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Risk associated behavior in premorbid multiple sclerosis: A case-control study

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Abstract

Background: It is generally accepted that individuals who subsequently develop MS are more likely to be smokers, have suffered glandular fever and to have a low blood vitamin D level. Previous research suggested that a unifying premise is risk-associated behavior before MS onset. This survey explores several health-adverse premorbid behaviors using a case-control design.

Methods: A questionnaire was completed by 94 patients with clinically definite MS. Their responses were compared to a control group of 59 who were patients with benign headache. Questions explored *pre-symptomatic* experience of: (a) alcohol, smoking, substance abuse, glandular fever; (b) blood transfusion; (c) hazardous sport, gambling (d) sexual history, gynecologic infection, number of pregnancies, terminations of pregnancy. Data were adjusted for age of first symptoms, gender and smoking.

Results: Compared to the headache group, MS subjects showed significant differences prior to symptom onset, adjusted for age of first symptoms, gender and smoking, with odds ratios for reporting or means and 95% confidence intervals as follows: (a) consuming alcoholic drinks, OR 6.91 (1.74 to 27.45; $p=0.006$) and at an earlier age, mean 16.9 y (16.4 to 17.5; $p=0.046$) (b) cigarette smoking, OR 2.24 (1.09 to 4.59; $p=0.028$) and to have smoked more per day, mean 9.45 (5.55 to 13.35; $p=0.001$) (c) history of glandular fever/infectious mononucleosis, OR 3.07 (1.11 to 8.49; $p=0.031$); (d) consumed recreational drugs, OR 3.90 (1.32 to 11.50; $p=0.014$), notably cannabis, OR 4.10 (1.40 to 12.09; $p=0.011$); (e) used a car seat belt, OR 4.45 (1.43 to 13.83; $p=0.010$); (f) attended all-night parties, OR 2.45 (1.12 to 5.36; $p=0.025$); (g) sunbathed, OR 2.770 (1.02 to 7.52; $p=0.046$); (h) had more sexual partners, mean 3.97 (2.00 to 5.95; $p<0.001$), more pregnancies, mean 1.43 (0.99 to 1.86; $p=0.015$) and one or more terminations of pregnancy, OR 5.05 (1.003 to 25.386; $p=0.049$).

Conclusion: All but one of the statistically significant variables (use of car seat belt) supports our hypothesis that MS subjects lead a riskier premorbid lifestyle. Strong associations were found for smoking, alcohol and glandular fever as suggested by others. Novel associations were found for recreational drug use; attending all-night parties; gambling on the lottery; more sexual partners, more pregnancies and one or more terminations of pregnancy. Such behavior during the MS prodrome may expose an individual to a variety of hostile environmental agents.
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1. Introduction

Smoking cigarettes, Epstein Barr virus (EBV), latitude and low vitamin D blood level are generally agreed to have an association with multiple sclerosis (MS). Each factor has a proposed genetic, immune or environmental explanation, but what is lacking is a common theme. It has been suggested that a unifying premise for some associations in the causal pathway of MS, is risk-associated behavior *before MS onset* (Hawkes, 2005). This hypothesis receives some support from a study of Latter Day Saints who lead a restricted life style and experience a lower than expected rate of MS (Hawkes et al., 2007). Conversely patients with MS are more likely to smoke (Hernan et al., 2001; Riise et al. 2003) and to be seropositive for herpes simplex type 2 (Hawkes et al., 2006).This study compares self-reported, risk-related lifestyle factors between MS patients and those with benign headache. Hitherto, many studies have focused on the manifesting stage of MS, but the prodromal period is of major etiologic importance, given that there may be significant changes in lifestyle once the diagnosis is known. The term 'risk' is used in its broadest sense to include any voluntarily chosen potentially health adverse behavior.

