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Evidence for Familial Factors That Protect against Dementia and Outweigh the Effect of Increasing Age

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Summary

A positive family history is associated with increased risk for dementia. It is not known whether a negative family history with long-lived relatives predicts a reduced risk for dementia. We studied the survival rate and the occurrence of dementia in 232 parents and siblings of 43 optimally healthy individuals ≥84 years of age and compared them with 233 parents and siblings of 51 random controls and 499 parents and siblings of 88 Alzheimer disease (AD) patients. Prevalence of dementia after age 60 years was .031 for the relatives of healthy elderly, .066 for the relatives of random controls, and .217 for the relatives of AD patients. The cumulative incidence of dementia by age 85 years was estimated as .041 (±.019) for the relatives of healthy elderly individuals, .102 (±.038) for the relatives of random controls, and .360 (±.037) for the relatives of AD patients. Hazard-ratio estimates suggest that the risk of dementia for the relatives of healthy elderly is 3 times lower than the risk for the relatives of random controls ($P < .03$) and is 11 times lower than the risk for the relatives of AD patients ($P < .00005$). An analysis of age at death indicated that the relatives of healthy elderly and the relatives of AD patients had a longer life span than did the relatives of random controls. These results suggest (1) that a segment of the population is at considerably lower risk for dementia and that a documented negative family history can help identify these individuals, (2) that, for genetic counseling, it is important to document a negative family history of dementia as well as a positive family history, and (3) that familial/genetic factors exist that reduce the risk of dementia and that association studies utilizing optimally healthy elderly may help identify genes that promote successful aging of the brain.

Introduction

The alarmingly high prevalence of dementing illnesses in general, and of Alzheimer disease (AD) in particular, is a source of anxiety for the elderly population. The known risk factors for typical late-onset AD are increasing age, positive family history, and allele ε4 of the apolipoprotein E (Apo E) gene on chromosome 19.

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Epidemiological studies show increasing prevalence of AD by age, although the estimated age-specific rates vary across populations. Evans et al. (1989) reported that in an East Boston community of the elderly, 10% of the individuals >65 years of age and 47% of those >85 years of age had AD. Bachman et al. (1992) reported significantly lower rates for the Framingham study. They estimated the prevalence of AD as 3% for those >65 years of age and 13% for those >85 years of age. The prevalence of all dementia in the Framingham study was 5% for those >65 years of age and 24% for those >85 years of age. A community survey in Manitoba estimated a prevalence of 0.5% for AD and 4.2% for all dementias in Cree-speaking Native Americans, in contrast to the non–Native American English-speaking residents, who had a prevalence rate of 3.5% for AD and 4.2% for all dementias (Hendrie et al. 1993). The

variation in the population prevalence rates may be partly due to ethnic differences in the frequencies of alleles that predispose to or protect against AD.

The risk of dementia is significantly higher in the presence of a family history. The reported increase in risk due to a positive family history ranges from two- to sixfold, depending on the criteria used for selecting control subjects. Studies comparing the incidence of AD-like dementia in the relatives of AD patients with that in the relatives of age-matched controls reported estimates of relative risk ranging from two to four times greater in AD patients (Mohs et al. 1987; Shalat et al. 1987; Breitner et al. 1988; Huff et al. 1988; Martin et al. 1988; Broe et al. 1990; Farrer et al. 1990; Van Duijn et al. 1991). One study selected optimally healthy controls of age 60–90 years and found that the risk to the relatives of patients was approximately six times higher than the risk to the relatives of healthy controls (Mayeux et al. 1991). This suggests that optimal health in the proband predicts a lower risk of dementia in relatives. In the previous studies, controls were age matched to the patients. It is not known if the risk to relatives is further reduced if the proband is very old and optimally healthy.

