Updates on the association of brain injury and Alzheimer’s disease

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Abstract:
The purpose of this minireview is to outline the updates made on the association of Alzheimer’s disease (AD) and brain injury. A review of the literature on this subject was conducted that included various aspects such as age of onset, severity of head trauma, and genetic influences. The results of this mini-review were that consistent associations of AD risk are seen when the severity of head trauma increases, the lag time decreases and when genetic links are present. Brain injury and AD have a complicated relationship that requires further studies to be fully understood.

Keywords:
Age of onset, genetic predisposition, head trauma, neurodegenerative disease, severity

Introduction

Over the years, there has been much controversy on whether a head or brain injury increases the risk of developing Alzheimer’s disease (AD). Research on this topic has included case-control, cohort, cross-sectional, and preclinical studies. Many of these studies have produced seemingly conflicting results regarding a possible association. However, there is more consistent evidence, in both observational and preclinical research, that a head trauma to an individual with a genetic predisposition for AD likely leads to an earlier age on onset of AD and that this association strengthens with increasing severity of head trauma.

This review focuses on the observational analyses that have investigated the role of head trauma in promoting the earlier age of onset of AD, the association between head trauma and AD with regards to severity of head trauma, and studies concerning the influence of genetic factors on these associations. While there has been a decrease in recent studies on this topic, the most recent information available is discussed along with older research.

Earlier Age of Onset

The association of head trauma with an earlier onset of AD has been investigated in multiple observational studies, as shown in Table 1. In research on dementia, it was concluded the a self-reported head injury was associated with 6 months earlier onset of dementia and AD type pathological changes. More specifically, from the National Alzheimer’s Coordinating Center Uniform Data Set, the onset of AD was found to be 2.5 years earlier in patients with a history of traumatic brain injury (TBI). This work shows a clear connection between earlier onset and head trauma; however, it remains unclear if the age at which the TBI occurred has any influence on the age of onset.

Older studies suggested that head trauma is associated with an earlier age of onset of AD due to data showing head trauma as a risk factor for AD only when the injury was within a certain lag time to the start of symptoms. In both studies, a
The Trauma-Severity Link

Looking at the difference in AD risk among multiple lag times helps gain a better view of the association between head and brain injury and AD; however, additional factors must be viewed to more fully understand this interaction, such as the severity of injury. Studies looking at the link between severity of head or brain injury and AD [Table 2] identify more severe trauma as increasing number of events, addition of loss of consciousness (LOC), and by using a grading scale of mild-to-severe TBI. Again, it is consistently seen in older studies that severity is an important factor in the risk for AD.\(^6\)\(^,\)\(^8\)\(^,\)\(^9\) These studies support the findings of more recent research, such as the previously discussed study by Tolppanen et al.\(^6\) This work also suggested a relationship between the amount of risk and severity or frequency of head trauma. Similarly to the increasing odds found in shorter lag times, increased odds ratios were also seen with increasing injury severity. An odds ratio of 1.19 was found for 1 previous head injury, 1.35 for 2, and 1.44 for 3–5. In addition, an odds ratio of 1.26 was found for mild TBI, whereas 1.46 was found for severe TBI.\(^6\)

These data suggest that patients are more at risk for AD as the number of head traumas they experience increases and that more severe brain injuries could have more deleterious effects on AD pathology. In an additional
Table 2: The association between head trauma severity and Alzheimer’s disease in observational studies

| Study                                                                 | Sample size | AD determination | Trauma determination | Results                                                                 |
|----------------------------------------------------------------------|-------------|------------------|----------------------|-------------------------------------------------------------------------|
| AD after remote head injury: An incidence study[4]                   | 271         | Clinical diagnoses | Head injury with LOC, with LOC over 5 min and within the last 30 years as separate groups | Head injury may be a risk factor for Alzheimer’s                        |
| Head or brain injuries and AD: A nested case-control register study[6] | 70,719 AD, 282,862 controls | Closely based on the NINCDS-ADRDA criteria | Hospitalized head trauma (stratified by number) and diagnosed TBI (stratified by severity) | Suggests association of head/brain injury with AD                     |
| Documented head injury in early adulthood and risk of AD and other dementias[8] | 3460 WWII male veterans | Multistep analysis for dementia and clinical diagnoses for AD | Hospitalized with diagnosis of head injury with LOC, posttraumatic amnesia or skull fracture | Moderate and severe head injury showed an association with increased risk of AD |
| Head injury and the risk of AD in the MIRAGE study[9]               | 2,233 AD, 14,688 1st degree family members | Probable or definite AD | Head injury interview | Suggests head injury as a risk factor for AD                             |
| Geriatric TBI and AD share patterns of white matter decline[10]      | 181         | MRI and DTI       | Mild TBI             | White matter fasciculi fractional anisotropy are statistically equivalent in AD patients and geriatric mTBI patients 6 months postsurgery |
| Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans[11] | 18, 6 control | Full diagnostic autopsy | Fatal head injury | Axonal accumulation of proteins implicated in AD following TBI          |
| Head trauma and in vivo measures of amyloid and neurodegeneration in a population-based study[12] | 589         | PIB-PET, fluorodeoxyglucose-PET, and MRI | Self-reported brain injury with at least momentary LOC or memory separated by cognitively normal or mild cognitive impairment postinjury | Head trauma was found to be associated with greater amyloid deposition consistent with Alzheimer’s neuropathology. These findings were more pronounced in head traumas that caused mild cognitive impairment |

