Genetic Susceptibility and Head Injury as Risk Factors for Alzheimer's Disease Among Community-dwelling Elderly Persons and their First-degree Relatives

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We performed a community-based study to investigate the relationship of genetic susceptibility and head injury to Alzheimer's disease (AD) in 138 patients with AD and 193 healthy elderly control subjects. Data concerning presence or absence of dementia and certain exposures were also obtained from 799 first-degree relatives of the patients and 1,238 first-degree relatives of the control subjects. Adjusting for age, gender, and other risk factors, the odds ratio for AD associated with head injury was 3.7 (95% confidence interval [CI], 1.4–9.7). The association was highest for head injuries that occurred after age 70. The risk of AD was higher in first-degree relatives of patients with onset prior to age 70 than in relatives of control subjects (risk ratio [RR] = 2.5; 95% CI, 1.1–5.6). The risk was not increased for relatives of patients with onset of AD at age 70 or older. Compared with relatives without head injury, the risk of AD was increased among both head-injured relatives of patients (RR = 5.9; 95% CI, 2.3–14.8) and head-injured relatives of control subjects (RR = 6.9; 95% CI, 2.5–18.9). Our results are consistent with the hypothesis that severe head injury and genetic susceptibility are associated with AD. Both associations concur with current concepts regarding the role of amyloid in AD. Although we regard head injury, like genetic susceptibility, to be a putative risk factor for AD, the temporal relationship between head injury and AD warrants further investigation.

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Cerebral amyloid deposition is likely to have a key role in the pathogenesis of Alzheimer's disease (AD) [1, 2], but the etiology of this process remains uncertain. There is an increased risk of AD in first-degree relatives of patients with AD [3–11], and some family occurrences are linked to specific chromosomes [12–14], implying a genetic cause. The observation of mutations in the amyloid precursor protein (APP) gene on chromosome 21 in some families with AD [15–19] also indicates that a genetic defect in amyloid production or metabolism could explain the heritable form of AD.

Head injury may also affect amyloid production. The release of beta-A4 amyloid protein in the brain has been detected within days following head injury [20], but it is not clear that this release also triggers formation of beta amyloid immunoreactive plaques, neuronal degeneration, or the other pathological features of AD, as is suspected with the APP mutation. The finding of antibodies to beta-A4 amyloid protein in a patient with presenile dementia following head injury [21] and among professional boxers in whom dementia developed [22], as well as in a number of case-control studies of patients with AD [23–28], implies that head injury might also be a cause of AD.

Because genetic susceptibility and head injury are consistent with the "amyloid hypothesis" for AD [1, 2], we examined their relationship to AD in community-dwelling elderly persons and their first-degree relatives. We posited that both would be associated with

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AD, and that the degree of risk imposed by head injury would be greater in persons with, than without, genetic susceptibility to AD.

Methods

Setting and Subjects

Data were obtained from patients and control subjects participating in a study of dementia in the elderly population residing in the Washington Heights and Inwood communities of New York City. We developed a registry for AD from a number of sources: regional hospitals (including inpatient and outpatient services), private practitioners in the community, federal and state health agencies, health maintenance organizations, and senior centers. Each site was also used to identify control subjects. The refusal rate for both patients and control subjects was less than 20% using this method. We previously reported the development of our diagnostic method and its relationship to the cultural and educational demographics of this community [29, 30].

Both risk factor and family history data were available from 138 patients with AD who met National Institutes of Neurological Disorders and Stroke criteria [31] for probable AD, had recent onset of symptoms (within 5 years), and had an informant (as defined herein) qualified and willing to answer questions about the patient's illness. All patients were examined by a neurologist or an appropriately trained internist or psychiatrist and underwent neuropsychological testing. Onset of disease was defined as the approximate age or date at which the first signs or symptoms of AD were present.

During the same period, a pool of elderly persons, aged 65 and older, had been identified as potential control subjects on the basis of community residence, age, and information indicating no known neurological or psychiatric disorder from the computerized registers at each of the same sites where patients had been identified. From a pool of 416 potential control subjects, the same risk factor and family history data were available in 193 (46%) healthy elderly persons who screened negatively for dementia and had no evidence of neurological or psychiatric disease on our detailed clinical examination, which included neuropsychological testing.

