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Review

Association of traumatic brain injury and Alzheimer disease onset: A systematic review

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ABSTRACT

Background: Inconsistencies regarding the risk of developing Alzheimer disease after traumatic brain injury (TBI) remain in the literature. Indeed, why AD develops in certain TBI patients while others are unaffected is still unclear.
Objective: The aim of this study was to performed a systematic review to investigate whether certain variables related to TBI, such as TBI severity, loss of consciousness (LOC) and post-traumatic amnesia (PTA), are predictors of risk of AD in adults.
Methods: From 841 citations retrieved from MEDLINE via PubMed, EMBASE, PSYINFO and Cochrane Library databases, 18 studies were eligible for the review.
Results: The review revealed that about 55.5% of TBI patients may show deteriorated condition, from acute post-TBI cognitive deficits to then meeting diagnostic criteria for AD, but whether TBI is a risk factor for AD remains elusive.
Conclusions: Failure to establish such a link may be related to methodological problems in the studies. To shed light on this dilemma, future studies should use a prospective design, define the types and severities of TBI and use standardized AD and TBI diagnostic criteria. Ultimately, an AD prediction model, based on several variables, would be useful for clinicians detecting TBI patients at risk of AD.

1. Introduction

TBI is defined as altered brain function or other evidence of brain pathology caused by an external force. TBI severity can be classified according to 3 levels: mild, moderate and severe. The Glasgow Coma Scale (GCS) score, duration of post-traumatic amnesia (PTA) and LOC duration are the main characteristics used to assess TBI severity. Various physical, cognitive [1], emotional and behavioral [2,3] consequences are frequently observed after TBI, as are functional difficulties and have significant social repercussions [1,4].

TBI severity (GCS score, LOC, PTA) is considered in predicting outcome in TBI patients [4–8]. More specifically, TBI severity affects the presence of long-term cognitive, psychosocial and functional consequences after TBI [9]. Indeed, moderate and severe TBI seem to be associated with more severe and persistent cognitive deficits [1]. For example, one study found low GCS at hospital admission and long length of hospital stay associated with increased physical disabilities and functional impairment at the time of discharge. In general, the link between TBI severity and outcome is approximately linear; the greater the severity, the greater the consequences [1]. Thus, GCS and PTA seem to be good predictors of negative outcome after TBI.

As many as 65% of patients with moderate-to-severe TBI report long-term problems with cognitive functioning [10]. Luukinen et al. [11] suggested that the occurrence of major head injury increases the risk of cognitive decline, which is much faster in older individuals with than without TBI [12,13]. Thus, TBI combined with age-related brain changes could exacerbate cognitive decline.

Interest is increasing in understanding and establishing a link between TBI and Alzheimer's disease (AD). An estimated 35.6 million people worldwide have AD, the most common form of dementia. However, the etiology is not well understood, and risk

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factors such as age, family history and genetic factors have been extensively studied. TBI may be a possible AD precipitating factor [14–16].

Although some studies have challenged the association between AD and TBI [17–24], a growing number of studies support a greater risk of AD developing after moderate and severe TBI [15,25–33]. More precisely, evidence appears to favor increased risk of late-life AD after a single moderate-to-severe TBI involving LOC in early or middle life [29–32,34–36]. Meta-analyses also support these conclusions [5,16,37]. Specifically, TBI severity may explain the association between TBI and AD. As well, post-TBI LOC may be strongly linked to risk of AD [38]. Surprisingly, these studies and meta-analyses do not specify which factors, other than LOC, that were considered during the diagnosis of moderate or severe TBI. Furthermore, LOC alone cannot be used to establish such a diagnosis, because it is not consistent with international TBI diagnostic criteria [39].

In previous studies, the link between TBI occurrence or severity (mild vs moderate or severe) and risk of AD remained controversial. Discrepancies in the criteria used to assess TBI severity across studies may explain the controversies in part. Variables related to TBI severity, such as the presence or duration of LOC, low GCS score and presence or duration of PTA, have a well-known impact on post-TBI outcome. These variables may play a role in the development of long-term decline and degenerative processes such as AD and may because associated with risk of AD. Surprisingly, previous studies and meta-analyses published in this field have never studied or compared the factors and variables specific to the measurement of TBI severity, such as GCS or PTA duration. Indeed, only the presence of LOC was considered in a few studies. Since studies are retrospective in nature and involved people with AD, TBI-related criteria are poorly documented. Similarly, the reviewed meta-analyses have never compared variables related to TBI severity; they only accounted for TBI occurrence regardless of its diagnostic features or severity. In short, in previously published studies, specific TBI-related variables, which are actual risk factors of AD, are unknown.

