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Genetic Epidemiological Study of Maternal and Paternal Transmission of Alzheimer's Disease

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Recent evidence for mitochondrial mutations associated with Alzheimers disease (AD) suggests the possibility of maternal transmission of this illness. We investigated this hypothesis by examining, in a variety of ways, the risk of a primary progressive dementia (PPD) in the parents (n = 650) and siblings (n = 1,220) of 325 AD probands. The results did not support maternal transmission in AD: The mothers of AD probands were not at greater risk of PPD than the fathers or the sisters of AD probands; the offspring of affected mothers were not at greater risk than the offspring of affected fathers or families with no affected parent; and, after selecting those proband families with evidence for increased familial loading, such families did not more frequently have affected mothers than fathers. In contrast, the cumulative risk of PPD in fathers of AD probands, while similar to that of mothers, was significantly increased over the brothers of AD probands. In addition, the cumulative risk curve of PPD in the offspring of affected fathers was significantly higher than the offspring of no affected parents. While no evidence for maternal transmission in AD was observed, unexpectedly, we did find evidence of increased paternal transmission. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88:378–382, 1999.

KEY WORDS: dementia; mitochondrial genes; genetic imprinting; family history; age at onset

INTRODUCTION

An important link between mutations of mitochondrial genes and Alzheimers disease (AD) is indicated by observed high levels of mitochondrial heteroplasmy—the relative mix of mutant and wild type alleles in mitochondrial DNA—in genes encoding subunits I and II of cytochrome *c* oxidase in AD patients [Davis et al., 1997]. The mitochondrial genome is exclusively inherited from the mother, but the extent of heteroplasmy is associated with aging and can vary in different tissues and organs within an individual. Nevertheless, increased heteroplasmy in blood cells of unaffected offspring of mothers with AD but not affected fathers is consistent with the possibility of maternal transmission rather than de novo mutations of these genes [Davis et al., 1997; Mattson, 1997]. While several recent studies have suggested that the apparent evidence for mitochondrial transmission may be an artifact [Hirano et al., 1997; Wallace et al., 1997; Davis and Parker-WD, 1998], maternal transmission of AD has also been supported in several [Duara et al., 1993; Edland et al., 1996], but not all [Payami and Hoffbuhr, 1993; Lautenschlager et al., 1996] genetic epidemiological studies focusing on this question.

In the present study, the hypothesis of maternal transmission in AD was tested using demographic and diagnostic information on the relatives of AD probands obtained through family informants. Several questions relevant to the hypothesis were investigated: (1) Is the cumulative risk of a primary progressive dementia (PPD) greater in mothers versus fathers of AD probands? (2) Is the relative risk (RR) of PPD in mothers compared with fathers greater than the RR in sisters compared with brothers? (3) Is the cumulative risk of PPD in the siblings of AD probands with affected mothers greater than both those with affected fathers and those with no affected parents? (4) Is the proportion of affected mothers greater than affected fathers in families specifically selected for high familial loading of AD? If maternal transmission is present in AD then one would expect affirmative answers to these questions.

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MATERIALS AND METHODS

Proband Sample

Patients seen at the memory disorders clinics of the Mount Sinai Alzheimer's Disease Research Center meeting National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimers Disease and Related Disorders Association criteria for probable AD are routinely referred for family history assessment. All such patients are evaluated by a psychiatrist trained to assess dementia, using a clinical history, evaluation of mental status, and physical and laboratory examinations. Some of the probands in the present sample were included in previous reports [Silverman et al., 1994; Li et al., 1995;], but there is no overlap with any other studies on the questions examined here.

