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REVIEW ARTICLE

Systematic Review of the Risk of Parkinson's Disease After Mild Traumatic Brain Injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis

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Abstract

Objective: To synthesize the best available evidence on the risk of Parkinson's disease (PD) after mild traumatic brain injury (MTBI).

Data Sources: MEDLINE and other databases were searched (1990–2012) with terms including "craniocerebral trauma" and "parkinsonian disorders." Reference lists of eligible articles and relevant systematic reviews and meta-analyses were also searched.

Study Selection: Controlled clinical trials, cohort studies, and case-control studies were selected according to predefined criteria. Studies had to have a minimum of 30 concussion cases.

Data Extraction: Eligible studies were critically appraised using a modification of the Scottish Intercollegiate Guidelines Network criteria. Two reviewers independently reviewed and extracted data from accepted studies into evidence tables.

Data Synthesis: Evidence was synthesized qualitatively according to modified Scottish Intercollegiate Guidelines Network criteria. Sixty-five studies were eligible and reviewed, and 5 of these with a low risk of bias were accepted as scientifically admissible and form the basis of our findings. Among these admissible studies, the definitions of MTBI were highly heterogeneous. One study found a significant positive association between MTBI and PD (odds ratio, 1.5; 95% confidence interval, 1.4–1.7). The estimated odds ratio decreased with increasing latency between MTBI and PD diagnosis, which suggests reverse causality. The other 4 studies did not find a significant association.

Conclusions: The best available evidence argues against an important causal association between MTBI and PD. There are few high-quality studies on this topic. Prospective studies of long duration would address the limitations of recall of head injury and the possibility of reverse causation.

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Traumatic brain injury (TBI) has been hypothesized as a causative or risk factor for Parkinson's disease (PD) on the basis of several different possible pathogenetic links. Inflammation is an integral part of the pathology of PD,[1] and TBI is well known to cause a breakdown of the blood-brain barrier and to induce an inflammatory reaction in the brain that can be long-lasting.[2-4] Mitochondrial function is impaired in PD,[5,6] suggesting that energy generation may be an important factor in the pathogenesis of PD. Mitochondrial function is disrupted after head injury, and glutamate release due to TBI further increases energy demands.[7,8] Thus, head injury may place deleterious metabolic stress on neuronal systems. Most relevant to PD-specific pathology, head injury leads to accumulation of synuclein,[9-11] which is a major component of the intraneuronal inclusions that are characteristic of PD.

These observations have motivated a number of studies examining the relation between TBI and PD. In developed countries, an estimated 1% of the population older than 65 years is affected by PD. Mild traumatic brain injury (MTBI) is the most common form of TBI, and is likely to be in excess of 600 per 100,000 person-years.[12] If MTBI contributes to the risk of PD, the public health implications are substantial. As part of a broader effort to update the World Health Organization Collaborating Centre Task Force on Mild Traumatic Brain Injury prognosis after MTBI,[13] we undertook a systematic review of these studies from 1990 to the present, summarize the evidence, and draw conclusions for the field.

Methods

We undertook 2 separate searches of the literature. Initially, we searched the electronic databases MEDLINE, PsycINFO, EMBASE, and CINAHL from January 1, 1990, to February 1, 2011, including the search terms "craniocerebral trauma," "head injury," "Parkinsonian Disorders," and "Parkinson*." In parallel, the International Collaboration on MTBI Prognosis (ICoMP) conducted a separate search as part of the World Health Organization Collaborating Centre Task Force on Mild Traumatic Brain Injury update on MTBI prognosis. The protocol registration, case definition, literature search, critical review strategy, and data synthesis are outlined in detail elsewhere.[14] The electronic databases MEDLINE, PsycINFO, Embase, CINAHL, and SPORTDiscus were systematically searched from 2001 to February 10, 2012, with search terms including "Parkinsonian Disorders," "craniocerebral trauma," "prognosis," and "recovery of function." The reference lists of all reviews and meta-analyses related to MTBI and articles meeting the eligibility criteria were screened for additional studies. In addition, ICoMP members provided information about studies of which they had knowledge but that were not found in the databases or reference lists.

Articles were screened for eligibility according to predefined criteria. Inclusion criteria included original, published peer-reviewed research reports in English, French, Swedish, Norwegian, Danish, and Spanish. Studies had to have a minimum of 30 MTBI cases and had to assess the outcome of PD. Accepted definitions of MTBI were those that complied with the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury definition[15] and the Centers for Disease Control and Prevention definition.[16] Articles using the term "concussion" were also eligible. Studies including open or penetrating head injury were not eligible. Studies including fractured skull were eligible as long as other criteria were compatible with the MTBI definition.

Eligible study designs were controlled trials, cohort studies, and case-control studies. Exclusion criteria included study designs such as cross-sectional studies, case reports and series, and cadaveric studies, biomechanical studies, and laboratory studies.

Eligible articles were critically appraised using a modification of the Scottish Intercollegiate Guidelines Network criteria.[17] Two reviewers independently reviewed and extracted data from accepted articles into evidence tables. There were no cases of disagreement. The evidence was synthesized according to the modified Scottish Intercollegiate Guidelines Network criteria, and a best-evidence synthesis was performed to provide clear and useful conclusions linked to the evidence tables. We also categorized the evidence on prognostic factors as exploratory or confirmatory using the phases-of-study framework described by Côté et al.[18] Phase I studies are hypothesis-generating investigations that explore the associations between potential prognostic factors and disease outcomes in a descriptive or univariate way. Phase II studies are exploratory analyses that focus on particular sets of prognostic factors or attempt to discover which factors have the highest prognostic value. Last, phase III studies are confirmatory studies of explicit prestated hypotheses that allow for a focused examination of the strength, direction, and independence of the proposed relation between a prognostic factor and the outcome of interest. Information from accepted phase III studies is considered the strongest evidence, followed by evidence from accepted phase II studies. Phase I studies do not consider independence of associations or confounding factors, and they are considered the most preliminary, hypothesis-generating studies.

List of abbreviations:

CI	**confidence interval**
ICoMP	**International Collaboration on MTBI Prognosis**
LOC	**loss of consciousness**
MTBI	**mild traumatic brain injury**
OR	**odds ratio**
PD	**Parkinson's disease**
TBI	**traumatic brain injury**
WHO	**World Health Organization**

Results

The literature search from 1990 to 2011 yielded 1885 citations related to PD and TBI. After careful screening, 65 articles were selected for full review and 4 were deemed admissible (fig 1). From the ICoMP search on MTBI prognosis covering 2001 to 2012, 1 additional eligible article was identified, reviewed, and accepted (fig 2). All 5 are case-control studies; there were no admissible cohort studies. These consist of 1 phase I,[19] 2 phase II,[20, 21] and 2 phase III studies.[22,23] The methods and results of these are summarized in table 1.

Rugbjerg et al[23] (phase III) identified an association between MTBI and PD, reporting an odds ratio (OR) of 1.5 (95% confidence interval [CI], 1.4−1.7) for MTBI in patients with PD compared with controls without PD. When the investigators considered the temporal association between the first diagnosis of PD and MTBI, the association was significant only when the injury occurred 9 or less years before the diagnosis of PD. When the analysis was restricted to MTBI occurring 10 or more years before the first recorded diagnosis of PD, there was no significant association. ORs for PD increased with decreasing intervals between the head injury and the diagnosis of PD. One phase II