Variability of Age at Onset in Siblings With Familial Alzheimer Disease

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Background: Variability of age at onset (AO) of Alzheimer disease (AD) among members of the same family is important as a biological clue and because of its clinical effects.

Objective: To evaluate which clinical variables influence the discrepancy in AO among affected relatives with familial AD.

Setting: Clinical genetic project of Spanish kindred with AD conducted by 4 academic hospitals in Madrid, Spain.

Methods: Age at onset of AD in 162 families and discrepancy in AO in intragenerational and intergenerational affected pairs were analyzed in relation to age, sex, maternal or paternal transmission, pattern of inheritance, and apolipoprotein E genotype.

Results: Maternal transmission of AD was significantly more frequent than paternal transmission (P < .001). In 27% of the affected individuals, AO occurred before the patient was 65 years old. Discrepancy in AO among siblings was within 5 years in 44% of the families, 6 to 10 years in 29%, and more than 10 years in 27% (range, 0-22). This discrepancy was independent of the sex of the sibling pairs and was significantly lower with maternal transmission of AD (P = .02). Segregation analysis showed no differences in the inheritance pattern between families with low (≤5 years) or high (>5 years) AO discrepancy. Age at onset in carriers of the apolipoprotein E ε4 allele was slightly younger. However, among siblings, an extra apolipoprotein E ε4 allele was not consistently associated with earlier onset of AD. Eighty percent of patients, independent of sex or mode of transmission, were already affected at their parents’ reported AO.

Conclusions: There is a wide discrepancy in AO in affected siblings that is not clearly explained by a single clinical variable or apolipoprotein E genotype. The interaction of many factors probably determines AO in each affected individual. However, maternal transmission of AD seems to result in a similar AO in offspring, and the risk of developing dementia after the parent’s reported AO decreases significantly.

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METHODS

The GENODEM Project involves 4 academic hospitals in Madrid (Fundación Jiménez Díaz, Hospital Clínico San Carlos, Hospital Ramón y Cajal, and Fundación Hospital Alcorcón) that use common standardized dementia protocols.

A total of 162 probands with a clinical diagnosis of probable AD according to standardized criteria,7 AO before 85 years, and at least 1 affected first-degree relative known to have a diagnosis of AD or having a similar clinical dementia (insidious onset, evolving in years, and unrelated to trauma or alcohol abuse) have been studied. For each proband, detailed data on family history of dementia were collected. For all affected individuals in each family, data on sex, AO of symptoms, and age at death were obtained. Special effort was made to ensure that AO data in siblings were as accurate as possible by reviewing medical records from other centers and by telephone interviews with the closest relative. For AO in parents, we relied on information provided by their offspring and double-checked it with several family members when available.

The following data were analyzed: general demographic data about the entire sample of families with AD including distribution of affected and unaffected members according to sex, maternal or paternal transmission, number of affected members per family, distribution of affected members according to AO, and influence of sex and parental transmission in AO. Both intragenerational and intergenerational discrepancy in AO within families were analyzed. Intrigeneration discrepancy was analyzed with consideration of differences across all affected siblings to establish the range of variability and within sibling pairs to consider the influence of sex, AO, age at death, and maternal or paternal transmission. Pattern of inheritance was analyzed by complex segregation analysis to compare the best-fit model of transmission between families with low (≤5 years) or high (>5 years) AO discrepancy. This analysis was carried out according to the unified model of complex segregation analysis implemented with POINTER software (Division of Biostatistics, Washington University Medical School, St Louis, Missouri).3 The model partitions the total variation of the underlying liability for AD into 3 independent components: a biallelic single major locus, a polygenic background, and a random environmental component.

Intergenerational AO discrepancy was examined comparing pairs of affected parent and offspring. We calculated cumulative survival rates with Kaplan-Meier curves, which expressed the probability of the descendents still being asymptomatic at a certain age in comparison with the parent’s reported AO. The effect of sex was also examined.

Age at onset in all probands and discrepancy in AO in 42 intragenerational sibling pairs were also examined according to APOE genotype. Blood samples were collected after the patient or surrogate gave informed consent. The study was approved by the Research Ethics Committee of Fundación Jiménez Díaz. APOE genotype was determined by polymerase chain reaction digestion according to the method of Hixson and Vernier.4 Differences in AO comparing APOE-concordant with APOE-discordant sibling pairs were tested using the t test. For discordant sibling pairs, differences in AO were considered positive when dementia developed earlier in the sibling with more ε4 alleles and negative when it developed later.

Table 1. Age at Onset of AD According to Sex and Transmissiona

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases</th>
<th>Age of Onset, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>169</td>
<td>69.3 (9.8)</td>
</tr>
<tr>
<td>Male</td>
<td>83</td>
<td>68.2 (8.0)</td>
</tr>
<tr>
<td>Transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>120</td>
<td>69.2 (8.9)</td>
</tr>
<tr>
<td>Paternal</td>
<td>47</td>
<td>67.7 (8.2)</td>
</tr>
</tbody>
</table>

Abbreviation: AD, Alzheimer disease.

aData are given as mean (SD). P values are not significant.

