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Head injury at early ages is associated with risk of Parkinson's disease

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ABSTRACT

Introduction: The literature on the effect of head injuries on the risk of PD is inconclusive. Some researchers have hypothesized that studies that have seen an effect are simply capturing injury related to pre-clinical PD. However in animal models brain inflammation, which can be initiated by head trauma, has been shown to produce PD-like effects. Furthermore, animal studies have found that early life inflammation in particular is of relevance for PD pathology.
Methods: We conducted an unmatched case–control study of 379 neurologist confirmed PD patients and 230 controls from the greater Boston, Massachusetts area with questionnaire data on history of head injury and other covariates. We used multivariable logistic regression to estimate adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI) for PD.
Results: When we excluded injuries that occurred less than 10 years prior to the diagnosis of PD (in order to avoid reverse causation), we found an increased risk of PD associated with a head injury that resulted in a loss of consciousness, but it did not reach statistical significance (OR = 1.57; 95% CI = 0.89–2.80). We found a significant (p = 0.04) effect of age at first head injury. For every 5 year earlier age at first head injury with loss of consciousness the OR for PD was 1.37 (95% CI: 1.01–1.86).
Conclusion: Our results suggest that head injury in early life increases the risk of PD.

1. Introduction

Parkinson's disease [PD] is a progressive neurodegenerative disease with an insidious onset [1]. Up to 95% of cases are considered sporadic or without a genetic cause [2]. It has been suggested that brain inflammation is a risk factor for PD [3–5]. In animal experiments, head trauma resulted in chronic brain inflammation through disturbance of the blood brain barrier and evolving white matter damage [4,6,7]. These findings have spurred a great interest in the impact that head injuries may have on the risk of PD.

Several studies have demonstrated an association between head injury and PD [8–13]. However, there is concern that these findings could be attributed to reverse causation, that is instability caused by prodromal PD could result in a higher risk of head injuries rather than the head injury causing PD. The few studies that have evaluated the timing of head injury have found that having a head injury closer to PD diagnosis was strongly associated with PD. This association decreased as the time between the head injury and PD diagnosis increased [11,14,15]. These findings suggest that reverse causation is a concern and needs to be considered in any analysis.

Animal experiments have found that early life brain

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inflammation caused by environmental exposures can result in persistent changes in the nigrostriatal pathway, accumulation of proinflammatory factors in the brain, and increased neurologic susceptibility to other environmental exposures [3,4,7,16]. Only one study has considered whether the age at which head injuries occur is related to PD risk [17]. Therefore, we examined the question of age at head injury and risk of PD in an unmatched case–control study based in Boston, Massachusetts.

2. Methods

2.1. Subject recruitment

Between 2003 and 2007, patients with PD were recruited from four movement disorder clinics in the Boston, Massachusetts area. Cases were evaluated twice by a neurologist with at least 6 months between each evaluation. Case status was confirmed using U.K. Brainbank criteria [18]. Individuals deemed eligible were enrolled and completed questionnaires that included questions about past head injuries. Controls were recruited from family, friends and in-laws of the cases, community targeted advertisements, and through recruitment of participants in the Harvard Cooperative Program on Aging study (HCPOA). HCPOA is a registry of elderly volunteers who have agreed to participate in studies. A total of 379 cases and 230 controls answered questions on head injury including the timing of those injuries.

This study was reviewed and approved by the Human Research Committees at the Harvard School of Public Health, the BWH, and the VA Boston Healthcare System. All participants gave written informed consent prior to participating in the study.