Thus, the goal of this systematic review was to define TBI-related variables to predict the risk of AD developing after TBI. More specifically, we aimed to examine whether variables related to TBI severity such as LOC, GCS and PTA were associated with the risk of AD developing.

2. Methods

The systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of studies evaluating health care interventions.

2.1. Search strategy

The search for articles in MEDLINE via PubMed, EMBASE, PSYINFO and the Cochrane Library databases up to May 2016 involved use of the keywords: adult, traumatic brain injury (TBI), head injury, concussion, mild TBI, moderate TBI, severe TBI, GCS, post-traumatic amnesia, loss of consciousness, neurodegenerative disease, AD, long-term, outcome, consequence. We included all studies of adult humans $\geq$ 18 years old with mild, moderate or severe TBI that were published in English or French, were prospective or retrospective, were published between 1985 and 2016 and assessed the relationship between TBI and AD. Both electronic and paper publications were searched when available. Finally, we searched the reference lists of reviews, meta-analyses or systematic reviews for articles on the link between TBI and AD.

2.2. Study selection

All articles retrieved were independently assessed for eligibility by 3 reviewers (JL, MMBD, LMV) who used a two-step evaluation. First, the reviewers independently screened all titles and abstracts of identified articles to determine whether they met the inclusion criteria. Then full texts of the chosen articles were assessed to confirm whether the articles met the inclusion criteria and that a link between TBI and AD was reported in the article. Any disagreements were resolved by discussion.

2.3. Data collection

Data were extracted from articles by using a standardized form and included severity of the assessed TBI with LOC, GCS and PTA; number of patients; setting; type of study; long-term post-TBI outcome, and the link between TBI and AD. Any disagreements were resolved by discussion.

3. Results

From 841 citations examined, 18 reports of studies were identified (Fig. 1). All included articles were published between 1985 and 2015. The studies were retrospective (72.2%) and prospective (27.8%). Most studies were conducted in the United States (55.6%), except 1 in Canada (5.6%), 1 in Australia (5.6%) and 7 in Europe (38.9%) (Table 1). The included studies involved 743,627 participants (range 60 to 720,933 participants) (Table 2).

The mean age of patients ranged from 43.1 to 81 years. In 10 studies, a lower age limit was used, which ranged from 18 to 70 years. In 8 studies, the age was not specified.

The most frequent exclusion criteria were neurological disorders, psychiatric diseases and medical disorders. A total of 16 studies (88.9%) used at least one of the previously described exclusion criteria. Previous TBI or a probable/possible AD diagnosis were the main inclusion criteria in all studies. Medical records, interviews, postal questionnaires, physical and neurological

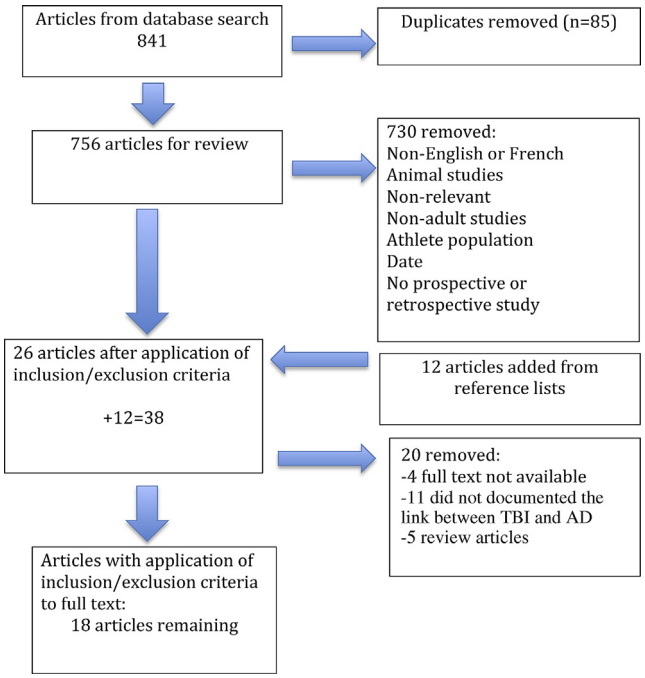

Fig. 1. Flow of articles in the systematic review. TBI: traumatic brain injury; AD: Alzheimer disease.

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