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Synergistic effects of traumatic head injury and apolipoprotein 4 in patients with Alzheimer's disease

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Synergistic effects of traumatic head injury and apolipoprotein-ε4 in patients with Alzheimer's disease

Article abstract—The apolipoprotein-ε4 allele increases the risk of Alzheimer's disease (AD), but cerebral deposition of β-amyloid with age, a genetic mutation, or head injury may contribute to the pathogenesis of this disease. We examined the risks of AD associated with traumatic head injury and apolipoprotein-ε4 in 236 community-dwelling elderly persons. A 10-fold increase in the risk of AD was associated with both apolipoprotein-ε4 and a history of traumatic head injury, compared with a two-fold increase in risk with apolipoprotein-ε4 alone. Head injury in the absence of an apolipoprotein-ε4 allele did not increase risk. These data imply that the biological effects of head injury may increase the risk of AD, but only through a synergistic relationship with apolipoprotein-ε4.

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Roberts et al[1] observed cerebral β-amyloid (βAP) deposits and neurofibrillary tangles in the brains of professional and amateur boxers who were demented before death and in individuals who died as a result of severe head injury. Further, some but not all epidemiologic studies have found an association between Alzheimer's disease (AD) and head injury.[2] Roberts et al[1] also found increased expression of β-amyloid precursor protein (βAPP) following trauma to the brain; this has been interpreted as an acute response to neuronal injury. They considered these observations to be compatible with a major role for amyloid deposition in the pathogenesis of AD because cerebral βAP deposition is considered a key step in a "neurotoxic" cascade leading to neuritic plaques and neuronal death.[3]

Because individuals homozygous or heterozygous for apolipoprotein-ε4 (Apo-ε4) are at significantly higher risk for AD than individuals with other genotypes,[4] and because the amount of cerebral βAP deposition in AD may be related to the specific Apo-E genotype,[5] we hypothesized that a history of traumatic head injury and the presence of an Apo-ε4 allele would have a synergistic effect on the risk of AD among community-dwelling elderly people.

Methods. Blood for genomic DNA testing was obtained from 113 patients meeting research criteria for AD and from 123 healthy elderly persons. Both groups of subjects resided in the same region of northern Manhattan and were identified in a population-based study of AD and related dementias. Eight of the 113 cases of AD were autopsy confirmed. Cases and controls were matched for age (within 5 years), gender, and ethnic group (African American, Hispanic, or white).

Genomic DNA was amplified by polymerase chain reaction, using reaction conditions modified from those described by Hixson and Vernier.[6] The genotypes were determined by the sizes of DNA fragments present, viewed and photographed under ultraviolet light after staining with 0.5 μg/ml of ethidium bromide. All genotypes were determined without knowledge of patient-control status.

Data collection. A semi-structured interview, previously established as reliable, was used to inquire about head injury with loss of consciousness.[2] For ethnic group classification, we used the format suggested by the 1990 United States Census Bureau.

Data analysis. Allele frequencies for patients with AD and controls were estimated by counting alleles and calculating sample proportions. Frequencies of Apo-E genotypes in patients and controls were compared using the chi-square test. The frequencies for the demographic variables (including ethnic group) and risk factors were compared between cases and controls using chi-square analyses. Both univariate and multivariate odds ratios for AD associated with Apo-ε4 were calculated from logistic regression adjusting for age and ethnic group.

Results. Patients with AD and controls were similar in age (AD 74.0 ± 10.5 [SD], controls 72.0 ± 9.1 [SD]), gender (% women: AD 74.5%, controls 69.1%), and ethnic group (African American: AD 50.7%, controls 49.3%; Hispanic: AD 48.9%, controls 51.1%; and white: AD 44%, controls 56%). AD patients had significantly fewer years of education than did controls (AD 8.5 ± 5.6, controls 10.4 ± 4.8; $p < 0.01$).

The allele frequency of Apo-ε4 was significantly greater among patients with AD than in controls (0.29 versus 0.16; $\chi^2 = 13.4$, $p < 0.001$). The Apo-ε4 allele frequency did not differ by age, gender, or years of education within either cases or controls. Apo-ε4 allele frequency was similar for patients with AD regardless of ethnic group (African American 0.33, Hispanic 0.34, and white 0.30), but differed significantly among controls (African American 0.28, Hispanic 0.13, and white 0.10; $\chi^2 = 11.2$, $p < 0.05$). The odds ratio (OR) for AD associated with homozygosity for Apo-ε4 was 3.9 (95% CI, 1.2 to 13.2, $p < 0.01$) and that associated with heterozygosity was 2.0 (95% CI, 1.2 to 3.6, $p < 0.01$) compared with other Apo-E genotypes. Adjustments for age, education, and ethnic group did not result in a change in the magnitude of the OR for AD associated with Apo-ε4 homozygosity or heterozygosity.

