Research article

Traumatic brain injury as a risk factor for Alzheimer disease. Comparison of two retrospective autopsy cohorts with evaluation of ApoE genotype

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Abstract

Background and Purpose: The impact of traumatic brain injury (TBI) on the pathogenesis of Alzheimer disease (AD) is still controversial. The aim of our retrospective autopsy study was to assess the impact of TBE and ApoE allele frequency on the development of AD.

Material and Methods: We examined 1. the incidence of AD pathology (Braak stageing, CERAD, NIA-Reagan Institute criteria) in 58 consecutive patients (mean age $\pm$ SD 77.0 $\pm$ 6.8 years) with residual closed TBI lesions, and 2. the frequency of TBI residuals in 57 age-matched autopsy proven AD cases. In both series, ApoE was evaluated from archival paraffin-embedded brain material.

Results: 1. TBE series: 12.1 % showed definite and 10.3% probable AD (mean age 77.6 and 75.2 years), only 2/13 with ApoEε3/4. From 45 (77.6%) non-AD cases (mean age 78.2 years), 3 had ApoEε3/4. The prevalence of 22.4% AD in this small autopsy cohort was significantly higher than 3.3% in a recent large clinical series and 14% in the general population over age 70. 2. In the AD cohort with ApoEε4 allele frequency of 30% similar to other AD series, residuals of closed TBI were seen in 4 brains (7%) (mean age $\pm$ SD 78.2 $\pm$ 6.4), all lacking the ApoEε4 allele. TBI incidence was slightly lower than 8.5% in the clinical MIRAGE study.

Conclusions: The results of this first retrospective autopsy study of TBI, ApoEε allele frequency, and AD confirm clinical studies suggesting severe TBI to be a risk factor for the development AD higher in subjects lacking ApoEε4 alleles. Further studies in larger autopsy series are needed to elucidate the relationship between TBI, genetic predisposition, and AD.

Introduction

While some genetic risk factors, e.g. apolipoprotein (ApoE)ε4, predispose the elderly to develop Alzheimer disease (AD), the role of traumatic brain injury (TBI) in the pathogenesis of AD is still controversial. Accumulating epidemiological evidence implicates TBI as a risk factor for the subsequent development of AD [for rev. see [1,2], while others reported no such association [see

[3,4]. In the MIRAGE study, head injury as a risk factor for AD appeared greater among subjects lacking ApoEε4 [5]. Among longitudinal studies [6–9], two reported a significantly increased riks of developing AD in subjects with previous history of TBI [8,9] A recent study of 1776 US World War II navy veterans showed that moderate and severe TBI in early adulthood, rated by the duration of loss of consciousness or posttraumatic amnesia, was associated with increased risk of AD and dementia in late life (assessed by clinical protocols). The risk increased with the severity of the TBI and showed a nonsignificant trend towards a stronger association between AD and TBI in men with ApoEε4 alleles [9]. Although it is well established that deposition of amyloid β peptide (Aβ) known to play an important role in the pathogenesis of AD, in fatal TBI is associated with an ApoEε4 allele [10,11] and that TBI may induce tau pathology with the formation of neurofibrillary tangles, another major histological marker of AD [12,13], the mechanisms by which TBI may induce the formation of AD pathology are still unknown, and several interpretations have been proposed [13,14]. Whereas previous case-control and longitudinal epidemiological studies on the association between TBI and AD were exclusively based on clinical protocols, we present here data of a retrospective autopsy study on the relations between TBI residual lesions, ApoE allele frequency, and AD pathology.