Interview with Informants and Control Subjects

For patients with AD, the informant was required to be a close family member or a spouse familiar with the patient's medical history, exposure to various risk factors, and family history. Patients and informants were interviewed together to maximize information gathering. Control subjects were interviewed directly without informants. By definition, control subjects were free of dementia, and thus were capable of providing accurate exposure information. We elected not to use a surrogate for control subjects in the interviews to avoid underreporting of exposures in control subjects [27].

Risk Factors

A structured interview was used to inquire about behaviors such as smoking, alcohol use, coffee consumption, dietary habits, antiperspirant use, insecticide exposure, exposure to household solvents, head injury, athletic activity now and in the past, previous hip or wrist fractures, and use of exogenous hormones. For several of the items, we attempted to determine the "dose" of the exposure with follow-up questions.

The interviews were given in English or Spanish, according to the preference of the patient's informant or the control subject. We also assessed the reliability of this information by repeating the interview 12 months later with the patient's informant or the control subject in 40 individuals.

Family History

A structured family history interview for AD and a number of other neurological and medical disorders in first-degree relatives (parents and full siblings) was used. The interview also inquired about head injury with loss of consciousness in each relative. An initial screening question, when answered affirmatively, triggered a set of follow-up questions designed to ascertain historical information necessary for diagnosis. Operational criteria were then applied to the answers to the follow-up questions to arrive at a diagnosis that was scaled according to the degree of certainty. The categories "definite," "probable," "possible," and "uncertain" required more than one affirmative response to the symptoms. The "doubtful" category was reserved for relatives with an affirmative response to the screening question but a negative response to all other symptoms. "Unknown" was reserved for family members from whom no information was available (i.e., an "unknown" response to the screening question).

We assessed reliability of the family history by repeating the interview with another informant for patients and with a family member for control subjects at a later time in 64 families of probands. Information was provided by two informants on a total of 605 first-degree relatives.

We reinterviewed the informants and the control subjects about relatives reported to have had head injuries to determine age and date at the time of the injury, duration of unconsciousness, and whether the person had been hospitalized.

Data Analysis

The frequencies for each demographic variable (including ethnic group) and environmental and medical risk factors were compared in patients and control subjects using chi-square analyses and Fisher's exact tests.

Odds ratios were calculated to assess associations between AD and certain risk factors, demographic variables, or other characteristics. Continuous variables were also dichotomized using a clinically meaningful cutpoint (i.e., age 70; 8 years' education). Both univariate and multivariate odds ratios were calculated from logistic regression models for each risk factor. The first stage of assessment included all demographic, medical, and environmental risk factors related to the study hypothesis. We then included variables associated with AD from other investigations. We examined differences with respect to the 3 ethnic groups represented in the community.

We used life table and survival methods to assess familial risk of AD [32]. Thus, cumulative incidence of AD was estimated in first-degree relatives of patients and control subjects. For this purpose, relatives of patients and relatives of control subjects were considered a "reconstructed" cohort [33], and each relative was considered to be at risk of AD from birth until current age or age at death (for those unaffected) or age at onset of AD.

Table 1. Selected Characteristics of Patients and Control Subjects

Characteristic	Patients (n = 138)	Control Subjects (n = 193)	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)[a]
Women (%)	80	81	. . .	. . .
Mean age (SD)	82.2 (7.9)	75.1 (6.8)	6.0 (2.6–13.8) (>70 yr)	5.6 (2.4–12.9) (continuous)
Mean years of education (SD)	6.6 (4.1)	8.7 (4.1)	1.4 (0.9–2.2) (<8 yr)	1.7 (0.9–2.2)
Head injury with loss of consciousness	15%	6%	2.6 (1.2–5.5)	3.7 (1.4–9.7)

[a] Logistic regression was used to calculate adjusted odds ratios. Variables included in the model were: gender, age, ethnic group, years of education, and head injury. Only these variables approached statistical significance.

95% CI = 95% confidence limits; SD = standard deviation.

