Interaction between apolipoprotein epsilon 4 and traumatic brain injury in patients with Alzheimer's disease and mild cognitive impairment

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Accepted for publication: December 28, 2006

Summary

Several pathogenetic factors seem to contribute to the development of Alzheimer's disease (AD). Some data point to a role for traumatic brain injury (TBI), but this suggestion is not universally supported. Mayeux et al. have shown that TBI increases the risk of AD, but only through a synergistic relationship with apolipoprotein epsilon (Apo E) 4. We present the results of a cross-sectional and longitudinal study of the relationship between these factors, conducted in northern and southern Italy. We studied 337 consecutive patients with probable AD and 63 subjects with mild cognitive impairment (MCI). Information concerning head injuries was collected by interview of informants and review of medical records. Twenty-one patients with AD and 9 with MCI were found to have a history of TBI with loss of consciousness. AD and MCI patients with a history of TBI, compared with control groups matched for age, sex, education and degree of mental impairment, showed more marked depressive and behavioural disturbances (Global Deterioration Scale and Neuropsychiatric Inventory, $p<0.05$). Six- and 12-month follow up of both groups did not show significant differences in the rate of progression of cognitive changes.

A high frequency of Apo E 4 was detected in the patients with TBI and cognitive impairment (40.5% in the AD and 11% in the MCI subgroups). The distribution of the epsilon 4 allele in our control group was 4%, comparable to that found in the Italian population. Distribution of the above parameters was similar in patients from northern and southern Italy.
The higher frequency of TBI and Apo E 4 genotype among AD and MCI patients confirms the synergistic interaction of environmental and genetic factors in the development of dementia. Our data do not suggest that the presence of these two factors influences the clinical presentation or the course of the disease.

KEY WORDS: Alzheimer's disease, apolipoproteins, mild cognitive impairment, traumatic brain injury.

Introduction

Studies of risk factors in Alzheimer's disease (AD) suggest the interaction of multiple pathogenetic factors, leading to the concept of "convergence syndrome" as proposed by Blass et al. (1). Traumatic brain injury (TBI) is one of the factors thought to be related to the pathogenesis of AD, its role first being suggested by epidemiological studies (2). This suggestion was later supported by the description of AD-like neuropathological changes in dementia pugilistica (3). Other epidemiological studies, however, have given rather ambiguous (4,5) or even conflicting findings (6-9).
Mayeux and collaborators were the first to show that TBIs may increase the risk of AD through a synergistic relationship with apolipoprotein epsilon (Apo E) 4 (10, 11). Data from the MIRAGE (Multi-Institutional Research in Alzheimer Genetic Epidemiology) project (12), as well as a recent review (13), have shown a complex relation between these factors. An interaction between Apo E and TBI is also suggested by some animal studies (14,15).
We present the results of a cross-sectional study of the relationship between TBI and Apo E conducted in northern and southern Italy. In addition to investigating genotypic factors and history of TBI in AD, we enroled a group of subjects with mild cognitive impairment (MCI), and a control group. We hypothesized that we would find an association between Apo E 4 and TBI not only in AD, but also in MCI patients. We further hypothesized that a history of TBI would be a predictor of a worse clinical outcome, including conversion from MCI to AD.

Materials and methods

The study included 337 consecutive patients with diagnosis of probable AD and 63 subjects with MCI. The pa-

