case and control individuals reported a similar mean number of packs/day (0.92 (0.76) vs 0.81 (0.57) vs 0.79 (0.52); one way ANOVA: $p = 0.48$). Assuming never coffee drinking/smoking as a reference and stratifying by the median number of cups/packs per day, the strength of the inverse association of BSP with coffee tended to increase with the amount consumed whereas no significant relationship was observed with packs/day (table 2). Similar results were obtained for current coffee drinking/smoking alone (not shown).

Table 2 Relationship between ever coffee drinking/cigarette smoking and dystonia, analysed according to the median number of cups of coffee/packs of cigarettes per day

	Cases (%)	Control subjects (%)	Adjusted OR (95% CI), p value
Case vs hospital control subjects			
Ever coffee drinking			
Never	39 (24)	24 (11)	1 (reference)
≤ 2 cups/day	97 (58)	121 (52)	0.44 (0.26 to 0.80), 0.009
> 2 cups/day	25 (15)	78 (34)	0.23 (0.11 to 0.48), <0.0001*
Missing data	5 (3)	5 (2)	
Ever cigarette smoking			
Never	111 (67)	116 (51)	1 (reference)
≤ 0.75 packs/day	29 (18)	61 (27)	0.68 (0.38 to 1.3), 0.2
> 0.75 packs/day	22 (13)	44 (19)	0.58 (0.3 to 1.2), 0.13
Missing data	3 (2)	7 (3)	
Case vs population control subjects			
Ever coffee drinking			
Never	39 (24)	20 (11)	1 (reference)
≤ 2 cups/day	97 (58)	105 (56)	0.49 (0.24 to 0.99) 0.046
> 2 cups/day	25 (15)	57(33)	0.19 (0.1–0.45), <0.0001*
Missing data	5 (3)	0	
Ever cigarette smoking			
Never	111 (67)	105 (56)	1 (reference)
≤ 0.75 packs/day	29 (18)	48 (26)	0.93 (0.5 to 1.8), 0.8
> 0.75 packs/day	22 (13)	34 (18)	0.72 (0.4 to 1.6), 0.4
Missing data	3 (2)	0	

OR were adjusted for age, sex, referral centre, duration of disease, years of schooling and ever coffee drinking/cigarette smoking, as appropriate.

*t test for trend.

Linear regression analysis yielded a statistically significant relationship between age of onset of BSP and number of cups/day (adjusted regression coefficient, 1.73; 95% CI 0.71 to 2.75; $p = 0.001$) but not to number of packs/day (adjusted regression coefficient, 0.33; 95% CI -2 to 1.3 ; $p = 0.69$). The adjusted coefficient of determination for coffee was 0.68, implying a moderately strong linear relationship.

DISCUSSION

Our multivariable analysis yielded a significant inverse association between BSP and coffee drinking. We also found an unadjusted inverse association with smoking that lacked significance after adjusting for potential confounders, despite the satisfactory power of the study and inclusion in the multivariable modelling of a number of variables that was adequate to the size of the case/control samples.⁹

A retrospective case control study may be subject to bias but we believe that our study design/procedures avoided or minimised bias. Recruiting consecutive BSP patients in a multicentre setting gave a case series resembling the general population of cases.¹⁻⁵ In the control groups, both of which were unselected in terms of the exposures of interest, the frequency of coffee drinking/cigarette smoking was similar to the Italian population for this age group.¹¹⁻¹² The hospital control population almost matched the BSP patients in terms of degree of medical surveillance required, clinical features and disease duration, which made differential recall unlikely. Recall bias could have been a concern in healthy controls¹³ but, if this were the case, the findings would have been opposite to those reported. The high and similar reproducibility found for self reported information in cases and control patients minimised the possibility of differential misclassification of exposure status. Although repeatability could not be checked in the population control subjects, we have no reason to suspect a lower quality of information in this group. Bias caused by the assessors being unblinded to the case/control status was also unlikely as the assessors were unaware of the study hypotheses. Patients with BSP may have avoided coffee or smoking because these habits can intensify involuntary eyelid spasms. If there were the case, however, the same would apply to hospital control subjects suffering from a condition resembling BSP, but yet it did not. Finally, stopping the exposure 10 years before the reported onset of disease did not change our results, which goes against a "cause and effect" bias.¹⁴

The strength of the association in both of the control groups, the increased effect as the amount consumed increased and the observation that for each single unit increase in cups/day age of onset of BSP increased significantly (on average by 1.7 years) raises the possibility that coffee in some way protects against the development of BSP. Several studies have shown a similar dose related protective effect of coffee in Parkinson's disease (PD).¹⁵⁻¹⁶ Considering that the caffeine content of a cup of Italian coffee (60–120 mg) is similar to the average content of a cup of American coffee (95–125 mg),¹⁷ the protective effect on the development of BSP might be exerted at caffeine doses greater than 120–240 mg, comparable with the caffeine doses suggested to be protective in PD.¹⁶