Cumulative incidence of AD in first-degree relatives was also estimated within strata defined by characteristics of the patients and the control subjects (i.e., age at onset of dementia in patients, gender and history of certain risk factors in patients or control subjects). Characteristics of the relatives (i.e., relationship to the patient or control subject, gender and history of certain risk factors in the relative) and ethnic group identity were also used as stratifying characteristics. Differences among different subgroups in cumulative risk were evaluated by the log rank test.

Univariate and multivariate Cox proportional hazards models [34] were used to calculate rate ratios for incidence of AD in relatives of patients versus relatives of control subjects, for various characteristics of the patients and the control subjects, and for characteristics of the relatives.

Results

Table 1 compares the demographic variables of patients and control subjects. Patients were significantly older and had significantly less education than control subjects, but there was no difference in gender. There were more Hispanics among control subjects than patients (66 vs 34%; $p < 0.05$).

Risk Factors

Agreement between the repeated interviews was in the range of good to excellent [35] for most questions. For example, head injury with loss of consciousness (κ = 0.89), limb fracture (κ = 0.83), smoking (κ = 0.68), and alcohol use (κ = 0.54) were considered adequate for examination of risk factors.

Patients had a history of head injury with loss of consciousness significantly more often than control subjects. A history of smoking was more frequent in control subjects than in patients, but this factor was not related to the hypothesis examined in this investigation. We found no differences between patients and control subjects in the frequency of reported alcohol use, hypertension, myocardial infarction, or any other risk factor examined.

Multivariate logistic regression was used to examine the independent effect of each risk factor while adjusting for associations with others. For this analysis, all variables described, as well as potential confounders such as ethnic group, were included in the initial model. Only age and history of head injury with loss of consciousness remained significantly related to AD (see Table 1). Age as a continuous variable did not change the association with head injury in a subsequent calculation (odds ratio [OR] for AD associated with head injury, 3.7; 95% confidence interval [CI], 1.4–9.7). The odds ratio for head injury associated with AD was increased for women (OR = 4.1; 95% CI, 1.5–11.2) but not men (OR = 1.0; 95% CI, 0.2–4.5).

Head injuries occurring after age 70 were associated with greatest risk (Table 2). The odds ratio for AD associated with head injury was higher for injuries with loss of consciousness exceeding 1 hour and those occurring less than 5 years before the onset of AD (see Table 2). Sixty percent of both head-injured patients and control subjects were hospitalized for the injury. Excluding head injuries within 2 years of the onset of AD for patients and within 2 years of current age for control subjects slightly reduced the magnitude of the association, but it remained significant (OR = 2.4; 95% CI, 1.1–5.6).

Twenty-eight percent (5 of 18) of head-injured patients reported previous alcohol use, compared with 70% (7 of 10) of head-injured control subjects ($p < 0.05$). There was no association in either group between head injury and use of any medication.

Family History

Agreement between different family informants was in the good to excellent range for AD (κ = 0.70), other conditions such as Parkinson's disease (κ = 0.61), heart attack (κ = 0.69), and head injury (κ = 0.57). Intraclass correlation coefficients [36] for diagnostic

Table 2. Comparison of Head Injuries in Patients and Control Subjects

Characteristic[a]	Patients	Control Subjects	Odds Ratios (95% CI)
No head injury	103	179	1.0 (reference)
Head injury			
Before age 70	7	10	1.2 (0.4–3.6)
After age 70	11	1	19.1 (8.0–45.6)
Unconsciousness			
1 hour or less	7	7	1.7 (0.6–5.1)
More than 1 hour	4	2	3.5 (0.9–14.2)
Latency			
More than 5 years	8	10	1.1 (0.4–3.6)
Less than 5 years	10	1	10.5 (3.6–30.7)

[a]Unconsciousness refers to the duration of unconsciousness following head injury; latency refers to the duration between head injury and onset of symptoms (for patients) or the current age (for control subjects). Numbers of patients and control subjects differ from those in the text due to incomplete information.

95% CI = 95% confidence limits.

certainty for AD, using the levels of diagnostic certainty as a continuum, were high (0.73), indicating substantial agreement and consistency.

