Review Article

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

Kara Klomparens[1], Yuchuan Ding[1,2]

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.[1] 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).[2] 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.[3-5] In both studies, a

[1]Department of Neurosurgery, School of Medicine, Wayne State University, [2]John D. Dingell VA Medical Center, Detroit, MI, USA

Address for correspondence:
Dr. Yuchuan Ding, Department of Neurosurgery, School of Medicine, Wayne State University, Detroit, MI, USA.
John D. Dingell VA Medical Center, 4646 John R Street (11R), Detroit, MI, 48201, USA.
E-mail: yding@med.wayne.edu

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Table 1: Association of earlier age of Alzheimer's disease onset and head trauma in observational studies

Study	Sample size	AD determination	Trauma determination	Results
Self-reported head injury and risk of late-life impairment and AD pathology in an AD center cohort[1]	649	AD type pathological changes in autopsy of brain	Self-reported head injury	Reports that head injury is associated with earlier onset, increased risk of cognitive impairment and dementia, increased risk of mortality and AD type pathological changes
TBI history is associated with earlier age of onset of AD[2]	7625	Clinical diagnosis of AD	Self-reported TBI with LOC	History of TBI can be associated with an early age of onset of AD
Head trauma and the risk of AD[3]	198 AD 198 control	Clinical diagnoses	Previous head trauma with LOC	Suggests association of head trauma with AD
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 AD
The Association Between Head Trauma and AD[5]	130 matched pairs	Clinical diagnoses	Head trauma with LOC or which caused the subject to seek medical care	Estimated risk of AD increased as time between the last head trauma and onset of disease symptoms diminished
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 Also describes stronger association with decreased lag time and increased severity
Monitoring of brain interstitial total tau and beta amyloid proteins by microdialysis in patients with TBI[7]	8	Total Tau and Aβ micro dialysis	Diagnosed moderate to severe TBI	High levels of interstitial T-tau and Aβ42 were found postinjury

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

relationship between decreased lag time and risk of AD can be seen, suggesting that while head trauma may not be directly associated with the acquisition of AD, it may play a role in the onset of the disease. More recent investigation of this trend went a step farther in an additional study to analyze the differences between multiple lag times. An odds ratio of 1.11 was found for a lag time of 25–40 years, 1.23 for 10–25 years, 1.34 for 5–10 years, and 1.88 for 0–5 years.[6] This increase in odds ratio gives more evidence that a head trauma is increasingly detrimental within shorter lag times to the disease. Perhaps, as individuals come closer to their onset of AD, they become more susceptible to a head trauma progressing the AD pathology, subsequently leading to an earlier age of onset.

Evidence of AD pathology was seen in the research using microdialysis on post brain injury patients.[7] The data in this study showed increased total Tau, an AD biomarker, up to 172 h post injury. The amount of Tau detected decreased as time went on, this could be a pathological reason behind lag times and the importance of when an injury occurs. If an individual has unknowingly started the pathological changes of AD and then suffered a brain injury temporarily increasing the amount of Tau; perhaps, this acts as a catalyst in the progression of AD and leads to an earlier onset of clinical disease.

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.[4,8,9] 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 Also describes stronger association with decreased lag time and increased severity
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, postraumatic 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.[2] 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 14,688 1st degree relatives	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]	7625	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: Results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia[16]	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
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 that a head trauma or brain injury 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 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.

References

1. Abner EL, Nelson PT, Schmitt FA, Browning SR, Fardo DW, Wan L, *et al*. Self-reported head injury and risk of late-life impairment and AD pathology in an AD center cohort. Dement Geriatr Cogn Disord 2014;37:294-306.
2. LoBue C, Wadsworth H, Wilmoth K, Clem M, Hart J Jr., Womack KB, *et al*. Traumatic brain injury history is associated with earlier age of onset of Alzheimer disease. Clin Neuropsychol 2017;31:85-98.
3. van Duijn CM, Tanja TA, Haaxma R, Shulte W, Saan RJ, Lameris AJ, *et al*. Head trauma and the risk of Alzheimer's disease. Am J Epidemiol 1992;135:775-82.
4. Schofield PW, Tang M, Marder K, Bell K, Dooneief G, Chun M, *et al*. Alzheimer's disease after remote head injury: An incidence study. J Neurol Neurosurg Psychiatry 1997;62:119-24.
5. Graves AB, White E, Koepsell TD, Reifler B, Van Bell G, Larson EB, *et al*. The association between head trauma and Alzheimer's disease. Am J Epidemiol 1990;131:491-501.
6. Tolppanen AM, Taipale H, Hartikainen S. Head or brain injuries and Alzheimer's disease: A nested case-control register study. J Alzheimers Assoc 2017;13:1371-9.
7. Marklund N, Blennow K, Zetterberg H, Ronne-Engström E, Enblad P, Hillered L. Monitoring of brain interstitial total tau and beta amyloid proteins by microdialysis in patients with traumatic brain injury. J Neurosurg 2009;110:1227-37.
8. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, *et al*. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000;55:1158-66.
9. Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, *et al*. Head injury and the risk of AD in the MIRAGE study. Neurology 2000;54:1316-23.
10. Rostowsky KA, Chaudhari NN, Calvillo M, Lee SK, Irimia A. Geriatric traumatic brain injury and Alzheimer's disease share patterns of white matter decline. Alzheimers Dementia 2019;15:1407-8.
11. Uryu K, Chen XH, Martinez D, Browne KD, Johnson VE, Graham DI, *et al*. Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. Exp Neurol 2007;208:185-92.
12. Mielke MM, Savica R, Wiste HJ, Weigand SD, Vemuri P, Knopman DS, *et al*. Head trauma and *in vivo* measures of amyloid and neurodegeneration in a population-based study. Neurology 2014;82:70-6.
13. Suhanov AV, Pilipenko PI, Korczyn AD, Hofman A, Voevoda MI, Shishkin SV, *et al*. Risk factors for Alzheimer's disease in Russia: A case-control study. Eur J Neurol 2006;13:990-5.
14. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. J Neurotrauma 2008;25:279-90.
15. Shishido H, Kishimoto Y, Kawai N, Toyota Y, Ueno M, Kubota T, *et al*. Traumatic brain injury accelerates amyloid-β deposition and impairs spatial learning in the triple-transgenic mouse model of Alzheimer's disease. Neurosci Lett 2016;629:62-7.
16. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, *et al*. Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology 1999;52:78-84.
17. Mehta KM, Ott A, Kalmijn S, Slooter AJC, van Duijn CM, Hofman A, *et al*. Head trauma and risk of dementia and Alzheimer's disease. Neurology 1999;53:1959-62.
18. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz JB, Keene CD, *et al*. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. JAMA Neurol 2016;73:1062-9.
19. Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, Hill GB, *et al*. Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156:445-53.