tients with probable AD were selected in accordance with the NINCDS-ADRDA criteria (16); those with MCI were selected using the criteria of Petersen et al. (17).
The quantification of cognitive and functional status was obtained using the following tests and scales:
Mini Mental State Examination (MMSE, range 0 to 30), and the *Clinical Dementia Rating Scale* (CDR), range 0 to 5, to assess global cognitive impairment (18,19);
Attention matrices: number cancellation task to evaluate selective attention (range 0-60)(20);
Corsi's span: short-term visuo-spatial memory test (range 0-10) in which the examiner shows a progressively growing sequence of visual stimuli (cubes arranged on a board), and the subjects try to repeat the sequence (20);
Digit span: short-term verbal memory test (range 0-10) in which the subjects listen to and try to repeat correctly a growing sequence of digits (20);
Mental Deterioration Battery (MDB) (21), comprised of eight tests, four that express the processing of verbal material and the other four the processing of visuospatial material. The verbal tests are: immediate and delayed recall of Rey's 15 words (range 0-75, 0-15 respectively), word fluency (FAS), phrase construction (range 0-25). The visuospatial tests are: Raven's 47 progressive coloured matrices (range 0-36), immediate visual memory (range 0-22), and copying of drawings freehand (range 0-12) and with landmarks (range 0-70).
Affective symptoms were assessed using the *Geriatric Depression Scale* (GDS) (22).
The *Neuropsychiatric Inventory* (NPI) and its subscales were used to evaluate behavioural symptoms and caregiver distress (23).
The *Instrumental Activities of Daily Living* (IADL) (24) and *Activities of Daily Living* (ADL) scales (25) were also applied to evaluate functional status.
Information concerning head injuries was collected by interview of multiple informants and review of medical records. The definition of traumatic events followed the guidelines proposed by Bevilacqua et al. (26). Accordingly, events were coded as follows:
– asymptomatic: no loss of consciousness, no amnesia, normal neurological examination;
– mild: no loss of consciousness, normal neurological examination, but vomiting and headache;
– moderate: post-traumatic amnesia of less than an hour, short loss of consciousness with complete recovery within an hour, normal neurological examination, but persisting headache and/or vomiting and/or post-traumatic confusion;
– moderate to severe: loss of consciousness or confusion, lasting up to 24 hours, post-traumatic amnesia for one to two hours, repeated and persistent headache and/or vomiting, possible signs or symptoms suggesting a focal neurological deficit;
– severe: loss of consciousness or confusion lasting over 24 hours, post-traumatic amnesia for one to seven days; there may or may not be presence of neurological signs.
The determination of the Apo E genotype was performed at the CNR Institute of Neurological Sciences, Cosenza, Italy.
Genomic DNA was extracted from leukocytes harvested from whole blood using standard methods and the Apo E genotyping was performed using the following oligonucleotide primers (reverse 5'-ACAGAATTCGCCCCGGCCTGGTACACTGCCA-3') and (forward 5'-TAAGCTTGGCACGGCTGTCCAAGGA-3'). Each reaction mixture was heated at 94°C for 5 min, and submitted to 35 cycles as follows: denaturation at 94°C for 30 s, annealing at 65°C for 30 s, followed by extension at 70°C for 1 min and 30s, then a final extension at 70°C for 10 min. After polymerase chain reaction amplification, 10 units of CfoI (Boehringer, Mannheim) were added directly to each reaction mixture for digestion of Apo E sequences and left for at least 3 h at 37°C. Each digested unit was loaded onto a 20% polyacrylamide non-denaturing gel and electrophoresed for 16 h at 100V, and then visualized by ultraviolet light after staining with ethidium bromide.
The statistical analysis of the data was carried out using SPSS 11. In addition to descriptive statistics and chi-square analyses, we carried out ANCOVAs and regression analyses with appropriate post hoc corrections.

Results

We considered three groups of subjects whose profiles and findings are detailed below:

Group 1 – Patients with AD

General features of the AD group. This group comprised 337 patients, 241 women (71.5%) and 96 men (28.5%). They presented mild to moderate severity of dementia (CDR 1-2, MMS ≥14). Their mean years of schooling were 5.6±2.3 (range 3-17) and their mean age was 76.5±7.8 years (range 51-92). All the patients had satisfactory nutritional status. At the time of first examination, 39% presented one concomitant disease while 12.5% had more than one, most commonly arterial hypertension, cardiopathies and diabetes mellitus. Drugs acting on the CNS were used by 52.5%; 12.2% used anticholinesterase inhibitors (namely, donepezil 67%, rivastigmine 29%, galantamine 4%).