Assessment of First Degree Relatives

As described in detail elsewhere [Silverman et al., 1994], family informants were interviewed with the Alzheimers Disease Risk Questionnaire (ADRQ) [Breitner and Folstein, 1984] and, when appropriate, the Dementia Questionnaire (DQ) [Silverman et al., 1986]. The ADRQ is used first to identify each first degree relative of an AD proband, collect demographic information on each of them, and to evaluate individually the presence of even a mild memory loss. If any such condition was suggested, the DQ was administered for that relative to assess and characterize a possible dementia. The DQ assesses, through informants, the presence and type of symptoms and course of a dementia, as well as the presence of any preexisting or concurrent conditions and illnesses that might account for a dementia other than AD. It is also used to estimate the age at onset of a dementia, defined as the age at which the first definite symptom emerged. Because we did not conduct a direct examination of these relatives, for relatives who met our family history criteria designed to identify AD we used the "PPD" designation rather than "AD." The previously published criteria for PPD [Silverman et al., 1990] are similar to *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) criteria for primary degenerative dementia of the Alzheimers type, but modified for informant-based assessment. These methods have been found to have good interinformant [Silverman et al., 1986] and test-retest reliability [Silverman et al., 1990], and the diagnoses derived from them agree well with both direct clinical assessment [Kawas et al., 1994] and neuropathology [Li et al., 1997].

Statistical Analysis

Because the cognitive status of the parents is central to the major analyses of this study, we included those families where both parents could be assessed for the presence of PPD. The actuarial life table method, using 1-year intervals, was used to calculate the cumulative risk for PPD in mothers versus fathers, and between siblings of AD probands grouped by the affected status of the parents. Differences between cumulative risk curves were tested using the Wilcoxon (Gehan) statistic (WS). The Cox proportional hazards model was used to calculate age-adjusted RR [Lee, 1992]. The use of family data with two or more individuals biologically related to one another may introduce dependence among failure times within families. Although, for such data, standard implementations of Cox proportional hazards survival analysis provide unbiased estimates of the regression coefficients from which RR statistics are derived, the estimates of their variances will tend to be biased downward as dependence is increased [King et al., 1996]. Thus we used MULCOX2, a program for Cox regression analysis that provides a more robust, unbiased estimate of the variance with clustered (e.g., by families) failure-time data [Lin, 1993].

RESULTS

Diagnostic information was collected on 650 parents and 1220 siblings of 325 AD probands. Four additional families with "conjugal" AD—both parents affected—were excluded. The probands were categorized according to whether there was no affected parent, an affected mother, or an affected father. Table I indicates the number of probands, their sex, and age-at-onset in each group. Prior to age adjustment, substantially more mothers had PPD than fathers: 48/325 (14.7%) versus 27/325 (8.3%) ($\chi^2 = 6.65$; d.f. = 1; $p < .01$). The onset age among the affected fathers was significantly earlier than the affected mothers. The mean age of parents among those where neither had PPD was significantly younger than the parents in the other two groups. In siblings, none of demographic characteristics considered differed significantly (Table I).

Separate PPD cumulative risk curves were constructed for mothers and fathers of AD probands (Fig. 1a). In fathers, the cumulative risk ultimately rose to 21.6 ± 4.0% by age 85. Among mothers, the cumulative risk was 29.0 ± 4.0% at age 85 and rose further to 36.7 ± 5.2% by age 91. The two curves were not significantly different (WS = 0.89, d.f. = 1, n.s).

For comparison purposes, we also constructed cumulative risk curves for brothers and sisters of AD probands (Fig. 1b). In brothers, the cumulative risk rose to 12.6 ± 4.8% by age 85, significantly lower than the risks observed in the fathers (WS = 7.78, d.f. = 1, $P = 0.005$) and the mothers (WS = 12.04, d.f. = 1, $P < 0.0005$). In sisters, the cumulative risk rose to 25.4 ± 3.9% by age 84 and 42.9 ± 8.7% by age 89, not significantly different from that observed in either the fathers (WS = 0.06, d.f. = 1, n.s.) or the mothers (WS = 0.06, d.f. = 1, n.s.). The risk curve for the sisters was significantly higher than for the brothers of the AD probands (WS = 8.43, d.f. = 1, $P < 0.005$).

