Conjugal Alzheimer Disease

Risk in Children When Both Parents Have Alzheimer Disease

Suman Jayadev, MD; Ellen J. Steinbart, RN, MA; Yueh-Yun Chi, PhD; Walter A. Kukull, PhD; Gerard D. Schellenberg, PhD; Thomas D. Bird, MD

Background: There is limited information regarding children’s risk of Alzheimer disease (AD) if both parents are affected.

Objective: To determine the risk of AD in families in which both parents have AD.

Design: Retrospective study.

Setting: University research center.

Participants: A total of 111 families in which both parents had a clinical diagnosis of AD.

Main Outcome Measure: Frequency of AD in the children of spouses with AD.

Results: The 111 couples with AD had 297 children surviving to adulthood; 22.6% of these adult children have developed AD. The risk of AD in these children increases with age, being 31.0% (38 of 122) in those older than 60 years and 41.8% (41 of 98) in those older than 70 years. Many children (79.0%) at risk in these families are still younger than 70 years, meaning that the occurrence of AD will increase in the coming years. A family history of AD beyond the parents did not change the risk of AD in the children but did reduce the median age at onset in affected children. The apolipoprotein E ε4 allele played an important part in this phenomenon but did not explain all cases of AD in the children.

Conclusions: When both parents have AD, there is an increased risk of AD in their children beyond that of the general population. The role of family history and the specific genes involved in this phenomenon require a better definition.

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ALZHEIMER DISEASE (AD) is a common cause of dementia in the US population and the leading cause of cognitive impairment in the elderly population. The early-onset familial form of AD, accounting for only 1% to 3% of all AD, has been associated with 3 genes: amyloid precursor protein, presenilin 1, and presenilin 2. Despite extensive work dedicated to understanding the basic biological mechanisms of these proteins in the central nervous system, the precise pathogenesis of AD remains elusive. Identification of susceptibility genes in late-onset AD can provide insight into the pathobiologic features of the disease and can offer empirical clinical information regarding risk of disease. Apolipoprotein E (APOE) is one such risk factor. Presumably, additional genes are involved in the proposed polygenic inheritance of late-onset AD. Because AD is so common in the general population, it is not uncommon for both spouses to develop the disease. Offspring of 2 such affected individuals would presumably carry a higher burden of these AD-associated genes. Consequently, children of these spouse pairs want to know their risk of AD and whether they have a greater risk than the general public.

In a small pilot study, Bird et al1 described an increased prevalence of dementia in offspring of 31 conjugal spouse pairs with AD. We have since greatly enlarged this study and collected data from more than 100 conjugal pairs with AD, allowing for analysis of the question of increased risk of AD in their children. In addition, in the previous study,1 most offspring were younger than 50 years, whereas, in the present study, more than 83% of the offspring are older than 50 years. We confirmed the pilot finding that, in children of spouse pairs with AD, there
is a higher rate of AD than would be expected in the general population. Our calculated AD incidence in offspring of affected spouses may be underestimating the overall risk in this population because 54% of them had not reached age 65 years. Although we found a high rate of AD in the offspring of conjugal couples, the presence of an additional family history of AD did not seem to affect this risk of AD. As expected, APOE plays a role in this phenomenon, but the e4 allele alone does not account for all AD cases in offspring, supporting the hypothesis that this is a complex polygenic phenomenon.

Families were ascertained from the University of Washington Alzheimer Disease Research Center registry, with informed consent approved by the institutional review board. One hundred eleven couples in which both spouses had a diagnosis of probable or definite AD were identified. (One family was recruited from the University of California, Davis.) All available medical records, family histories, imaging studies, and autopsy results were obtained. Available living parents were interviewed and examined. In addition to written records, family history was obtained through in-person or telephone interviews with living family members. A diagnosis of mild cognitive impairment was not considered a diagnosis of AD in either parents or children. Clinical criteria for AD were those suggested by McKhann et al. Age at onset was determined to be the age at which family members and medical records agreed that the individual first began showing signs of memory loss or behavioral changes. Affected parents and offspring for whom DNA was available underwent APOE genotyping using previously described methods.

Statistical analysis of risk was performed using a nonparametric Kaplan-Meier estimate to draw the survival curve and, thus, the cumulative risk curve for children’s ages at dementia onset. The number of children without dementia was computed at each observed age at onset, divided by the number of children who were still unaffected just before that age. The estimated survival function is the product of any earlier computed probabilities. The plot of the Kaplan-Meier survival curve is a step function in which the estimated survival probabilities are constant between adjacent ages at dementia onset and decrease at each observed age at onset. The cumulative risk, which is equivalent to 1 minus the survival probability, results in an increasing step function of the cumulative risk curve for dementia onset. When the sex effect was considered, 2 separated curves were computed, each using the data from only 1 sex.