2.2. Exposure and covariate assessment

Head injury status was assessed via questionnaire. Our primary exposure was head injury with loss of consciousness. Both cases and controls were asked to respond to the following questions: “Have you ever lost consciousness as a result of a head injury?,” and “At what age was your first head injury that resulted in loss of consciousness.” Those reporting a head injury were also asked about the total number of head injuries. From these responses we created a dichotomous variable for head injury (ever/never). A question on head injuries without loss of consciousness was introduced after the start of recruitment and so was answered by only 241 cases and 219 controls. This variable was used only in sensitivity analyses either only among those participants with this variable or among all participants and including a missing indicator for those without it. Unless otherwise specified, we use the term head injury to refer to head injury with loss of consciousness. In our base analyses, to help avoid reverse causation, we lagged exposure by 10 years prior to PD diagnosis. That is, we excluded any head injuries that occurred less than 10 years prior to PD diagnosis for the cases and less than 19 years prior to the questionnaire date for the controls, which was on average the same overall time before the questionnaire among the cases (because the average time from diagnosis to the questionnaire among cases was 9 years). In sensitivity analyses we also conducted additional analyses after excluding head injuries in the 15 and 20 years prior to PD diagnosis (and equivalent extensions in the controls) to reduce the chance of reverse causation even further. Additional data included in these analyses and obtained via questionnaire, were age, gender, race, education, and smoking status.

2.3. Statistical analysis

Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were estimated using multivariable logistic regression. Total number of head injuries was analyzed both as a continuous variable and as a categorical variable (0, 1, >1). Age at first head injury was analyzed as a categorical variable (no head injury and tertiles of age at first head injury based on the distribution among the controls). The significance of the trend over age at first injury was assessed in models treating age at first injury as a continuous variable and including an indicator for ever having a head injury, with all those without one assigned a constant for age, in order to keep all subjects in the analysis. To test the potential non-linearity of associations with these continuous variables, we used natural splines and selected the best model fit using the Akaike information criterion (AIC). For both age at first head injury and the total number of head injuries, better fit was obtained with linear models in all cases. Thus, only the linear results are reported.

Models were adjusted for age at the date of visit (years), its square, sex, race (white, non-white), highest level of education (high school or less, attended college, graduated college, post-graduate school), and smoking status (ever, never). In sensitivity analyses we adjusted for ever having a head injury without loss of consciousness, so that the reference group was those who never had any head injury with or without loss of consciousness. In a sensitivity analysis for our model evaluating the effect of age at first head injury, we also controlled for number of head injuries. We used missing indicator variables when covariate data was missing. Analyses were conducted using SAS software (version 9.3; SAS Institute, Inc. Cary, NC) [19] and R statistical software (version 3.1.1; R Development Core Team; 2013) [20] for models that utilized splines.

3. Results

Patients with PD were more likely to be male, white, have a higher level of education, and less likely to have ever smoked compared with the controls (Table 1). On average the cases were diagnosed with Parkinson's disease 9.4 years (sd = 6.8 years) prior to answering the questionnaire. The median age at first head injury was 15 (Interquartile range = 10–18) among the cases and 18.5 (Interquartile range = 12–44.5) among the controls (Table 2).

The odds ratio (OR) for PD among those with a head injury at any age was elevated, but did not reach statistical significance (Table 3). When head injuries within the 15 or 20 years prior to PD diagnosis (and equivalent periods among controls) were excluded to more stringently avoid reverse causation, the OR for PD were similar, although none of the OR quite reached statistical significance (Table 3). The OR for PD was 1.46 (95% CI = 0.75–2.86) for those with one head injury and 1.54 (95% CI = 0.53–4.52) for those with more than one. When treating head injuries as a continuous variable, the OR per injury was 0.99 (95% CI = 0.74–1.31). The OR for PD increased with earlier age of injury and this association was significant (p = 0.04). The OR per 5 years younger age at first head injury was 1.40 (95% CI: 1.15–1.91). In the same model, when additionally controlling for total number of head injuries, results were similar (OR = 1.37; 95% CI = 1.01–1.86). The OR by categories of age at first head injury compared with those who never had a head injury from our base model are shown in Fig. 1.

In sensitivity analyses that included additional adjustment for head injury without loss of consciousness, results were generally similar. For example, the OR for PD among those with a head injury with loss of consciousness in analyses excluding injuries in the ten years before PD diagnosis (and the equivalent period among controls) was 1.41 (95% CI: 0.78–2.53) when including all participants and using a missing indicator for those without data on head injury without loss of consciousness. The OR was 1.72 (95% CI: 0.88–3.35) when restricting to those participants with data on head injury