Among patients with AD, 45 (32.6%) had a first-degree relative with a dementia diagnosis ranging from definite to uncertain (relaxed criteria), compared with 61 (31.7%) of control subjects. When more stringent criteria were used to classify relatives as affected (i.e., including only definite, probable, and possible), 8 (5.8%) of the patients with AD and 8 (4.2%) of the control subjects had an affected family member. Odds ratios were calculated using logistic regression to adjust for age differences between patients and control subjects, and neither comparison was significant (relaxed criteria, 1.2; 95% CI, 0.7–2.0 and stringent criteria, 1.5; 95% CI, 0.5–4.4).

FAMILY HISTORY STUDY. There was no difference in gender or the number of parents or siblings, but the average years at risk was higher for the relatives of patients than for those of control subjects (68.1 vs 64.8; $p < 0.01$). Among the relatives of patients, 83 of 799 (10%) were reported to have evidence of AD ranging from definite to uncertain. Among relatives of control subjects, 88 of 1,238 (7%) were reported to have symptoms suggestive of AD using the same criteria. Using the more restricted criteria, we found that 10 (1.3%) of the relatives of patients and 8 (0.6%) of the relatives of control subjects were affected.

Compared with relatives of control subjects, cumulative risk of AD was increased in relatives of patients with onset prior to age 70, but not in relatives of patients with onset at age 70 or older (Table 3; Figure). The association between head injury with loss of consciousness and AD was similar in relatives of patients (risk ratio [RR] = 5.9; 95% CI, 2.3–14.8) and relatives of control subjects (RR = 6.9; 95% CI, 2.5–18.9) (Table 4).

We recalculated the cumulative risk of dementia in the relatives of patients, excluding the probands with a history of head injury, to examine only "genetic susceptibility." Relatives of patients with onset before age 70 still had an increased risk (RR = 2.9; 95% CI, 1.1–7.2) compared with relatives of control subjects, whereas relatives of patients with onset after age 70 showed no increased risk (RR = 1.1; 95% CI, 0.8–1.5) compared with the same control subjects.

We were able to confirm in all but 3 families that the head injury preceded the onset of dementia in the relatives with dementia. In 2 families, the family informant was not certain at the time of the second interview that the head injury had actually occurred. These 2 relatives were reclassified as being without head injury. During the follow-up interview in the other family, we were able to determine that the relative in question was demented for at least 1 year prior to head injury. This patient was considered as having dementia but without antecedent head injury. Unfortunately, the date of the head injury or the exact age of the relative at the time of the injury was known in only 7 relatives. Thus, we were unable to calculate latency and to compare details about the injuries in the 2 groups. The cumulative risk of dementia to age 90 was 61.5% among head-injured relatives of patients and 53.8% among head-injured relatives of control subjects. We were unable to examine the combined effect of head injury and genetic susceptibility in relatives of patients

Table 3. Cumulative Risk of Alzheimer's Disease in First-degree Relatives of Patients and Control Subjects Without Head Injury Stratified by Age at Onset of Dementia in the Proband

	Total Relatives	Total Demented	Cumulative Risk to Age 90[a]	Rate Ratios (95% CI)
Relatives of patients				
Onset <70	58	6	0.631 (0.23)	2.4 (1.1–5.6)
Onset >70	646	69	0.287 (0.04)	1.0 (0.6–1.8)
Relatives of control subjects	1,133	82	0.245 (0.03)	1.0 (reference)

[a] Numbers in parentheses are the standard error.

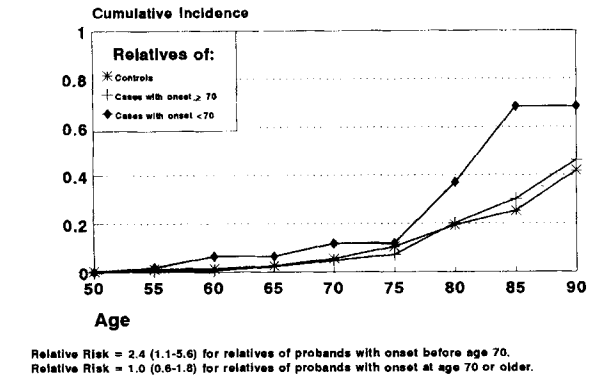
95% CI = 95% confidence limits.