Table. Independent effects of apolipoprotein-ε4 (Apo-ε4) and head injury among patients and controls

Head injury	Apo-ε4 (one or more alleles)	Alzheimer's disease	Controls	Odds ratio (95% CI)*	Adjusted for age and education (95% CI)*
No	No	52	78	1.0, reference	1.0, reference
No	Yes	48	35	2.0 (1.2-3.6)†	2.0 (1.1-3.5)†
Yes	No	6	9	1.0 (0.3-2.9)	1.0 (0.3-3.2)
Yes	Yes	7	1	10.5 (1.3-88.7)†	10.2 (1.2-89.0)†

* 95% confidence interval for the odds ratio. In this stratified analysis, we had 80% power to detect an odds ratio of 9.6 or more for the interaction.
† Statistical significance, $p < 0.05$.

Thirteen patients (11.5%) with AD had a history of head trauma associated with loss of consciousness that preceded onset of dementia by at least 2 years, whereas 10 (8.1%) controls reported a similar injury. The distribution of head injury was similar across ethnic groups. The OR for AD associated with head injury was 1.5 (95% CI, 0.5 to 3.5, p = 0.5). To examine the relationship between the presence of Apo-ε4 and head injury in terms of their joint and independent effects on the risk of AD, we stratified the cases and controls by these two variables (table). There was no difference in age, gender, or ethnic group among the cases and controls across the four strata. Using as the reference group persons with neither a history of head injury nor an Apo-ε4 allele, we estimated the OR for AD associated with both a history of traumatic head injury and the presence of at least one Apo-ε4 allele (OR = 10.5; 95% CI, 1.3 to 87.8), traumatic head injury alone (OR = 1.0; 95% CI, 0.3 to 2.9), and the presence of Apo-ε4 alone (OR = 2.0; 95% CI, 1.1 to 3.5), adjusting for age by logistic regression. Thus, the OR for the joint effect of head injury and Apo-ε4 exceeded that expected from the independent effects of both risk factors (ie, 1.0 × 2.0 = 2.0), suggesting a synergistic relationship. We also formally tested for interaction using logistic regression. In this model, the OR for Apo-ε4 was 2.1 (95% CI, 1.2 to 3.6, $p < 0.01$), that for head injury was 1.0 (95% CI, 0.3 to 3.1, p = 1.0), and that for the interaction (ie, Apo-ε4*head injury) was 5.1 (95% CI, 0.6 to 43.8, p = 0.1).

Discussion. This investigation provides evidence to suggest a synergistic relationship between an environmental risk factor (head injury) and a marker of genetic susceptibility to AD (Apo-ε4). Although the number of patients and controls with head injury we report is modest, the frequency of this risk factor approximates the lifetime frequency we observed in a previous study in this community.[2] In the absence of Apo-ε4, the OR for head injury was not elevated; thus, our results indicate that the effect of head injury on AD risk may be restricted to persons either homozygous or heterozygous for Apo-ε4. The findings are most consistent with a model in which an environmental risk factor has no effect alone, yet it exacerbates the effect of genetic susceptibility.[7] The OR for interaction using logistic regression was elevated; however, it was not statistically significant, but this analysis was very conservative. To detect a significant interaction of the same magnitude using this approach we would need nearly twice as many subjects.[8] As such, our conclusions must remain tentative, but they are consistent with two major views on the pathogenesis of AD.

The pathology of dementia in boxers was considered to consist mostly of neurofibrillary tangle formation, but Roberts et al,[1] using immunostaining, identified βAP deposits in brain as well. Moreover, they also detected diffuse deposits of βAP, not neurofibrillary tangles, in the upper layers of the neocortex of patients with fatal head injuries but no history of dementia, as well as increased βAPP immunoreactivity in all head-injury cases examined.[1] The latter observation might suggest that βAPP is increased as an acute-phase response to neuronal injury, which, in turn, leads to βAP deposition in cortex. The amyloid hypothesis converges on the role of cerebral βAP deposition as the initial event leading to the formation of neuritic plaques and subsequent neuronal death. βAP deposition may result in cell death by binding to specific molecules on the cell surface or by rendering neurons more susceptible to excitotoxic, ischemic, or other metabolic constituents.[3] Because Apo-E is involved in cholesterol transport, it may sequester proteins such as amyloid in response to brain injury.[4] Poirier et al[9] found Apo-E mRNA and the number of Apo-E immunoreactive cells increased following electrolytic lesions of rat hippocampus, and proposed that Apo-E could be a trophic factor secreted by astrocytes for membrane synthesis and synaptogenesis in response to injury. Thus, individuals with one or more copies of the Apo-ε4 allele might be more likely to deposit βAP in cortex following head injury than individuals with other genotypes.