Allele ε4 of Apo E is strongly associated with late-onset AD in Caucasians (Corder et al. 1993; Mayeux et al. 1993; Payami et al. 1993; Yu et al. 1994), but it may not be so in blacks (Mayeux et al. 1993). Even in Caucasians, this allele is neither necessary nor sufficient for the development of AD (Payami et al. 1993). These findings suggest the existence of another risk factor, possibly a gene, for late-onset AD. It is not known if the Apo E locus or the putative second gene for late-onset AD has alleles that are associated with reduced risk for AD. Also, there may be alleles at the amyloid precursor protein (APP) gene on chromosome 21 and at the AD locus on chromosome 14, which cause early-onset familial AD, that confer resistance to AD. If such "protective" alleles exist, then there must exist families in which AD is rare.

The aim of this study was to identify families with low risk of AD-type dementia. We studied the family histories of a group of optimally healthy, very old (age ≥85 years) individuals. Parents and siblings of healthy elderly were compared with parents and siblings of a group of random controls and with parents and siblings of AD patients, for risk of dementia and for longevity. Decline of cognitive health is associated with increasing age; therefore it is important to know the survival experiences of the groups being compared for risk of dementia. The hypothesis of this study was that the relatives of healthy elderly have a longer life span and a lower risk of dementia than are predicted for the general population.

Subjects and Methods

Subjects

The healthy elderly probands were 43 Caucasian individuals who are participating in The Oregon Brain Aging Study (OBAS), a longitudinal study of the effect of aging on cognition (Howieson et al. 1993). At the time of enrollment in OBAS, all subjects were >84 years of age, were independent in activities of daily living, had no chronic medical conditions, and were on no medication that affects cognition. Each subject underwent detailed standardized neurologic, psychometric, and magnetic-resonance-imaging evaluations to rule out any evidence of dementia (Howieson et al. 1993).

The random control subjects were 51 Caucasian volunteers from The American Association of Retired Persons in Portland and the Oregon Health Sciences University. They were selected randomly, regardless of the presence or absence of memory problems, with the aim that they would represent the general population in that age group. Since the cognitive health of these subjects was not critical to this study, they were not evaluated clinically.

The patient group consisted of 88 Caucasian individuals with the diagnosis of AD (McKhann et al. 1984). They were recruited consecutively from the Alzheimer Disease Center's clinics at the Oregon Health Sciences University and Portland's Veteran's Affairs Medical Center.

All analyses were restricted to the first-degree relatives (parents and siblings only) of the three groups of probands. Offspring of the probands were excluded, because they had not reached the age of dementia onset and were therefore uninformative. The second-degree relatives were not included, because the data were less reliable than those for the first-degree relatives. Henceforth, the term "relative" refers to parents and siblings.

Family histories were obtained by a standard questionnaire and were verified by interviews with two family members. Follow-up interviews were performed at least once a year, to confirm the original data, mark the progression of the disorder in the affected individuals, and note any new cases of dementia in the family. Medical and autopsy records were reviewed to confirm the family history data.

Dementia was defined as progressive memory disorder observed over a period of 1 year, accompanied by

decline in at least one cognitive function. Most of the demented relatives had a clinical diagnosis of AD. But since some of the affected relatives (mostly deceased parents) were never diagnosed, and since 16% of demented individuals had comorbidities that confounded the diagnosis of AD, we did not further classify the affected relatives beyond the designation "dementia."

Age at onset was defined as the age when the decline in memory was first noticed. Age at onset was unknown for 16 of the relatives of AD patients. To be conservative, these individuals were assigned an age at onset that was only 2 years younger than their last known age. (Using either family mean age at onset or average duration of disease, which is ~10 years, would have probably been more realistic and would have resulted in even greater differences between the relatives of AD patients and the other two groups than was observed here.)

Data Analysis

The relatives were grouped by age (current age or age at death). The prevalence of dementia was estimated by the proportion of affected individuals in each age group. The prevalence of dementia in the relatives of healthy elderly was compared with that in the other two groups of relatives by using Z statistics.