Using the Cox proportional hazards model, mothers had a nonsignificantly increased RR of 1.4 (95% CI: 0.8, 2.3) for PPD compared with fathers, while sisters had a significantly increased RR of 3.0 (95% CI: 1.6, 5.6) of PPD compared with brothers. The RR in the mothers of AD probands compared with the sisters of AD probands was 1.0 (95% CI: 0.8, 1.4), indicating essentially identical rates of illness in females from the two generations. In contrast, the RR of PPD in fathers of AD pro-

TABLE I. Demographic and Disease Characteristics in Alzheimers Disease Probands, Their Parents, and Siblings Grouped by Primary Progressive Dementia (PPD) in the Mother or Father

	Probands			Parents		Siblings				
Proband groups	n	female[a] (%)	onset[b] (SD)	onset[c] (SD)	age[d] (SD)	n	female[e] (%)	age[f] (SD)	PPD[g] (females)[h]	onset[i] (SD)
No affected parents	250	143 (57.2)	67.7 (10.4)	NA	70.0 (17.6)	956	504 (52.7)	65.1 (16.7)	46 (36)	73.2 (8.5)
Affected mother	48	28 (58.3)	67.1 (9.2)	75.5 (8.8)	75.7 (13.7)	168	89 (52.9)	63.6 (17.9)	8 (7)	72.3 (8.2)
Affected father	27	10 (37.0)	63.3 (9.1)	70.9 (10.4)	75.6 (11.3)	96	52 (54.2)	61.4 (14.1)	7 (5)	65.3 (10.0)

[a] $\chi^2 = 4.17$, d.f. = 2, n.s.
[b] $F(2,317) = 2.26$, n.s.
[c] $t = 2.05$, d.f. = 73, $P < 0.05$
[d] $F(2,625) = 6.67$, $P < 0.001$
[e] $\chi^2 = 0.07$, d.f. = 2, n.s.
[f] $F(2,1191) = 2.59$, n.s.
[g] $\chi^2 = 1.05$, d.f. = 1, n.s.
[h] male/female ratio among PPD cases: $\chi^2 = 0.56$, d.f. = 1, n.s.
[i] $F(2,60) = 2.57$, n.s.