Our results would also be compatible with a recent hypothesis forwarded by Strittmatter et al,[10] who proposed that the absence of Apo-ε3 results in more rapid tau phosphorylation, leading to instability of the microtubule system in neurons and the formation of paired helical filaments and neurofibrillary tangles, thereby increasing the risk of AD.

Thus, the formation of neurofibrillary tangles in people with a history of head injury who become demented might be related to their Apo-E genotype as well to any direct effect of the trauma.

The exact mechanism underlying the role of Apo-E in the pathogenesis of AD remains unresolved, but the Apo-E genotype may specify a degree of genetic susceptibility to AD that can be exacerbated by the effects of other genes or environmental risk factors such as traumatic head injury.

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References

1. Roberts GW, Gentleman SM, Lynch A, et al. β-Amyloid protein deposition in the brain after severe head injury. J Neurol Neurosurg Psychiatry 1994;57:419-425.
2. Mayeux R, Ottman R, Tang M-X, et al. Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. Ann Neurol 1993;33:494-501.
3. Selkoe DJ. Physiological production of the amyloid β-amyloid protein and the mechanism of Alzheimer's disease. Trends Neurosci 1993;16:403-409.
4. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993;43:1467-1472.
5. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: High affinity binding to beta-amyloid and increased frequency of type 4 allele in late onset familial Alzheimer's disease. Proc Natl Acad Sci USA 1993;90:1977-1981.
6. Hixson J, Vernier D. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhAl. J Lipid Res 1991;31:545-548.
7. Ottman R. An epidemiologic approach to gene-environment interaction. Genet Epidemiol 1990;7:177-185.
8. Smith PG, Day NE. The design of case-control studies: the influence of confounding and interaction effects. Int J Epidemiol 1984;13:356-365.
9. Poirier J, Hess M, May PC, Finch CE. Cloning of hippocampal poly(A) RNA sequences that increase after entorhinal cortex lesion in adult rat. Brain Res Mol Brain Res 1991;9:191-195.
10. Strittmatter WJ, Weisgraber KH, Goedert M, et al. Hypothesis: microtubule instability and paired helical filament formation in the Alzheimer disease brain are related to apolipoprotein E genotype. Exp Neurol 1994;125:163-171.

Sneddon's syndrome is a thrombotic vasculopathy: Neuropathologic and neuroradiologic evidence

Article abstract—We report the first case of pathologic findings from brain biopsy in a patient with Sneddon's syndrome. The observations suggest that Sneddon's syndrome is not a vasculitis but is more comparable to the autoimmune vasculopathies such as the antiphospholipid antibody syndrome. Vascular thrombosis and emboli from cardiac sources are the likely causes of stroke in most cases. The success of warfarin in the treatment of antiphospholipid syndromes and the failure of immunosuppression and aspirin in the treatment of Sneddon's syndrome argue that warfarin anticoagulation may be the most appropriate intervention currently available.

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Sneddon's syndrome is the association of cerebral vascular disease and livedo reticularis (racemosa).[1-5] Its prevalence and its etiology are unknown.[3] The average time to diagnosis of Sneddon's syndrome is 10 years from the onset of symptoms, and it is likely an underdiagnosed condition.[3] Although some studies have reported that up to 35% of patients with this syndrome test positive for antiphospholipid antibodies,[4] most test negative.[2,3,5,6] Reports of dermatologic pathology have been conflicting; while some have revealed vasculitic features including small-vessel endothelitis and inflammatory obstruction,[2,6] others describe a noninflammatory vasculopathy restricted to small and medium-sized arteries.[3,5] The brain pathology has been inferred from MRI and CT studies; no brain biopsies and only one limited autopsy specimen have been reported.[3,7] In addition, only a few reports[2-6,8] have included angiographic or single-photon emission computerized tomographic (SPECT) studies.

We report the unusual case of a young woman with a progressive vascular dementia due to Sneddon's syndrome and discuss the results of her clinical and laboratory evaluation, including cerebral angiography, in the context of the histopathologic findings in her brain biopsy.