Material and Methods

We examined two autopsy series from the research files of the Ludwig Boltzmann Institute of Clinical Neurobiology brain bank, Vienna, Austria, between 1977 and 2000. This material was mainly derived from a large teaching hospital with associated chronic hospital (together around 3000 beds) in Vienna, Austria. In this retrospective study, exact informations about IQ, education, and other major risk factors for AD were not available. 1. In a consecutive series of 58 patients over age 60 (mean ± SD 77.0 ± 6.8) years with residual closed TBI pathology we looked for the incidence of AD pathology. 2. In a consecutive series of 57 age-matched autopsy proven AD cases (mean ± SD age 77.6 ± 7.3 years) we looked for the presence of morphological TBI residuals. All patients were Caucasians and immunocompetent. All brains were examined histologically using routine stains including modified Bielschowsky silver stain and immunohistochemistry with a battery of antibodies against ABl-42, PHF tau (antibody AT-8), ubiquitin, and α-synuclein for the demonstration of Lewy bodies. The classification of AD was performed according to the Khachaturian criteria [15], the Consortium to Establish a Registry for Alzheimer Disease (CERAD) criteria [16], the Braak staging of neuritic Alzheimer lesions [17], and the National Institute on Aging (NIA)-Reagan Institute classification for the postmortem diagnosis of AD [18]. Evaluation of

ApoE alleles was performed in all cases of both cohorts from archival paraffin-embedded brain material using a semi-nested PCR method [19]. Since ApoE genotyping was performed retrospectively in cohort 1, no controls for older, non-TBI subjects were available. Statistical evaluation was performed using Chi-square test and the Mann-Whitney U-test.

Results

1. TBE series

Among the 58 autopsy cases over age 60 with residuals of closed TBI of various degrees and distribution, 7 brains or 12.1% (4 males and 3 females aged 69 to 83, mean ± SD 77.6 ± 6.4 years, revealed the pathological features of definite AD, i.e. Khachaturian positive, CERAD B or C, Braak stages 5 or 6, with a great likelihood of AD as cause of dementia according to the NIA-Reagan criteria. Only one of them exhibited ApoEε4, all the others were ε3/3 and ε2/3 (3 each). All these brains, in addition to severe neuritic AD pathology showed posttraumatic lesions of limited extent and various distribution, mainly old contusions in bilateral frontobasal areas (n = 1), frontotemporal (n = 1), right frontobasal and temporal(n = 2) with additional old cerebellar contusion (n = 2), and right frontal pole (n = 1). TBI history dated back 10 to 30 years prior to the death, but was unknown in 2 of these patients. The duration of AD ranged from 4 to 7 years. Two additional AD cases – 2 males aged 69 and 82 years, respectively – were excluded since the TBI due to falls had occurred 2 to 4 months prior to death after the development of severe dementia. Both brains showed definite AD (CERAD C, Braak stage 5); both were ApoE ε2/3. Further 6 cases or 10.3% (3 men and women each, aged 65-85, mean ± SD 75.2 ± 6.4 years) were pathologically classified "probable" AD, meeting positive Khachaturian criteria, CERAD B, Braak 3 or 4; with intermediate likelihood of AD as cause of dementia according to the NIA-Reagan criteria; only one of them had ApoEε3/4 allele, the others ε3/3 or ε2/3. In these patients, closed TBI had occurred between 8 and 39 years prior to death and many years before development of cognitive impairment, the duration of which ranged from 3 to 7 years. Neuropathology, in addition to AD lesions, revealed bilateral old traumatic contusional deficits or scars in frontobasal and temporopolar areas (n = 2), in the right frontopolar and temporal, and in the left frontobasal and temporal or in the left parietal region (2 cases each). None of these subjects had a history of chronic alcoholism, Korsakoff syndrome or any morphological signs of Wernicke encephalopathy or essential concomitant cerebrovascular lesions except for occasional mild lacunar state in the basal ganglia. None of them meet the morphological criteria for mixed type dementia (combination of AD and vascular encephalopathy), of Parkinson disease (PD) or of dementia with Lewy bodies (DLB) [20].

In the remaining 45 non-AD cases (77.6%; 36 men and 9 women aged 61 to 85, mean ± SD 78.2 ± 7.8 years), the ApoE allele frequency was ε3/3 (n = 39), ε3/4 and ε2/3 (n = 3 each) comparable to that in the general aged population [21–23]. Old traumatic brain lesions in this cohort were seen mainly in the frontobasal, frontopolar and temporopolar areas, less frequently frontobasal and frontopolar or temporal/ temporopolar unilaterally or bilaterally. In two of these cases (aged 85 and 86 years), neuropathology revealed additional PD of the Lewy body type with no only very few cortical Lewy bodies, thus excluding DLB [20].