Features of the AD-TBI group. Twenty-one of the 337 AD patients had a history of moderate to very severe TBI: post-traumatic coma lasting less than an hour in four, less than 24 hours in six, and more than 24 hours in 11. The interval between the TBI and the examination was less than five years in four cases, between five and 10 years in seven cases and over 10 years in 10 cases. They had a younger mean age (71.8 years) than the AD group as a whole, and a higher proportion of males (11/21).
Forty-two cases were selected from the original 337 patients to serve as controls (AD-C) on the basis of comparable social and demographic features, age, schooling and severity of dementia. In 20% of both groups, there was a family history of dementia. As seen in Table I, which details the main socio-demographic and functional variables in the two groups, the TBI group showed more severe affective and behavioural disorders (they had significantly higher GDS and NPI scores) and increased use of antidepressive and anxiolytic medications (38% vs 19% in the AD-C group).
Both groups were seen three times: at baseline and after 6 and 12 months (Table II). Only one patient from each group was lost to follow up. As expected, both

Table I - Socio-demographic and functional data of Alzheimer's disease patients with and without a history of traumatic brain injury.

	AD-TBI (n=21)	AD-C (n=42)
Age	71.8±7.3	72.1±7.1
Gender (M/F)	11/10	22/20
Education in yrs	5.6±2.1	5.6±2.1
Dementia features		
MMSE	19.8±3.6	20.4±3.4
GDS	12.5±5.1	9.5±4.4*
NPI	25.4±9.1	19.7±8.9*
Disease duration in months	32±20	38±16
Functional status		
IADL	4.7±2.5	5.1±1.8
ADL	5.1±1.3	5.5±0.9
Comorbidity		
Hypertension	7	15
Diabetes	1	3
Ischaemic cardiopathy	3	6
Tumours	2	4

* p<0.05 TBI patients vs controls.
Abbreviations: AD-TBI=Alzheimer's disease patients with history of traumatic brain injury; AD-C=control group of Alzheimer's disease patients without history of traumatic brain injury; MMSE=Mini Mental State Examination; GDS=Global Deterioration Scale; NPI=Neuropsychiatric Inventory; IADL=Instrumental Activities of Daily Living scale; ADL=Activities of Daily Living Scale.

groups showed a cognitive and functional decline over the follow up. An ANCOVA performed on the data presented in Table II with TBI as a variable failed to show any significant difference between the two groups.

Group 2 – Patients with MCI

General features of the MCI group. This group comprised 63 patients, 39 women (62%) and 24 men (38%). Their mean age was 71.5±8 years (range 51-86). The onset of cognitive disorders had occurred, on average, 12.3±5.3 months prior to the baseline examination (range 6-24 months). The cognitive disorder mainly involved episodic memory.

Features of the MCI-TBI group. Nine of the 63 patients with MCI presented a history of head injury, generally more severe than that found in the AD-TBI group. Indeed, only one subject had experienced a trauma of moderate severity (post-traumatic loss of consciousness lasting less than an hour). In three cases, the TBI was moderate to severe, and in five cases it was severe. The interval between the TBI and the examination was less than five years in two cases, between five and 10 years in two cases, and over 10 years in five cases.
Eighteen of the original 63 patients were selected to serve as controls on the basis of comparable social and demographic features, age, and schooling. Co-morbid events were present with the same frequency and distribution in the two groups.

Table II - Neuropsychological characteristics at baseline and at 6- and 12-month follow up of patients with Alzheimer's disease with and without a history of traumatic brain injury.