CHARACTERISTICS OF SPOUSE PAIRS WITH AD AND THEIR OFFSPRING

There were 111 affected spouse couples; 48 of these 222 persons (21.6%) had AD confirmed by autopsy. The mean (SD) age at onset of dementia was 74.5 (8.5) years in the 174 parents for whom age at onset was known (Table 1). For the 89 mothers with a known age at onset, the mean (SD) was 75.1 (8.5) years, and for the 85 fathers in whom age at onset was known, the mean (SD) was 73.9 (8.5) years. These 111 spouse couples had 313 children, 297 of whom survived to adulthood (age 18 years).

Sixty-seven of the 297 children (22.6%) who survived to adulthood had been given a clinical diagnosis of AD at the time of ascertainment. Mean (SD) age at disease onset in these children was 66.3 (10.3) years (range, 48–87 years). Mean (SD) age at onset in women was 67.6 (10.1) years, and in men was 64.7 (10.5) years (n = 29). Seven diagnoses were confirmed by autopsy, and otherwise confirmation of diagnosis was made through medical record review, family and patient interviews, or examination by 1 of us (S.J., E.J.S., or T.D.B.). The age at last contact with the family was known for 306 total and 240 unaffected children (10 children were ≥18 years, and age ranged from infancy to 87 years). Of the 240 unaffected individuals, 189 (78.8%) had not yet reached age 70 years, suggesting that the incidence of AD (22.6%) is an underestimation of the final incidence rate of AD in this population. To address this issue, we calculated the presence of AD in specific age groups (Table 2). There were 261 children 50 years or older, 66 (23.3%) of whom were given a diagnosis of AD. In children 60 years or older (n = 187), the diagnosis of AD (n = 38) was 31.0%.

### METHODS

Families were ascertained from the University of Washington Alzheimer Disease Research Center registry, with informed consent approved by the institutional review board. One hundred eleven couples in which both spouses had a diagnosis of probable or definite AD were identified. (One family was recruited from the University of California, Davis.) All available medical records, family histories, imaging studies, and autopsy results were obtained. Available living parents were interviewed and examined. In addition to written records, family history was obtained through in-person or telephone interviews with living family members. A diagnosis of mild cognitive impairment was not considered a diagnosis of AD in either parents or children. Clinical criteria for AD were those suggested by McKhann et al. Age at onset was determined to be the age at which family members and medical records agreed that the individual first began showing signs of memory loss or behavioral changes. Affected parents and offspring for whom DNA was available underwent APOE genotyping using previously described methods.

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### RESULTS

**Table 1. Characteristics of Conjugal Couples With AD and Their Offspring**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couples/individuals with AD, No.</td>
<td>111/222</td>
</tr>
<tr>
<td>Age at AD onset, mean (SD), y (n=174)</td>
<td>74.5 (8.5)</td>
</tr>
<tr>
<td>Mothers (n=89)</td>
<td>75.1 (8.5)</td>
</tr>
<tr>
<td>Fathers (n=85)</td>
<td>73.9 (8.5)</td>
</tr>
<tr>
<td>Offspring, No.</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>155</td>
</tr>
<tr>
<td>Females</td>
<td>158</td>
</tr>
<tr>
<td>Subtotal</td>
<td>313</td>
</tr>
<tr>
<td>Offspring who survived to adulthood (&gt;18 y), No.</td>
<td>297</td>
</tr>
<tr>
<td>Offspring with AD, No.</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>29</td>
</tr>
<tr>
<td>Females</td>
<td>38</td>
</tr>
<tr>
<td>Subtotal</td>
<td>67</td>
</tr>
<tr>
<td>Affected offspring age at AD onset, mean (SD), y</td>
<td>66.3 (10.3)</td>
</tr>
<tr>
<td>Male</td>
<td>64.7 (10.5)</td>
</tr>
<tr>
<td>Female</td>
<td>67.6 (10.1)</td>
</tr>
<tr>
<td>Autopsies, No.</td>
<td></td>
</tr>
<tr>
<td>Spouse father</td>
<td>20</td>
</tr>
<tr>
<td>Spouse mother</td>
<td>28</td>
</tr>
<tr>
<td>Offspring</td>
<td>7</td>
</tr>
<tr>
<td>Subtotal</td>
<td>55</td>
</tr>
</tbody>
</table>