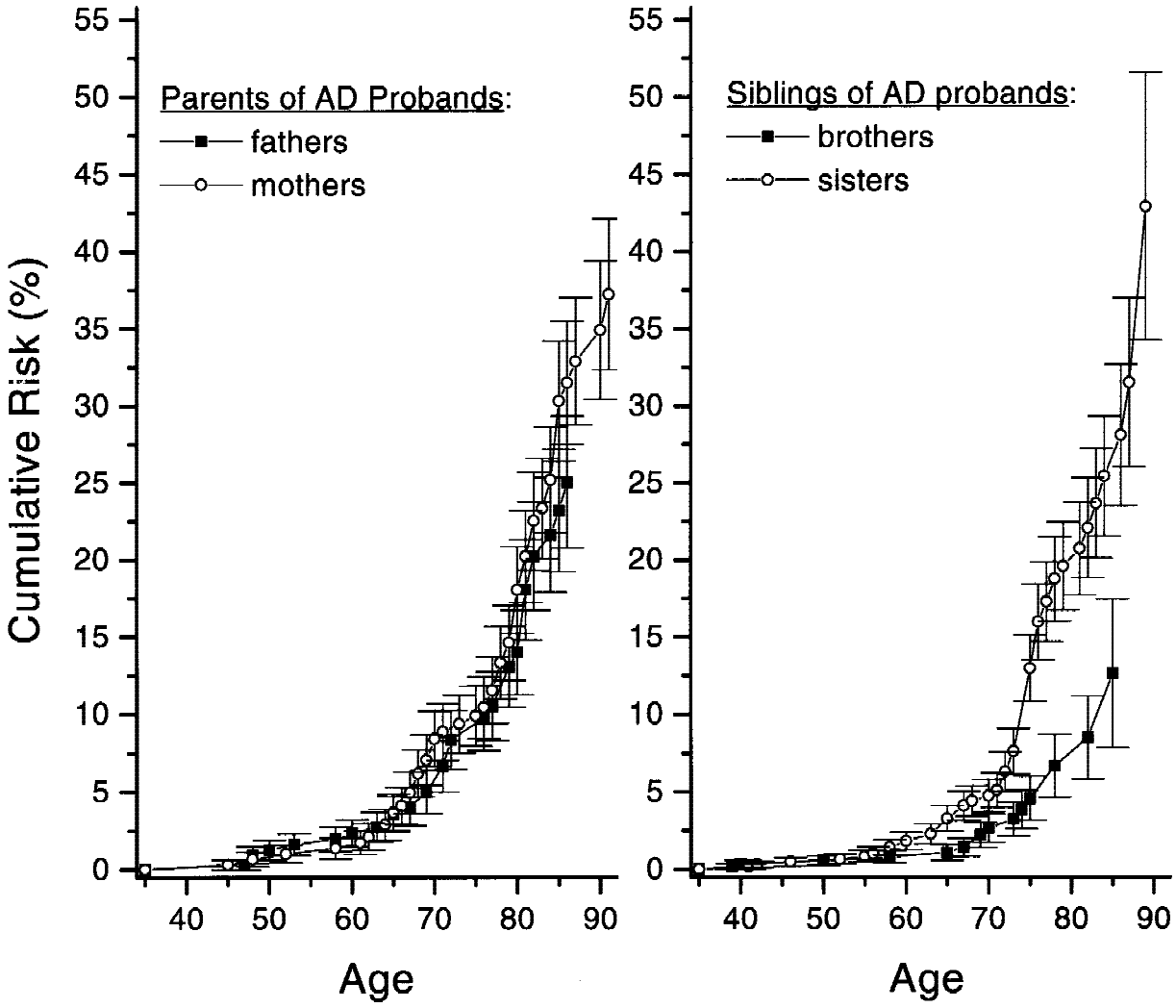

Fig. 1. Cumulative risk of PPD in mothers versus fathers of AD probands **(left)** and brothers versus sisters of AD probands **(right)**.

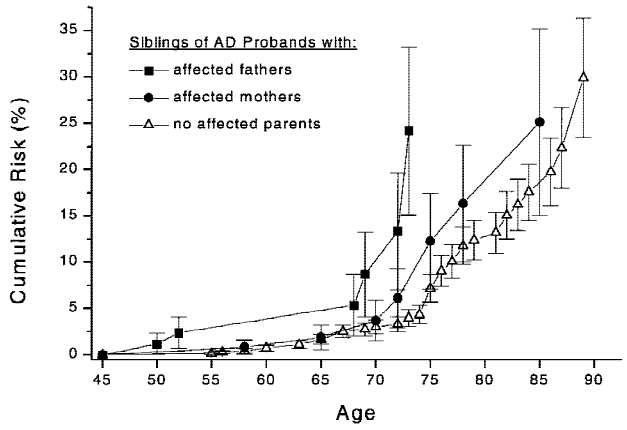

Fig. 2. Cumulative risk of PPD in siblings of AD probands with an affected father versus an affected mother versus no affected parents.

bands compared with the brothers of probands was 2.2 (95% CI: 1.1, 4.4), indicating the risk of PPD to fathers of AD probands was more than twice as high as it was to brothers of AD probands.

Cumulative risk curves were constructed for the three groups of proband siblings (Fig. 2). Across the three groups, the cumulative risk curves were significantly different (WS = 7.19, d.f. = 2, $P < 0.05$). In pair-wise comparisons, the cumulative risk curve among the siblings with affected mothers was similar to the siblings with no affected parents (WS = 0.13, d.f. = 1, n.s.) and marginally lower than the siblings with affected fathers (WS = 2.75, d.f. = 1, $p = 0.09$). The siblings with affected fathers had a significantly different and steeper curve than the siblings with no parent affected (WS = 7.38, d.f. = 1; $p < .01$).

There were 13 families of AD probands (4%) with a strong familial loading for AD, defined by the presence of one parent and at least one sibling with PPD: six with affected mothers, seven with affected fathers ($0^2 = 0.08$; d.f. = 1; n.s.).

A subset of 82 probands was genotyped for the apolipoprotein E (APOE) gene following standard methods [Hixon and Vernier, 1990]. The frequency of the APOE-$\varepsilon 4$ allele were roughly similar in probands with affected mothers (30%) versus affected fathers (35%) versus no affected parents (31%), and the proportion of probands with zero, one, or two of copies of this allele were similar in each group ($\chi^2 = 3.21$, d.f. = 6, n.s.).