	AD-TBI			AD-C		
	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months
GDS	12.3±5	11.3±.6	12.3±6	9.6±4.3	9.9±5.1	10.3±4.5
NPI	25.5±9	27.5±10	28.3±13	19.9±9	21.3±12	24.4±14
IADL	4.6±2.5	4.3±2.3	3.7±2	5.1±1.7	4.5±1.6	3.9±1.7
ADL	5.2±1.2	4.8±1.3	4.5±1.2	5.4±0.9	5.2±1.1	4.7±1.1
MMSE	19.9±3.6	18.5±36	17.3±3.8	20.5±3.4	19.2±3.3	18.3±3.9
AM	32±9	28±12	22.8±14	36±8	33±11	24±10
DS	3.5±0.5	3.3±0.6	3.0±0.6	3.7±0.6	3.3±0.5	3.1±0.7
Corsi	3.5±0.7	3.2±0.5	3.1±0.6	3.8±0.7	3.7±0.7	3.4±0.8
MDB						
Verbal tests						
RI	18.9±6.5	16.6±6.7	14.4±7.1	19.9±6.1	18.7±7.4	16.5±7
RD	1.4±1.8	1.4±1.7	1.1±1.9	1.6±1.6	1.5±1.4	1.3±1.5
FAS	13.8±5	12.4±7.7	9.2±7.1	14.7±5.6	13.9±7	11.4±7
SC	13±6.5	11.4±6	6.8±6.3	13.9±6.6	12.4±6.2	8.8±7
Visuospatial tests						
CD f	8.6±2.3	8.0±2.3	6.9±2.8	8.9±2.7	8.5±3.1	7.5±3
CD l	46±14	42±15	38±16	49±14	47±17	41±15
IVM	13±2.8	12±3.1	10±3	15±4.8	13.2±6	11.5±5
PM	16.2±4.5	14.4±8	11.1±7.7	16.5±5.5	13.1±7.8	12.3±6.7

Abbreviations: AD-TBI=Alzheimer's disease patients with history of traumatic brain injury; AD-C=control group of Alzheimer's disease patients without history of traumatic brain injury; GDS=Global Deterioration Scale; NPI=Neuropsychiatric Inventory; IADL=Instrumental Activities of Daily Living scale; ADL=Activities of Daily Living scale; MMSE=Mini Mental Status Examination; AM=Attention Matrices; DS=Digit Span; Corsi=non verbal span; MDB=Mental Deterioration Battery; RI=Rey's 15 word list, immediate recall; RD=Rey's 15 word list, delayed recall; FAS=word fluency (letters); SC=sentence construction; CD f=copy of drawings, freehand; CD l=copy of drawings, with landmarks; IVM=immediate visual memory; PM=Raven's progressive matrices.

Table III - Neuropsychological test results at baseline, and at 6- and 12-month follow up of patients with mild cognitive impairment with and without a history of traumatic brain injury.

Tests	MCI-TBI (n=9)			MCI-C (n=18)		
	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months
MMSE	24.9±2.3	23.8±2.7	22.9±3.6	25.8±2.6	24.5±3.2	23.8±3.4
AM	42.1±8.9	41.6±7.7	42.6±8.7	44.0±8.4	44.5±7.4	43.9±7.4
DS	3.9±0.6	3.9±0.7	3.9±0.7	4.0±0.7	4.1±0.7	4.0±0.7
Corsi	4.2±0.4	4.0±0.6	4.0±0.7	4.5±0.9	4.4±0.8	4.4±0.9
RI	25.8± 7.5	23.9±7.8	23.6±8.8	26.5±8.3	25.3±7.5	24.7±7.8
RD	3.1±2.3	2.7±2.5	2.4±2.3	2.8±2.5	2.5±2.1	2.2±2.2
FAS	23.5±9.5	23.0±10.0	21.0±9.8	24.0±9.6	23.4±9.1	22.9±10.0
SC	17.5± 6.8	17.8±7.5	17.7±7.9	18.2±5.9	18.1±6.1	18.3±6.0
CD f	9.9±1.7	9.5±2.3	9.2±2.0	9.6±1.8	9.5±2.0	9.3±2.2
CD l	66.9±3.2	67.9±3.4	66.4±1.6	65.7±4.3	65.8±3.9	65.3±4.5
IVM	17.6±3.2	17.8±3.0	18.0±4.0	17.5±3.8	17.6±3.7	17.4±3.6
PM	23.5±4.7	22.8±4.8	21.8±5.0	24.6±4.9	24.3±5.5	23.4±5.1

Abbreviations: MCI-TBI=patients with mild cognitive impairment and a history of traumatic brain injury; MCI-C=control group of patients with mild cognitive impairment and no history of traumatic brain injury; MMSE=Mini Mental State Examination; AM=Attention Matrices; DS=Digit Span; Corsi=non verbal span; RI=Rey's 15 word list, immediate recall; RD=Rey's 15 word list, delayed recall; FAS=word fluency (letters); SC=sentence construction; CD f=copy of drawings, freehand; CD l=copy of drawings, with landmarks; IVM=immediate visual memory; PM=Raven's progressive matrices.