**Table 2. Occurrence of AD in Offspring of Spouses With AD**

<table>
<thead>
<tr>
<th>Offspring</th>
<th>Age Group, y</th>
<th>Total No.</th>
<th>Affected With AD, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥18</td>
<td>297</td>
<td>67 (22.6)</td>
</tr>
<tr>
<td></td>
<td>≥50</td>
<td>261</td>
<td>66 (25.3)</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>187</td>
<td>58 (31.0)</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>140</td>
<td>50 (35.7)</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>98</td>
<td>41 (41.8)</td>
</tr>
</tbody>
</table>

**Abbreviation:** AD, Alzheimer disease.
One hundred forty children were 65 years or older, and 50 of those (35.7%) were affected. In those 70 years or older (n = 98), the proportion affected was 41.8%.

INCREASED RISK OF AD IN OFFSPRING OF CONJUGAL PAIRS

Using a statistical risk model, we sought to determine the cumulative risk of AD. Consistent with the apparent increased frequency of AD in the study population, we found that children of spouses with AD comparatively have a high risk of AD (Figure 1A). By age 70 years, the cumulative risk of AD in children of spouse pairs with AD was approximately 20%. At age 80 years, the cumulative risk reaches beyond 60%. We do not have an internal control of children having 1 parent with AD or children with neither parent with AD. However, in comparing the risk curves generated for this study population with those calculated for the controls in the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) study,4 the present data support the hypothesis that children of sporadic AD conjugal pairs have a greater cumulative risk of AD than would be expected in either the general population or among children with 1 affected parent. To assess the impact of sex on risk, women and men were analyzed separately (Figure 1B). Although there seems to be a trend toward increased risk in women older than 70 years, the difference is not significant (P = .17).

FAMILY HISTORY AND AD PREVALENCE IN OFFSPRING

We next hypothesized that family history of AD may impart a higher “dose” of genetic factors contributing to AD. We assessed whether a positive family history of AD was associated with a higher rate of dementia in offspring. Of the 258 offspring for whom a wider family history was known, 106 did not have a family history of AD beyond their parents (Table 3). Twenty-three of these 106 chil-

Table 3. Family History of AD and Risk in Offspring

<table>
<thead>
<tr>
<th>Family History Beyond Parents</th>
<th>Total No.</th>
<th>Affected With AD, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>106</td>
<td>23 (21.7)</td>
</tr>
<tr>
<td>Positive</td>
<td>152</td>
<td>22 (14.5)*</td>
</tr>
<tr>
<td>Unilateral</td>
<td>105</td>
<td>13 (12.4)*</td>
</tr>
<tr>
<td>Bilateral</td>
<td>47</td>
<td>9 (19.1)*</td>
</tr>
</tbody>
</table>

Abbreviation: AD, Alzheimer disease.
*Not significant (χ² test).
were similarly not significant using a χ² test. The differences among 3 subgroups—negative family history beyond parents, unilateral family history on 1 parental side, and bilateral family history on both parental sides—were similarly not significant using a χ² test with 2 df.

Although the presence of AD did not seem to be affected by the presence of a family history, age at onset of AD correlated with a positive family history. Using Kruskal-Wallis nonparametric correlation statistical analysis, there was a significant trend in the median age at onset based on family history (P = .008) (Figure 2). Children of parents with no AD family history (beyond the parents) had an older age at onset (72 years; n = 23) compared with those who had 1 parent with an AD family history (age at onset of 60 years; n = 13). Children of parents who both had a positive family history had the youngest median age at onset (57 years; n = 9).

There were too few APOE genotypes (17 in total) in children with AD to perform meaningful statistical analysis. However, it was clear that the ε4 allele was overrepresented in the affected offspring, with 7 of 17 individuals having the APOE 4/4 genotype and 8 with APOE 3/4. Only 2 individuals had APOE 3/3, and both had a young age at onset (49 and 53 years).

ILLUSTRATIVE FAMILIES

Two families illustrating the broad range of findings in this study are shown in Figure 3 and Figure 4. One family has numerous instances of dementia on both parental sides (bilateral positive family history). None of the 5 children have developed AD, but the oldest is only 65 years old (Figure 3). In the other family, 6 of 8 children have developed AD (5 autopsy confirmed) (Figure 4). Affected children underwent genotyping and were APOE 2/4 or 4/4.