2. Methods

2.1. Questionnaire design

Questions that probed for a variety of risk- associated or health adverse behaviors were piloted on patients and members of hospital staff to ensure clarity of design and ease of subsequent statistical analysis. The questions explored *pre-symptom* experience of: (a) alcohol, smoking, substance abuse, glandular fever; (b) blood transfusion; (c) hazardous sport, health promoting activity, gambling; (d) sexual history: age of coitarche, abuse, sexual orientation, gynecologic infection, number of pregnancies, terminations of pregnancy. Most questions required responses such as yes/no, never/occasionally/regularly or numeric answers. Data were adjusted for age of first symptoms, gender and smoking.

2.2. Participants

Following local ethical approval, we approached patients who lived within the Barking and Havering Health District (Essex, UK). For the MS group (cases) we invited participation from patients with clinically definite MS according to the MacDonald Criteria, second revision (Polman et al., 2005). For the control (headache) group we requested participation from patients with benign headache, namely migraine without aura, tension or cervicogenic headache. Potential volunteers were approached by our MS research nurse or lead author and given an information sheet that described the theoretical background to the study, the scope of questions involved, and a caution that many would be personal in nature. If written agreement was obtained, they completed an anonymous questionnaire at the hospital, alone and in private. All had been examined by a consultant neurologist and those with other neurological or medical conditions were excluded. For every subject, the inclusion criteria were: age 25-55 y, Minimental Status Score of 27/30 or greater; an MRI brain scan within the preceding 6 months that was normal in the headache group or confirmed demyelination in the MS group. There were a total of eight refusals or incomplete questionnaires, five from the MS group (4.8%) and three from the headache group (3.7%). Refusals were noted after potential volunteers had read the information and consent sheet. Participants aged below 16 y at commencement of symptoms were excluded from analysis. This removed 2MS cases (2.08%) and 18 headache controls (23.34%) and had the effect of removing from analysis those who were children in the period about which we were asking lifestyle questions.

2.2.1. Cases

After exclusions, there were 79 females and 15 males (total 94) with clinically definite MS according to the MacDonald Criteria (second revision 2005).

2.2.2. Controls

(Headache group): After exclusions, there were 37 females and 22 males (total 59) with benign headache, namely migraine without aura, tension or cervicogenic headache.

2.3. Statistical analysis

Questions were not included in the report of the analysis where there was a non-significant difference between cases and controls and either the power for test of 20% difference between the two groups fell below 60%, or there were fewer than 10 positive responses. Twenty questions which elicited a categorical response were analyzed and reported as odds ratios adjusted by use of logistic regression for age at first symptom, gender and smoking. Eight questions which elicited a quantitative response were analyzed as means, adjusted by linear or Poisson regression. SPSS version 20 was used for all analyses.

3. Results

Details of the cases and controls are given in Table 1. Note that the headache group included a smaller proportion of women, was approximately 4.8 y younger at date of interview, mean age 43.0 vs. 47.8 y but 0.9 y older at first symptom: mean age 32.9 vs. 32.0 y. Age at first symptoms, gender and smoking were included in the statistical analyses to improve precision and remove any confounding. Log odds ratios and 95% confidence limits are shown in Fig. 1 for those assessments that elicited a categorical response. Corresponding odds ratios are in Table 2. Means with standard errors are shown in Table 3 for assessments that elicited a quantitative response. Compared to the headache group, MS subjects showed statistically significant differences prior to symptom onset, adjusted for age of first symptoms, gender and smoking as follows: (a) more likely to have consumed alcoholic drinks occasionally or frequently ($p=0.006$), and to have started consuming alcohol at an earlier age ($p=0.046$); (b) more likely to have smoked cigarettes occasionally or frequently ($p=0.028$); if a smoker, to have smoked more cigarettes per day ($p=0.001$); (c) reported a history of glandular fever/infectious mononucleosis ($p=0.031$); (d) ever consumed recreational drugs ($p=0.014$); consumed cannabis ($p=0.011$); (e) used a car seat