The most obvious candidate for the protective effect is caffeine, but the low frequency of decaffeinated coffee intake in Italy prevented us from indirectly examining the effects of caffeine on BSP. The association of caffeine and BSP may be biologically plausible given the pro-dopaminergic activity exerted by caffeine through an antagonistic action on adenosine receptors.¹⁸ This has been called into play to explain the observed protective effect on the development of PD.¹⁶ Analogous to PD, a relative hypodopaminergic status has been proposed in the pathophysiology of BSP.¹⁹⁻²⁰

In conclusion, our findings raise doubt about the association of smoking and BSP but strongly suggest coffee as a protective factor. Regardless of the implications for our understanding of the aetiology and treatment of primary BSP (an adenosine receptor antagonist is commercially available), the effect of coffee should be considered when seeking additional environmental/genetic risk factors.

ACKNOWLEDGEMENTS

This work was supported by a 40% grant from the Italian Ministry for Education, University and Research (MIUR) "Epidemiology, genetics and pathophysiology of adult-onset dystonia".

Authors' affiliations

G Defazio, D Martino, M S Aniello, P Livrea, Department of Neurological and Psychiatric Sciences, University of Bari, Italy
G Abbruzzese, L Avanzino, C Trompetto, Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Italy
P Girlanda, M Buccafusca, G Majorana, Department of Neurosciences, Psychiatry and Anaesthesiology, University of Messina, Italy
M Tinazzi, Department of Neurology, University of Verona, Italy
G Fabbrini, C Colosimo, A Berardelli, Department of Neurological Sciences, Neuromed, University of Rome "La Sapienza", Italy

Competing interests: None.

Correspondence to: Professor Giovanni Defazio, Department of Neurological and Psychiatric Sciences, University of Bari, Piazza Giulio Cesare 11, I-70124 Bari, Italy; gdefazio@neurol.uniba.it

Received 7 March 2007

Revised 20 April 2007

Accepted 20 April 2007

REFERENCES

- Defazio G, Abbruzzese G, Livrea P, *et al*. Epidemiology of primary dystonia. *Lancet Neurol* 2004;**3**:673–8.
- De Cavalho Aguiar PM, Ozelius LJ. Classification and genetics of dystonia. *Lancet Neurol* 2002;**1**:316–25.
- Defazio G, Hallett M, Berardelli A. Do primary adult-onset focal dystonias share etiologic factors? *Brain* 2007;**130**:1183–93.
- 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.
- Fahn S, Bressman SB, Marsden CD. Classification of dystonia. In: Fahn S, Marsden CD, DeLong MR, eds. *Dystonia 3, advances in neurology*, vol 73. Philadelphia: Lippincott-Raven, 1998:1–10.
- Wang A, Jankovic J. Hemifacial spasm: clinical findings and treatment. *Muscle Nerve* 1998;**21**:1740–7.
- Cohen J. A coefficient of agreement for nominal scales. *Edu Psychol Measure* 1960;**20**:37–46.
- Barrio JJ. The intraclass correlation coefficient as a measure of repeatability. *Psychol Rep* 1966;**19**:3–11.
- Schlesselman JJ, Stolley PD. *Case-control studies: design, conduct, analysis*. Oxford: Oxford University Press, 1982.
- Fleiss JL. *Statistical methods for rates and proportions*, 2nd edn., New York: Wiley 1981.
- Gallus S, Pacifici R, Colombo P, *et al*. Tobacco dependence in the general population in Italy. *Ann Oncol* 2005;**16**:703–6.
- Ragonese P, Salemi G, Morgante L, *et al*. A case-control study on cigarette, alcohol, and coffee consumption preceding Parkinson's disease. *Neuroepidemiology* 2003;**22**:297–304.
- Rothman J, Greenland S. Case-control studies. In: *Modern epidemiology*, 2nd edn. Philadelphia: Lippincott Raven, 1998:93–115.
- Szklo M, Javier Nieto F. *Epidemiology beyond the basics*. Maryland: Aspen Publishers, 2000.
- Hernan MA, Takkouche B, Caamano-Isorna F, *et al*. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 2002;**52**:276–84.
- Ascherio A, Zhang SM, Hernan MA, *et al*. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Ann Neurol* 2001;**50**:56–63.
- McCusker RR, Goldberger BA, Cone EJ. Caffeine content of specialty coffees. *J Anal Toxicol* 2003;**27**:520–2.
- Fisone G, Borgkvist A, Usiello A. Caffeine as a psychomotor stimulant: mechanism of action. *Cell Mol Life Sci* 2004;**61**:857–72.
- Schiccatano EJ, Basso MA, Evinger C. Animal model explains the origins of the cranial dystonia benign essential blepharospasm. *J Neurophysiol* 1997;**77**:2842–6.
- Micheli F, Scorticati MC, Folgar S, *et al*. Development of Parkinson's disease in patients with blepharospasm. *Mov Disord* 2004;**19**:1069–72.