Table 4. Cumulative Risk of Alzheimer's Disease in Head-injured First-degree Relatives of Patients and Control Subjects Stratified by Age at Onset of Dementia in the Proband

	Head Injury	Total Relatives	Demented	Cumulative Risk of AD to Age 90[a]	Rate Ratios (95% CI)
Relatives of patients	Yes	8	5	0.615 (0.19)	6.9 (2.5–14.8)
	No	704	75	0.310 (0.04)	1.1 (0.8–1.5)
Relatives of control subjects	Yes	10	4	0.538 (0.23)	5.9 (2.3–14.8)
	No	1,133	82	0.245 (0.03)	1.0 (reference)

[a]Numbers in parentheses are the standard error.

95% CI = 95% confidence limits.



Comparison of the cumulative risk (incidence) to age 90 of presumed Alzheimer's disease among the 58 first-degree relatives of patients with Alzheimer's disease whose onset was before age 70 and the 646 first-degree relatives of patients with Alzheimer's disease whose onset was after age 70 to the 1,133 first-degree relatives of the control group. Relative risk is equivalent to an incidence rate ratio, comparing the incidence rates of the relatives of the patients with that of the control subjects. The relative risk for first-degree relatives of patients with onset before age 70 was 2.4 (95% confidence interval, 1.1–5.6). The relative risk for first-degree relatives of patients with onset after age 70 was 1.0 (95% confidence interval, 0.6–1.8).

in whom disease onset occurred before age 70 because none of the relatives of these patients was reported to have had a head injury.

Discussion

Our investigation and results differ in important ways from previous studies. All the patients and control subjects were over 65 and identified through a community-based registry of AD and related disorders in Northern Manhattan. None of the patients were from a specialty clinic, and none of the control subjects were spouses or caretakers of the patients. We found that the odds of having had a prior head injury accompanied by loss of consciousness were increased for patients with AD compared with a group of elderly control subjects. We also found that risk of AD among family members was increased only for relatives of patients with onset of AD before age 70. We detected a similar association between head injury and AD in the first-degree relatives of both patients and control subjects. Furthermore, the magnitude of increased risk related to head injury was similar in first-degree relatives of patients and first-degree relatives of control subjects, implying no additional effect related to a family history of AD.

Our results directly confirm those of Mortimer and associates [28], who reported an association between head injury and AD that was not increased by the effects of family history of AD. A potential interaction could have been missed because none of the relatives of patients with early-onset AD (before age 70), in which we found increased familial risk, had experienced a head injury.

We found that head injury was more strongly associated with AD in women than in men, which is unique to our investigation; however, we may have had too few men in the study to observe this association in men, because 70% of the population older than 65 in northern Manhattan are women. The collaborative reanalysis indicated no increased risk with head injury among the 1,300 women whose data were reviewed [25]. Falls with and without head injury increase rapidly with increasing age, and most injuries in the elderly require hospitalization [37]. At younger ages, men are more likely to have head injuries than women, but this trend changes in the elderly; men and women are at equal risk for falls and head trauma [37]. The advanced age of our cohort may have allowed us the opportunity to observe this association in women. We believe it should be investigated further.

We found that head injuries in control subjects were associated with alcohol use, but we did not see this relationship in patients. Nelson and colleagues [38] found alcohol use a risk factor for head injuries in men but not in women. We also found no relationship to medication use in either group. Alcohol, tranquilizers, and dementia have been identified as the main risk factors for falls in the elderly [39, 40], although they

have not been specifically associated with falls that result in head injury.

Does head injury satisfy the criteria for causality as a putative risk factor [41]? Although the size of the estimated relative risk associated with head injury has ranged from as low as 0.6 to as high as 18.0 [28], many estimates have not been statistically significant [42–48]. The combined frequency of head injury from a series of published and unpublished studies was 9.6% for patients and 4.7% for control subjects [28]. Thus, the association is present in the majority of published studies and in pooled data, but it is a modest association.