MRI: Magnetic resonance imaging, PIB: Pittsburgh compound B, PET: Positron-emission tomography, AD: Alzheimer’s disease, TBI: Traumatic brain injury, LOC: Loss of consciousness, DTI: Diffusion tensor imaging, NINCDS: National Institute of Neurological and Communicative Disorders and Stroke, ADRDA: Alzheimer’s Disease and Related Disorders Association

study, it was found that 6 months after a mild TBI, two white matter fasciculi in the brains of geriatric patients showed statistically equivalent variations to that of AD patients’ brains.[10] Furthermore, in a study on axonal protein accumulation in postmortem TBI patients, similar protein accumulations to AD patients, such as Amyloid β, were discovered.[11] These changes in white matter and axonal proteins are a potential explanation of the pathology behind severe brain injury being a risk for AD.

Similarly, research was done to investigate neuropathology in individuals who had previous head trauma resulting in LOC or memory loss. Participants were separated into cognitively normal (less severe injury) and mild cognitive impairment (more severe injury) groups and given Pittsburgh compound B positron emission tomography (PET), fluorodeoxyglucose-PET, and magnetic resonance imaging tests.[12] The results showed increased amyloid deposition in both groups; however, the deposition was greater in the group with the more severe injury.[12] Amyloid deposition in the brain is consistent with neuropathology of Alzheimer’s disease. It is possible that increased amyloid post head injury is the underlying reason for the increases in risk shown in the previous studies. While there are potentially more changes in neuropathology following a head injury, this work suggests that head injuries lead to increased AD pathology, in at least one mechanism, and that this effect is further increased in more severe head injuries.

Genetic Influences

There has been much more conclusive work done on the genetic factors that can lead to AD such as a case–control study on the risk factors for AD in Russia which concluded that both head trauma and family history are the risk factors for AD.[13] Furthermore, associations between head trauma with genetic links and AD were also found in observational studies [Table 3]. In one of the previous older studies, the influence of genetics in head trauma and AD association was also investigated. It was concluded that not only was risk of AD proportional to severity of head injury, but it was heightened among first-degree relatives.[9] This correlation shows a likelihood of an underlying
hereditary link between these factors. As mentioned previously, the onset of AD in a recent population-based study was found to be 2.5 years earlier in those with a history of TBI.[15] This study also concluded that the presence of the Alzheimer’s risk allele, Apoe4, also reduced the time of onset by 2.3 years independently from head trauma. Furthermore, in individuals with both a history of TBI and presence of Apoe4, the mean onset of AD was 2.8 years earlier.[2] This suggests that while genetic factors and head trauma separately increase the risk of earlier onset AD, the effects of head trauma on a genetically predisposed individual could be more detrimental than one risk factor alone. Recent research also concludes that the presence of the Apoe4 allele is associated with increased risk of worse long-term outcomes following a TBI.[14] Long-term deleterious outcomes of brain injury associated with Apoe4 could be the link between Alzheimer’s genetic predisposition with head trauma and AD.

In a reviewed preclinical article, research was found to support the hypothesis that head trauma increases the risk of AD in genetically predisposed individuals. Shishido et al. examined triple transgenic AD mice for histological and cognitive changes following a TBI. The authors found that 28 days following the TBI, there was an increase in the hippocampal Amyloid β deposition, consistent with AD pathology, and a decrease in the spatial learning ability of the mice.[15] It was concluded that TBI was associated with a progression of AD pathology and that this effect was enhanced in those genetically predisposed to AD. This work was consistent with the neuropathological changes found in the previous study showing increased Amyloid deposition in individuals with more severe head trauma.[11] Therefore, it is suggested that due to neuropathological changes, head and brain injury may have a larger effect on the risk of AD in those who have inherited Alzheimer’s-related genetic factors.