Table IV - Neuropsychological test results in incidental cases of traumatic brain injury (I-TBI) and controls without TBI (I-C) at baseline, 6 months and 12 months follow-up.

Tests	Baseline TBI (n=16)	6 Months	12 Months	Baseline I-C (n=12)	6 Months	12 Months
MMSE	25.6±2.1	26.9±1.7	26.8±1.8	27.9±1.5	28.0±1.3	27.8±1.5
AM	39.1±6.6	40.5±6	42.0±7.0	47.5±4.2	47.8±5	49±74.6
DS	3.8±0.7	3.9±0.6	3.9±0.6	4.2±0.7	4.1±0.7	4.2±0.6
Corsi	4.3±0.5	4.4±0.6	4.5±0.6	4.6±0.5	4.7±0.5	4.7±0.5
RI	32±7.2	34.9±6.5	35.8±7.1	39.6±8	38.8±8	40±7
RD	5.6±2.0	6.1±1.7	6.2±1.8	7.7±2.4	7.9±2.3	7.5±2.6
FAS	24.8±7.5	26.6±6.3	26.9±7.4	30.4±7	31.4±6.7	30.7±5.7
SC	16.9±6.4	17±76.2	17.1±6.1	19.7±3.1	19.9±3	20±3.2
CD f	10.1±2.1	9.9±21.4	10.2±1.3	9.8±0.9	10±1.2	9.9±1
CD l	66.5±3.0	67.0±3.3	67.1±3.1	67.6±1.7	67.7±1.8	67.9±1.7
IVM	17.3±1.5	17.5±1.9	17.6±1.6	18.2±1.6	18.3±1.7	18.4±1.5
PM	24.2±5.2	25.4±4.7	25.7±4.8	28.5±3.6	28.3±4	28.6±3.7

Abbreviations: I-TBI=incidental cases of traumatic brain injury; I-C=controls without traumatic brain injury; MMSE=Mini Mental State Examination; AM=Attention Matrices; DS=Digit Span; Corsi=non verbal span; RI=Rey's 15 word list, immediate recall; RD=Rey's 15 word list, delayed recall; FAS=word fluency (letters); SC=sentence construction; CD f=copy of drawings, freehand; CD l=copy of drawings, with landmarks; IVM=immediate visual memory; PM=Raven's progressive matrices.

Table V - Apo-E allele frequencies.

	Total n=58	AD-TBI n=21	MCI-TBI n=9	Trauma n=16	Study controls n=25	Nationwide controls
E2	6%	0	0	9.5%	16.5%	7.3%
E3	75%	59.5%	89%	84.5%	79.5%	87.2%
E4	19%	40.5%	11%	6%	4%	5.5%

Abbreviations: AD-TBI=Alzheimer's disease patients with history of traumatic brain injury; MCI-TBI=patients with mild cognitive impairment and a history of traumatic brain injury.

As seen in Table III the TBI patients showed, at baseline, a trend towards a worse cognitive performance compared with the controls, which, however, never reached statistical significance. At 12 months, the MCI-TBI group showed increased impairment in terms of MMS ($p<.05$), long-term episodic memory (delayed Rey $p<.05$) and visuospatial abilities (free drawing copy $p<.05$). However, ANCOVA failed to show an effect of the "trauma" variable.

A follow-up analysis of the clinical data and of the cognitive profile of the 27 cases showed that 24 cases still showed MCI after 12 months, whereas the picture of three patients, one with TBI and two without, had converted to one of dementia.