2. AD cohort

Among 57 consecutive autopsy cases of definite AD aged 71 to 91 years with a mean ± SD of 77.6 ± 7.3 years the ApoeEε4 allele frequency was 30% (ε4/4 n = 6; ε3/4 n = 11) which was comparable to that in other AD series ranging from 24 to 38% [21–25]; all the others were ε3/3 or 2/3. Residuals of closed TBI were seen in 4 brains or 7.0 %, 2 men and women each aged 71-91 (mean ± SD 78.2 ± 5.6) years, all lacking ApoeEε4 alleles. They had suffered closed head injuries 7 to 54 years prior to death and, like in cohort 1, many years before onset of cognitive deterioration. A male dying at age 71 years has suffered a blow to the right parietal region with several hours unconsciousness 54 years prior to death; two women aged 76 and 91 years had suffered TBI with unknown duration of unconsciousness in car accidents 7 and 30 years before death, and a male aged 75 years had TBI with short unconsciousness due to a fall on the occiput 8 years prior to death, and a duration of AD of about 2 years. None of them had experienced repeated TBI as boxers or other sportsmen. Neuropathology, in addition to definite AD changes (Khachaturian positive, CERAD stage B or C, Braak stages 4 or 5, i.e. intermediate or high likelihood of AD as the cause of dementia according to the NIA-Reagan criteria), revealed old contusional scars in the frontobasal and temporal areas (n = 3) and in the parietal region (n = 1).

Discussion

To the best of our knowledge, this is the first study to detect AD pathology in a consecutive autopsy series of post-traumatic brain lesions and to look for the presence of residual brain lesions of closed TBI in a cohort of autopsy proven AD cases. The prevalence of 22.3% of probable and definite AD in a rather small cohort of subjects with a mean age of 75 to 77.6 years and residuals of closed TBI is considerably higher (p < 0.001) than 3.3% in the recent clinical US series of VA subjects who sustained moderate to severe TBI during World War II [9]. It was also higher than the prevalence of AD in the general Caucasian population showing a wide range between 3 and 11% for those older than 65 years (p < 0.001), about 14% for

those older than 70, and between 7 and 50% for subjects older than 85 years [26–31]. In comparison to AD patients showing an ApoEε4 prevalence of 24 to 38% [21–25], it was only 15.4% in the present cohort of AD cases with residual TBI lesions. The extent and distribution did not seem to influence later developrent of AD. Since in the majority of the patients later developing AD, TBI history 10 to 30 years prior to death and the mean age of these patients was comparable to the non-AD cases, one might exclude the possibility that a greater injury may have a bigger effect on AD development, especially when interacting with older age which is the most significant factor in AD [see [1]]. Since in this retrospective study no exact information on pre-morbid intellectual levels and education were available, no suggestions about brain reserve capacity (BRC) as a potential moderating factor on risk variables related to AD expression can be made.

The prevalence of residuals of previous closed TBI in 7% of a consecutive series of autopsy-proven AD aged 71 to 91 (mean 77.6 ± 7.3) years, all lacking an ApoEε4 allele, was slightly lower than in the large clinical MIRAGE study, where TBI with loss of consciousness in AD probands was reported in 8.5% [5]. This study like ours indicates that closed head injury is a higher risk factor for the development of AD among subjects lacking ApoEε4 alleles compared to those having them. This is in accordance with recent experimental data showing that transgenic mice expressing human ApoEε4 are more susceptible than those expressing ApoEε3 to closed head injury, probably related to a protective effect of ApoEε3 and an ApoEε4-related pathological function [32].

In conclusion, the results of this first retrospective study on the association of TBI and ApoE allele frequency on the development of AD confirm clinical studies suggesting some influence of severe TBI on the development of AD, being a higher risk factor for AD among subjects lacking ApoEε4 alleles compared to those having them. However, further studies in larger autopsy series of TBI and AD are needed to further elucidate the relationshipt between closed TBI, ApoE allele, and the development of AD.

Competing interests

None Declared

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