Cumulative incidence of dementia was calculated by the Kaplan-Meier survival analysis method. The relatives were considered a cohort at risk from birth to onset of dementia (event) or until death or last contact (censored). Every parent and sibling whose cognitive health status was known was included in the analysis. Only one individual was omitted, because his age was unknown. For this study, the event was the onset of dementia; therefore, the estimated cumulative survival was the proportion of individuals who were cognitively healthy. The Kaplan-Meier survival curves were compared using log-rank statistics. The Cox proportional hazard model was used to estimate the hazard ratios, after the appropriateness of the proportional hazards assumption was tested. Parents and siblings were first analyzed separately and then were pooled.

Survival experiences of the three groups were assessed by estimating their age-specific cumulative incidence of death, by using life-table and Kaplan-Meier methods. SPSS software (release 5; 1992) was used for estimating survival proportions and hazard ratios.

Results

The characteristics of the probands are shown in table 1. There were approximately the same number of men and women among healthy elderly. There were more women volunteers in the random-control group than men. There were more men with AD than women, because half of our patients were recruited from the Veteran's Affairs Medical Center. The healthy elderly were considerably older than the individuals in the other two groups. Since the probands were not included in the analyses, the difference in their age and gender ratio had no bearing on the results. Only 14% of the healthy elderly had a positive family history of dementia, as compared with 22% of random controls and 52% of AD patients.

The characteristics of the first-degree relatives are shown in table 1. In all three groups the gender ratio was 1:1 and the average family size was similar. The relatives of random controls and of AD patients had similar age distributions, but the relatives of healthy elderly were significantly older. (Higher ages are expected to have higher incidence of dementia, but, in fact, the relatives of healthy elderly had the lowest incidence of dementia, despite being older; see below.)

More women were affected with dementia than men, in every group, in accord with previous studies, which have reported a higher prevalence of AD in females than in males (Katzman et al. 1989; Aronson et al. 1990; Bachman et al. 1992). The average age at onset was similar for the affected relatives in all three groups.

Dementia was rare in the relatives of healthy elderly. The three groups of relatives had significantly different age-specific prevalence (table 2) and cumulative incidence (fig. 1) rates, with the highest values being estimated for the relatives of AD patients, intermediate values for the relatives of random controls, and the lowest values for the relatives of healthy elderly. The risk of dementia by age 90 years, as estimated by the cumulative incidence rates, was .44 (±.05) for the relatives of AD patients, .20 (±.06) for the relatives of random controls, and .06 (±.03) for the relatives of healthy elderly. Within each group, incidence of dementia did not differ for parents and siblings. The hazard-ratio estimates (table 3) suggest that the risk of dementia for the relatives of healthy elderly is 3 times lower than the risk for relatives of random controls and that it is 11 times lower than the risk for the relatives of AD patients.

The age-specific cumulative incidence of death was similar for the relatives of healthy elderly and the relatives of AD patients, but it was significantly higher for the relatives of random controls. The cumulative incidence of death was .07 (±.02), .07 (±.01), and .09 (±.02)

Table 1

Characteristics of the Probands and Their Parents and Siblings

	Healthy Elderly	Random Controls	AD Patients
Probands:			
No.	43	51	88
Gender	24 F, 19 M	41 F, 10 M	35 F, 53 M
Age (years) (mean±SD)	85–101 (89.28±4.47)	49–87 (72.90±8.28)	47–92 (73.11±9.63)
Age at onset (years) (mean±SD)	...	...	38–89 (67.59±10.45)
Family history	6 (14%)	11 (22%)	46 (52%)
All parents and siblings:			
No.	232	233	499[a]
Gender	108 F, 124 M	119 F, 114 M	251 F, 247 M
Age range (years) (mean±SD)	2–105 (73.35±18.51)	1–99 (67.16±19.56)	1–100 (68.12±18.43)
Mean family size (±SD)	5.42 (±2.31)	4.57 (±2.42)	5.67 (±2.57)
Affected parents and siblings:			
No.	6	12	84
Gender	4 F, 2 M	8 F, 4 M	47 F, 37 M
Age at onset (years) (mean±SD)	55–89 (74.17±11.64)	40–90 (76.83±14.21)	47–94 (73.06±9.03)
Mean no./fam (±SD)	.14 (±.35)	.24 (±.47)	.95 (±1.24)