Group 3 – Incidental cases of recent TBI and their controls

This group included 16 subjects over 60 years of age without a history of cognitive or behavioural changes prior to a recent TBI. Three had suffered a mild trauma, 11 a moderate and two a moderate-to-severe TBI. A group of 12 subjects matched for age, gender and schooling, but without TBI, cognitive or behavioural changes, was used as controls.

Table IV shows the cognitive performances of the two subgroups. The patients with TBI showed a cognitive disorder in executive functions (Raven's PM $p<0.05$) and episodic memory (Rey immediate and delayed recall $<.05$), which tended to improve during the follow-up period.

Analysis of the Apo E genotype

The analysis was carried out in all patients with TBI (21 AD, 9 MCI) as well in the 16 incidental cases and their 12 controls. The results from these 58 subjects were compared to the distribution within the population of AD patients of the same age as defined by the IMSEB Centre, National Research Council, Cosenza, Italy (27). Table V shows that 19% of the total 58 cases had an E 4 allele; this rose to 31.7% when considering the patients with cognitive deterioration (either AD or MCI) and TBI. In the AD-TBI group, it reached 40.5%. This compares to 4% in a control group drawn from our own patients made up of 25 subjects without TBI, and to 5.5% in the overall AD population.

An analysis of the geographical distribution showed no difference between northern Italian and southern Italian subjects.

Discussion

We found that 6.5% of an unselected group of patients with AD had a significant TBI. This result has to be compared to the 8.3% recorded in the MIRAGE study and the 11.5% found in the study by Mayeux et al. (11). The discrepancy between our finding and those of the other two studies could be explained by the different methods used to record head trauma. Our method was quite conservative. A higher frequency can be expected to emerge in studies considering a single informant, whereas those, like ours, that consider the reports of multiple informants and the content of medical records are likely to find a lower percentage. As stated by Guo et al. (12), a high level of association between head injury and AD may be in part "simply an effect of recall bias" with relatives over-reporting head injury in patients with dementia. Despite its relatively small size, our MCI group showed a considerably higher percentage of TBI (14.3%). This is partially explained by the fact that the MCI group included a higher percentage of males.

The distribution of Apo E 4 showed a very marked increase in AD-TBI compared to the AD-C patients. An increase was also found in the MCI-TBI patients compared to those without trauma. These results strongly suggest a synergistic interaction of environmental and genetic factors in the development of dementia, due to the higher frequency of TBI and Apo E 4 genotype among AD patients.

Our finding of a synergistic interaction is in agreement with several previous studies (10,28-31). Also, Friedman et al. (32) demonstrated a strong association between Apo E 4 and a poor clinical outcome following TBI, implying genetic susceptibility to the effect of brain injury. The results reported by Plassman et al. (33) are along the same lines, even though a trend towards a stronger association between AD and head injury in patients with more Apo E 4 alleles was found only in men and was not significant. On the other hand, Chamelian et al. (34) did not find an association between Apo E 4 and TBI outcome. Two studies give more complex results. Guo et al. (12) found that the influence of head injury on the risk of AD appears to be greater among persons lacking Apo E compared with those having one or two Apo E 4 alleles. Another autopsy-based study (35) gave similar results. These two studies would indicate an additive rather than a synergistic relation between TBI and Apo E 4.

Some studies do not support an association of TBI with AD (6-9). However, our findings as well as those of other studies reporting an association are compatible with the results of several animal studies. For instance, Sabo et al. (14) showed that transgenic mice expressing human Apo E 4 have a worse outcome following closed head injuries. Another study has shown that repetitive TBI accelerates brain Abeta accumulation and oxidative stress as well as cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis (15).

The neuropsychological profile of AD patients with TBI did not differ from that of AD patients without TBI. This was also true of the MCI patients. Furthermore, a previous brain trauma was not found to contribute to a more rapid conversion to dementia. Although the follow-up period in this study was not very long, our data thus far suggest that the presence of Apo E 4 and a history of TBI contribute to the appearance of AD, but do not influence its clinical presentation or course.

Acknowledgments

This study was partially funded by grants from TF MINISAN 2000 "Interazione fra apo-E e fattori ambientali nella malattia di Alzheimer".

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