DISCUSSION

While the crude proportion of the mothers with PPD was significantly larger than the fathers, the cumulative risk of PPD, controlling for differences in age structure and longevity, did not significantly differ, providing no support for maternal transmission in AD. The present sample is among the largest published samples from a single research center and larger than all those earlier studies reporting support for maternal transmission. [Duara et al., 1993; Edland et al., 1996] Yet even if there is a true increased risk in mothers over fathers of AD probands that went undetected in the present sample, given that the female-to-male RR in the parental generation was lower than it was in the sibling generation and that mothers and sisters of AD probands were observed to have virtually identical risks, such a difference would be more readily explained by the well-documented sex difference in AD [Fratiglioni et al., 1997] than by a specific maternal effect. Comparisons of siblings of AD probands by parental affected status similarly failed to support maternal transmission. Furthermore, despite the greater number of affected mothers overall, affected fathers were slightly more frequent in the more strongly familial AD pedigrees. Thus, none of the analyses we conducted provided evidence in favor of maternal transmission.

It is an important to note that the AD proband cohort in this study is a clinic-based sample, which may not be representative of the AD population as a whole. For example, the average age at onset among the AD probands was much earlier than one would expect from a community-based sample [Evans et al., 1989]. At the same time, most of the other studies that have looked at this question have ascertained their proband sample through clinics [Duara et al., 1993; Edland et al., 1996; Lautenschlager et al., 1996] or through ascertainment strategies designed to identify families with increased genetic loading [Payami and Hoffbuhr, 1993]. As a result, the question of maternal transmission in AD has been investigated only in samples with relatively early onset. Future investigations of population-based or nursing home samples are required to examine this question in more typical later onset AD proband samples.

The present results contrast with several earlier studies in which the female-to-male RR of AD was greater (though not necessarily statistically significantly so) in the parental generation compared with the sibling generation. [Edland et al., 1996] In addition, the results are not consistent with evidence that high levels of maternally transmitted heteroplasmy in mitochondrial genes are associated with AD [Davis et al., 1997; Mattson, 1997]. However, other large genetic epidemiologic studies have also failed to support maternal transmission in AD [Payami and Hoffbuhr, 1993; Lautenschlager et al., 1996] and several recent molecular genetic studies have suggested that the apparent increased heteroplasmy observed earlier in AD patients was in fact an artifact [Hirano et al., 1997; Wallace et al., 1997; Davis and Parker-WD, 1998]. Clearly, the evidence is conflicting and further work is needed to help resolve these discrepant results.

Unexpectedly, results consistent with paternal transmission in AD were obtained. The risk curve for PPD in the siblings of AD probands with affected fathers was significantly increased compared with those with no affected parents and was also increased, albeit at a marginal level, over siblings with affected mothers. These results are similar to an earlier and very large multicenter family history study of AD [Lautenschlager et al., 1996]. In addition, while fathers and mothers had similar age-adjusted risks of PPD, as already noted, the risk curve in fathers was significantly increased compared with the brothers of AD probands,

with fathers having more than twice the risk of PPD than males in the sibling generation.

One possible interpretation of increased paternal transmission in AD is the presence of paternal genetic imprinting, in which DNA methylation patterns lead to differential allelic expression depending upon whether it derives from the mother or father [Reik, 1996]. This possibility was previously suggested for AD [Farrer et al., 1991]. Another more likely possibility is that the increased risk associated with affected fathers of AD probands may instead be related to the increased familial risk in early-onset AD [Silverman et al., 1994]. Compared with women, the decreased longevity in men tends to lead to disproportionately fewer cases of late onset AD and hence relatively larger concentrations of early onset disease. This may be even further augmented by the fact that the female sex is an independent risk factor for AD [Fratiglioni et al., 1997]. Indeed, in our study the age at onset of PPD in the affected fathers was significantly earlier than that of the affected mothers. Thus, the steeper cumulative risk curve for PPD in siblings of AD probands with affected fathers perhaps follows from the possibility that a larger proportion of the fathers carried genetic factors associated with AD, unrelated to imprinting. In this regard, however, it is interesting to note that the frequency of APOE-ε4 in the proband, a risk factor for AD that is also associated with earlier onset [Saunders et al., 1993], did not differ by parental affection status in the subgroup of probands that could be genotyped. However, other yet to be identified genetic risk factors are also apparent in AD [Li et al., 1996]. Notwithstanding this alternative explanation, the intriguing possibility of paternal genetic imprinting should be further pursued.

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