[a] One sibling of unknown gender died in infancy.

by age 40 years, for the relatives of healthy elderly, the relatives of AD patients, and the relatives of random controls, respectively; .16 (±.02), .15 (±.02), and .19 (±.03) by age 60 years; and .50 (±.03), .47 (±.03), and .59 (±.04) by age 80 years. The hazard-ratio estimates were 1.29 (P = .02) and 1.23 (P = .04) when the overall cumulative incidence of death in the relatives of random controls was compared with that in the relatives of healthy elderly and the relatives of AD patients, respectively, and was 1.05 (not significant) when the relatives of healthy elderly were compared with the relatives of AD patients.

Discussion

This study suggests that both cognitive health and longevity can aggregate in families. In recent years several genes have been identified that can cause or confer susceptibility to dementia of the Alzheimer type. These include mutations in the amyloid gene on chromosome

Table 2

Prevalence of Dementia in the Parents and Siblings of the Probands

Age (years)	Relatives of Healthy Elderly			Relatives of Random Controls			Relatives of AD Patients		
	Affected	Unaffected	Prevalence	Affected	Unaffected	Prevalence	Affected	Unaffected	Prevalence
60–69	0	32	0	0	63	0	11	106	.094
70–79	3	60	.048	4	57	.066	21	112	.158*
80–89	2	65	.030	4	34	.105	41	61	.402***
≥90	1	31	.031	4	16	.200*	11	24	.314**
Total >60	6	188	.031	12	170	.066	84	303	.217***
Total >70	6	156	.037	12	107	.101*	73	197	.270***

NOTE.—The prevalence rates in the relatives of healthy elderly were compared with those of the other two groups by Z statistics; statistically significant differences are denoted by asterisks.

* $P < .05$.