Comments on Observational Studies that Denied Association

In the reviewed studies that denied an association between head trauma and AD [Table 4][16-19] a commonality was self-reported head trauma, making the data susceptible to recall bias. The degree of severity of the head trauma also seemed to be neglected or not fully analyzed. In the EURODEM analysis, head trauma was not found to be associated with AD; however, the reported head trauma was calculated regardless of age, and therefore, would not be able to compare to the other analyses that specify a lag period between head trauma and onset of AD.[16] Furthermore, one study concluded that only mild head trauma was not a risk factor for acquisition of AD, but did not have conclusions about severe trauma or indications of LOC involvement.[17] As previously discussed, trauma severity, genetics, lag times, and modes of trauma report were all found to be of great importance to the conclusion of an association between head/brain injury and AD. Failure to consider these aspects could account for the opposing conclusions found in these articles. These limitations should be considered when holistically analyzing the relationship between head or brain injury and AD.

Table 3: The association between genetics, head trauma and Alzheimer’s disease in observational studies

| Study                                                                 | Sample size | AD determination | Trauma determination | Results                                           |
|----------------------------------------------------------------------|-------------|-------------------|----------------------|---------------------------------------------------|
| Head injury and the risk of AD in the MIRAGE study[9]                | 2,233 AD    | Probable or definite AD | Head injury interview | Suggests head injury as a risk factor for AD       |
| TBI history is associated with earlier age of onset of AD[2]          | 14,688 1st degree relatives | Clinical diagnosis of AD | Self-reported TBI with LOC | History of TBI can be associated with an early age of onset of AD |

AD: Alzheimer’s disease, TBI: Traumatic brain injury, LOC: Loss of consciousness

Table 4: Denial of association of head trauma and Alzheimer’s disease in observational studies

| Study                                                                 | Sample size | AD determination | Trauma determination | Results                                           |
|----------------------------------------------------------------------|-------------|-------------------|----------------------|---------------------------------------------------|
| Rates and risk factors for dementia and AD:                           | 528         | Cognitive tests to diagnose with dementia, AD or stroke-AD    | Self-reported head trauma with LOC | Head trauma with LOC did not increase risk of AD significantly |
| Results from EURODEM pooled analyses.                                 |             |                   |                      |                                                   |
| EURODEM Incidence Research Group and Work Groups. European Studies of Demential[4] |             |                   |                      |                                                   |
| Head trauma and risk of dementia and AD[17]                          | 6,645       | Based on classification for AD by NINCDS and ADRDA            | Reported head trauma to physician including # of head traumas, time since trauma and duration of LOC | Mild head trauma is not a major risk factor for AD in the elderly |
| Association of TBI with Late-Life Neurodegenerative Conditions and Neuropathological Findings[18] | 7,130 older adults, 1,589 came to autopsy | Checked for AD pathology at autopsy | Self-reported TBI with LOC | No association with AD |
| Risk Factors for AD: A Prospective Analysis from the Canadian Study of Health and Aging[19] | 4,615 with 194 AD | Clinical diagnosis | Risk factor questionnaire, self-reported | Head trauma not associated with AD |

AD: Alzheimer’s disease, TBI: Traumatic brain injury, LOC: Loss of consciousness, NINCDS: National Institute of Neurological and Communicative Disorders and Stroke, ADRDA: Alzheimer’s Disease and Related Disorders Association
Conclusion and Future Studies (Perspective and Prospective)

Over the years, research on head trauma as a risk factor for AD has shown varying results and conclusions. However, when analyzing data from multiple observational studies and preclinical data, consistent associations of AD risk are seen when the severity of head trauma increases, the lag time decreases and when genetic links are present. This suggests that if a head trauma or brain injury to an individual with a genetic predisposition for AD likely leads to an earlier age of onset of AD, and that this association strengthens with increasing severity of the injury.

Further research on this subject needs to be performed to more clearly analyze the relationship between head trauma and AD. Potentially, a larger scale retrospective analysis could be performed on patients with AD looking at previous head trauma and genetic factors. Furthermore, further preclinical research on triple, double, single, and nontransgenic AD mice with and without being subjected to a head injury could be done to collect more information on the progression and incidence of AD pathology.

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Conflicts of interest
There are no conflicts of interest.

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