COMMENT

We demonstrated a 22.6% overall rate of AD in the adult offspring of affected conjugal couples with AD. Of the 223 living offspring, the mean age was 62 years, showing that many of the children have not yet reached the ages having the highest risk of AD. It is therefore probable that the prevalence of AD in this study group will be even higher once more offspring have lived beyond age 70 years.

The Government Accountability Office and others estimate that the AD prevalence in the population older than 65 years is 6% to 13%. Variability is likely related to sample size, study design, and date as well as patient characteristics. However, the pervading theme in all AD prevalence and incidence studies is the prediction of increasing numbers and prevalence rates of AD in the decades to come.

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Observations of “familial clustering” of AD had led to detailed epidemiologic studies of increased risk in siblings and offspring of patients with AD. Although the possibility of monogenic inheritance with decreased penetrance had been suggested to explain empirically observed increased risk in family members, a complex polygenic inheritance of late-onset AD is most likely.

Few prospective studies of children of parents with AD have been performed. A pilot study by Jarvik et al showed no significant decrease in cognitive ability in middle-aged offspring of probands with AD. Increased risk of AD in first-degree relatives of patients with AD has been reported multiple times. Risk analysis available for first-degree relatives has limited application to estimating risk in children in sporadic AD. Children are more likely to harbor the same genetic background that contributed to AD in their parents, more so than other relatives. In addition, offspring of 2 affected parents have inherited this confluence of risk factors twice. Lautenschlager et al in the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) study, demonstrated this effect in their analysis of 1694 probands with AD and risk in their family members. Of the 5590 total siblings in their study, 75 siblings of 21 probands were born to 2 affected parents (conjugal AD). Those individuals had a higher lifetime risk of AD (54%) than did siblings with only 1 affected parent (37%). This portion of the MIRAGE study differs from the present study in several ways, but the observation of the cumulative effect of having more than 1 affected parent is comparable.

We also analyzed the impact of family history on risk of AD in conjugal families with AD. We found no statistically significant correlation between the presence of a family history and AD prevalence in offspring. A pooled analysis of the prospective European Studies of Dementia also reported a nonsignificant increased risk of 1.6 in individuals with 2 or more first-degree relatives affected with AD, suggesting that family history may not be as influential as once thought. The distinction that having an affected parent increases risk in offspring whereas having additional affected relatives does not confer a stronger risk may reflect gene dose. For example, it is possible that the degree of genetic variation between an individual and his or her uncle may be great enough to “dilute” the AD-conferring genetic background present in the family. However, in the present study, family history affected age at onset in children, onset being earlier in those with a more extensive family history.

In calculating cumulative risk, there seemed to be a slightly increased trend in lifetime risk in women older than 70 years compared with age-matched men, although the difference in risk did not reach statistical significance. More than half (52.1%) of the 48 female offspring 70 years or older were affected. In contrast, 32.0% of the 50 male offspring 70 years or older had a diagnosis of AD. The effect of sex on AD risk has been somewhat controversial. Multiple studies have demonstrated increased risk in older women vs men, whereas others have suggested similar patterns of cognitive decline and AD risk in older men and women. The MIRAGE study reported increased risk in older women when studying individuals with affected family members. Effects of sex may interplay with genetic predisposition, and women in whom genetic factors are more influential in the development of AD may be at increased risk compared with their male counterparts.

The only widely accepted susceptibility gene for late-onset AD is the APOE ε4 allele, which confers an approximate 3-fold risk in the heterozygous state (compared with having no APOE ε4 allele) primarily by accelerating the age at onset. However, given that 50% of patients with AD do not carry an APOE ε4 allele, there remain unidentified polygenic factors beyond APOE contributing to risk in late-onset AD. In the present study, the APOE ε4 genotype played an important role but did not fully explain the increased risk of AD in the children of spouses with AD, supporting the likelihood of additional genetic factors. Studies attempting to correlate genetic sequence variants with increased risk of sporadic AD have been numerous, although difficult to replicate. These candidate genes include sequence variants of inflammatory genes or their promoters and variants in the sortilin-related receptor SorL1, ubiquilin, and many others.

In summary, the risk of AD is likely to be higher in the offspring of conjugal pairs with AD, supporting the hypothesis of polygenic inheritance. The data discussed herein represent information collected during several decades and cannot reflect changes in the incidence rates of AD in the general population across time. Families with a significant AD history may be more likely to be referred to an AD research center and, thus, the present patients may be “enriched” for a particularly AD-prone subgroup. Following these families as the offspring continue to age will provide increasingly informative data.

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REFERENCES