** $P < .001$.

*** $P < .00001$.

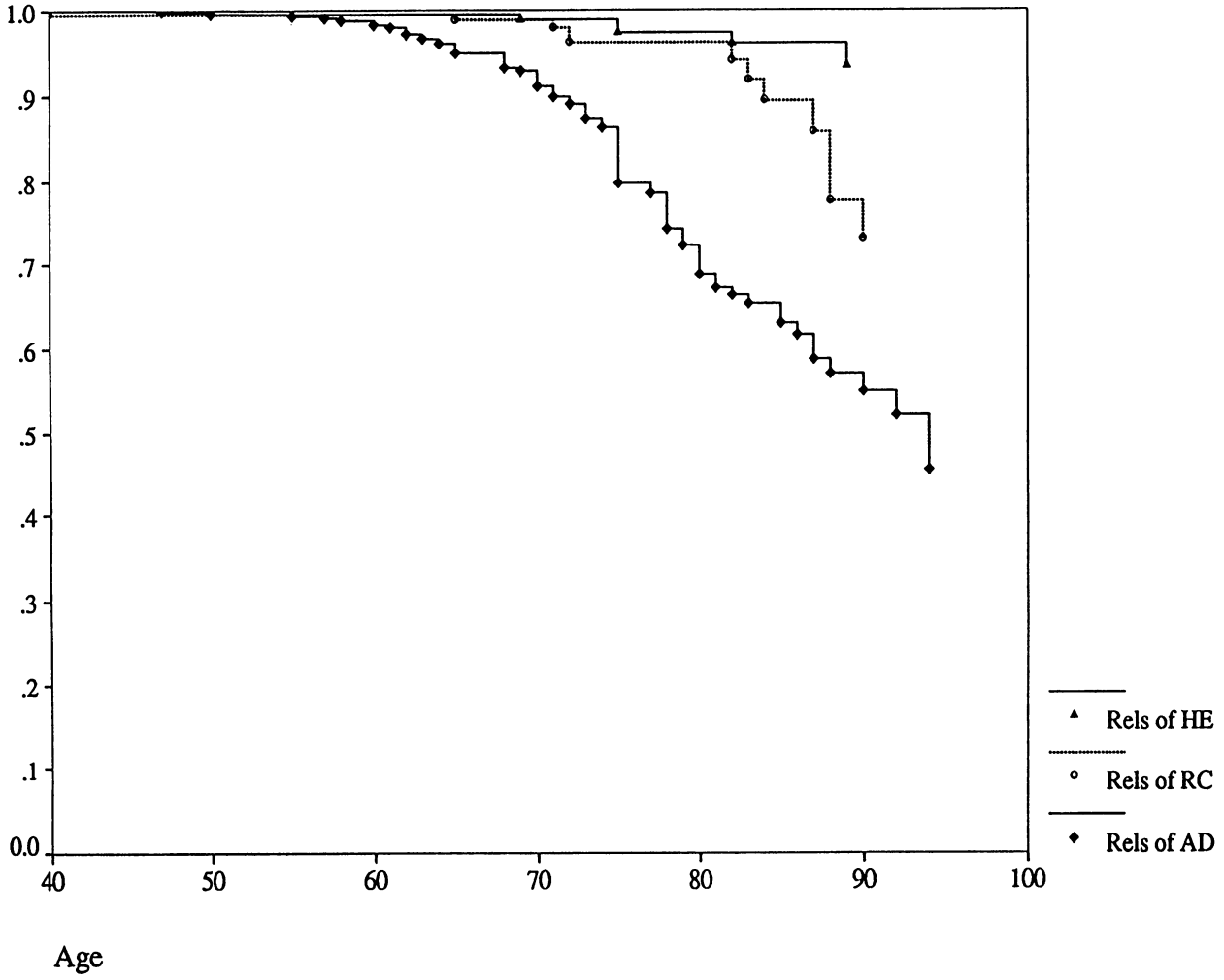

Figure 1 Kaplan-Meier survival analysis for cognitive health: age-specific cumulative proportion of nondemented relatives. Rels of HE = relatives of healthy elderly; Rels of RC = relatives of random controls; and Rels of AD = relatives of AD patients. Significance of the difference between curves, as determined by log-rank statistics, are $P < .0005$ for relatives of healthy elderly vs. relatives of AD patients, $P < .02$ for relatives of healthy elderly vs. relatives of random controls, and $P < .0005$ for relatives of random controls vs. relatives of AD patients.

21 (Chartier-Harlin et al. 1991; Goate et al. 1991), an as-yet-uncharacterized gene on chromosome 14 (Mullan et al. 1992; Schellenberg et al. 1992), allele ε4 of the Apo E locus on chromosome 19 (Corder et al. 1993; Mayeux et al. 1993; Payami et al. 1993; Yu et al. 1994), and allele HLA-A2 of the major histocompatibility complex on chromosome 6 (Small and Matsuyama 1986; Payami et al. 1991). Just as some families have a high risk of dementia because they inherit and transmit a susceptibility allele, other families may possess alleles that protect them from developing dementia.

Identification of alleles associated with cognitive health can provide clues to successful aging of the brain, as well as to the mechanisms that underlie disease. These "protective" alleles may be identified either through their reduced frequency in patients or through their increased frequency in individuals who apparently are resistant to disease, such as the healthy elderly in this study. The latter may be advantageous in some cases—e.g., when the allele in question is rare. In a study of familial AD, we observed a nonsignificant reduction in the frequency of the ε2 allele of Apo E in the patients (Yu et al. 1994). Since ε2 is rare (allele frequency in Caucasians = .07), testing for a reduced frequency in patients poses a problem with the sample size necessary to reach significance. An alternative is to test