The relationship between head injury and AD is consistent with a hypothesis that cerebral amyloid deposition may lead to formation of neuritic plaques and neuronal destruction [1, 2]. Deposited amyloid is thought to competitively inhibit its own proteolysis, resulting in an accumulation in neurons that destroys the cell membrane and cytoskeleton and leads to neuronal degeneration [1]. However, the neurotoxicity of amyloid has not been firmly established in laboratory animals and remains a controversial topic [49, 50]. According to Roberts and associates [20], beta-A4 amyloid can be detected in the brains of individuals within days of a severe head injury and has been observed post mortem in head-injured victims.

We found that patients had experienced head injuries later in life than control subjects. In fact, we found that the odds of having had a head injury was significantly higher among patients over the age of 70. This finding may indicate that head injuries in older individuals lead to a different pathogenic process than similar head injuries in younger persons. The metabolism of beta-A4 amyloid can be altered with advancing age and there may be reduced capacity for proteolysis of expressed amyloid [51, 52]. Our study indicates that patients older than 70 were at highest risk of head injury and that they were likely to have had head injuries within 5 years of the onset of symptoms.

Because both AD and head injuries increase with age, their temporal association warrants further study. AD has an insidious onset and, because head injuries that occur in later life appear to carry the greatest risk, it is possible that AD increases the frequency of head injuries rather than the converse. Graves and associates [26] found that the increased risk of AD associated with head injury persisted after excluding injuries within 5 years of the onset of AD. The relationship between head injury and AD persisted in our data as well after excluding head injuries within 2 years of onset of symptoms. This concern, however, limits the extent to which head injury can be viewed as a definitive risk factor for AD until the issue of temporal sequence is investigated directly.

Head injury has occasionally been implicated in the causal pathway of other degenerative diseases, such as Parkinson's disease and amyotrophic lateral sclerosis; however, those associations have been inconsistent [48].

Neither a study of dementia in elderly volunteers [45] nor an investigation using the medical record linkage system at the Mayo Clinic [48] provided supporting evidence of an association between head injury and AD in prospective studies. The minimal detectable risk in the study of volunteers [45] was 8.0; therefore, a modest association, such as that reported herein, might not have been detectable. In the other investigation [48], head injury was defined with the requirement of seeking medical attention, and AD diagnoses were abstracted from clinical records that did not include other risk factors, such as family history. Those investigators also did not specifically consider head injuries after age 70.

We observed family history of dementia as a risk factor for AD only in the group with disease onset prior to age 70. Other investigators have interpreted their studies [3, 4] as indicating autosomal dominant transmission, because surviving relatives of patients have a 50% probability for development of dementia. These investigators contend that sporadic patients with AD may have had family members with the "AD genotype" who died before becoming demented [3, 4]. We cannot support this view. The current report and our earlier study [5] found not only risk of AD among first-degree relatives of patients with AD, similar to others [3, 4], but also higher risks in relatives of our control subjects. Possible explanations for this difference may be selection bias in those studies, the older age of persons in our community, or some other unexplained factor.

We used a case-control design to examine cross-sectional data from a prevalent cohort of patients and control subjects that has inherent limitations. The temporal sequence of exposure is difficult to firmly establish. Data from surrogate interviews have been regarded as reliable, although validity has not been established [53]. Use of informants for the patients with AD, but not for the control subjects, could have caused differential misclassification of exposures in the patients. The likely direction of bias would have been toward overreporting of head injury in the patients by the surrogate informants, which could explain in part the association. However, informants were not aware of the study hypothesis, and questions regarding head injury were imbedded in the context of a general health questionnaire. We preferred greater accuracy in reporting of exposures from control subjects and had little choice with regard to the patients with AD. The potential for recall bias is very high and it is difficult to estimate the magnitude of the effect on classification of exposure; however, we believe this approach should

have maximally influenced reporting of family history, which it apparently did not. We also were unable to examine directly and interview the first-degree family members of patients and control subjects and relied on a family informant. Although this method proved reliable by us and others [3, 4], validity of the family history method in AD has not been established.

Our data support the concept that head trauma with loss of consciousness may be an important risk factor for AD, particularly in elderly individuals. Our data also indicate that the risk of AD is increased for first-degree relatives of patients whose disease begins before age 70, but not for relatives of patients with later age at onset. Both observations concur with the concepts concerning the role of amyloid in the etiology of Alzheimer's disease.

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