Table 3

Hazard Ratio (HR) for Dementia in Parents and Siblings of the Probands

	Relatives of AD Patients			Relatives of Random Controls		
	HR	95% Confidence Interval	*P*	HR	95% Confidence Interval	*P*
Relatives of random controls	3.63	1.98–6.65	<.00005			
Relatives of healthy elderly	10.80	4.71–24.77	<.00005	2.97	1.12–7.93	<.03

healthy elderly for increased frequency of ε2. Data from this group may also help sort out the relative importance of genes, such as ε4, that are associated with susceptibility to AD. Although all studies to date have found an association between ε4 and both familial and sporadic AD in Caucasians, the strength of association and the estimates of risk have differed considerably (Corder et al. 1993; Mayeux et al. 1993; Payami et al. 1993; Strittmatter et al. 1993; Yu et al. 1994). The Apo E profile of healthy elderly will provide a unique insight and may help resolve some of the questions surrounding the ε4-associated risk for AD.

At the present time, risk assessment for dementia is based on whether the individual has a positive family history. In such a case, the risk is estimated on the basis of the incidence rates in the relatives of AD patients (Breitner 1991). When the family history is not significant, the risk estimate is derived from the reported prevalence rates for the general population (Evans et al. 1989; Bachman et al. 1992). The present study suggests that some families are at considerably lower risk for dementia than is predicted for the general population and that documented negative family history can help identify the low-risk families.

The rare occurrence of dementia in families of healthy elderly is unlikely to be a methodological artifact, because the protocol used for gathering the family histories of healthy elderly was the same as that used for the other two groups, and the results obtained for the families of random controls and of AD patients were similar to those reported by others. For example, the cumulative incidence of dementia by age 75 years in the relatives of AD patients was .14 ± .02, which is in the range of the previously reported estimates, which are .11 ± .03 (Breitner et al. 1988) to .17 ± .05 (Martin et al. 1988). Similarly, for the relatives of random controls, the estimated cumulative incidence by age 75 years was .04 ± .02, as compared with the reported range of .02 ± .01 (Breitner et al. 1988) to .08 ± .04 (Martin et al. 1988).

The family-history method has been shown to be reliable (Breitner et al. 1988; Huff et al. 1988). Nevertheless, recall bias was a concern in the present study, particularly for the first signs of memory loss, which in an AD family may be attributed to the beginning of AD but which in the families of random controls and of healthy elderly may be considered a consequence of aging and therefore may not be reported. To reduce this potential bias, only individuals whose memory loss progressed over the period of 1 year were considered affected. This was probably a conservative method, because it presumably excluded a disproportionately higher number of affected individuals from the families of AD patients and of random controls than from the families of healthy elderly, in an inverse relationship to the frequency of dementia, thereby narrowing the gap between them. Assigning a conservatively late age at onset to the 16 affected members of AD families whose ages at onset were unknown also may have reduced the difference between the three groups. Despite the efforts to overcome bias, and despite the evidence that our study is in line with others, we still may have a higher rate of false-positive diagnosis in AD families and a higher rate of false-negative diagnosis in families of random controls and healthy elderly.

Longevity appears to have a familial component. Both the families of healthy elderly and the families of AD patients seem to live longer than the relatives of random controls. It was surprising to find that AD families had a higher survival rate, similar to that of the families of healthy elderly. This may be because of their genetic relationship to AD subjects: the subjects had lived long enough to develop AD, and they were relatively healthy except for having AD (because AD is clinically diagnosed by exclusion); therefore, if a genetic component to longevity and general health is assumed, their relatives would be expected to be long-lived as well.

The likelihood of becoming demented increases with age; thus one would expect to find more affected indi-

viduals in long-lived families. Most of the relatives of healthy elderly were not demented at old age, which suggests that genetic factors that promote cognitive health can outweigh the predisposing effect of increasing age.

It is of interest that 8 of the 43 probands who were optimally healthy at age ≥84 years have since developed dementia. It appears as though dementia may be an integral part of aging and that the time of onset is governed by the presence or absence of risk factors.

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