![Figure 1. Distribution of age at onset of Alzheimer disease in probands and affected siblings.](image-url)
RESULTS

DEMOGRAPHIC AND GENERAL AO DATA

A total of 162 probands or families were recruited. There was a mean of 3 affected members per family, with 504 affected cases of 2024 individuals in the family trees. The number of affected female members was significantly higher (30%) than affected male members (17%) ($P = .001$). Of all affected individuals, 66% were women and 34% were men. Maternal transmission was more frequent than paternal transmission (120 vs 47; $P < .001$).

Mean±SD AO in the probands was 69±9 years (age range, 29-85 years). Reliable AO data were also available for 90 siblings of a total of 252 affected individuals. The distribution of affected individuals according to AO is shown in Figure 1. For 27% of the affected individuals AO occurred before these persons were 65 years old; in 73% AO occurred when these persons were 65 years old or older. There were no differences in AO between men and women ($P = .34$) or between maternal and paternal transmission ($P = .36$; Table 1).

DISCREPANCY IN AO WITHIN AFFECTED PAIRS

Intragenerational Discrepancy

Information about AO in several affected siblings was available in 79 families and demonstrated a wide discrepancy (Figure 2). The value chosen was the highest discrepancy in AO among all affected siblings in a family, that is, 1 value per family. This discrepancy was within 5 years in 44% of the families, 6 to 10 years in 29%, and more than 10 years in 27%. There was a tendency toward a smaller difference when the AO in the proband was higher ($P = .06$).

The discrepancy in AO between sibling pairs was independent of sex ($P = .31$) (Figure 3A). Mean±SD discrepancy was 4.9±3.6 years between sisters, 3.2±3.5 years between brothers, and 4.2±4.0 years when the sibling pair was a brother and a sister. The mean±SD discrepancy in AO within sibling pairs was significantly lower with maternal transmission of AD (3.9±3.7 years vs 6.3±5.2 years with paternal transmission; $P = .02$; Figure 3B). Complex segregation analysis showed that both families with a high (>5 years) or low (≤5 years) discrepancy in AO among siblings better fit in the same model of inheritance (Table 2).

Intergenerational Discrepancy

Data on AO in parents were available for 119 families. The mean±SD differences in AO were similar for paternal transmission to son (n=12; 1.3±5.3 years) or daughter (n=22; 3.3±6.5 years) compared with maternal transmission to son (n=18; 3.7±8.6 years) or daughter (n=67; 2.9±6.6 years). Figure 4 shows cumulative survival rates (ie, percentage of still asymptomatic offspring) at a certain age compared with reported AO in the parent. Only about 20% of affected offspring had no symptoms at the AO in their parent (cumulative survival rate, 0.23), and this percentage was the same for maternal or paternal transmission. At 5 years after AO in the parent, only 6% of offspring affected were still without symptoms.

APOE GENOTYPE

Sixty-six percent of 106 individuals with AD carried the APOE 3/4 (53%) or APOE 4/4 (13%) genotype, and 34% carried the APOE 3/3 genotype. Distribution of female and male carriers was similar for the 3 APOE genotypes. There were no carriers with APOE ε2 alleles. Mean±SD AO in APOE 4/4 carriers was younger (66±5 years) compared with APOE 3/4 (69±7 years) and APOE 3/3 carriers (71±6 years) ($P = .11$) (Figure 5A).

APOE genotype was available for 42 sibling pairs (Figure 5B). The distribution of 29 APOE-concordant siblings...
ling pairs and mean ± SD difference in AO was APOE 3/3 (n = 6; 6.3 ± 5.2 years), APOE 3/4 (n = 16; 3.5 ± 3.0 years), and APOE 4/4 (n = 7; 6.5 ± 3.4 years), and for 13 APOE-discordant sibling pairs was APOE 3/4 vs APOE 4/4 (n = 8; 4.2 ± 2.4 years) and APOE 3/3 vs APOE 3/4 (n = 5; 6.6 ± 2.9 years). There were no APOE 3/3 vs APOE 4/4 sibling pairs. The mean ± SD difference in AO in APOE-concordant sibling pairs (5.1 ± 3.9 years) was not significantly different from that in discordant sibling pairs (5.1 ± 2.8 years; P = .16). When sibling pairs were APOE discordant (1 of the pair had 1 APOE ε4 allele more), only in 50% of this occurrence the sibling with more ε4 alleles had an earlier AO than its pair (positive value in Figure 5).

Our study findings show a wide variability in AO of symptoms in siblings with familial AD that is not dependent on a single clinical variable or APOE genotype, although it points to maternal transmission as a clinical feature that may decrease this difference. They also show that most affected individuals already have symptomatic disease at their parents’ reported AO.

Several studies suggest that AO is a clinical feature strongly determined by genetic factors. This is supported in that it is more homogeneous within families than between families; 40% of the variance of this trait can be explained by familial effects, amyloid precursor protein and presenilin-1 and presenilin-2 mutations are associated with specific AO ranges, and some genes have been identified as influencing AO in AD, including the APOE genotype. In this series, in almost half of the families (44%), the difference in AO was within 5 years among families.
siblings, but more than half of the families had a much wider range of difference (6-22 years). The discrepancy in AO was not influenced by sex of the affected siblings, and there did not seem to be a different pattern of inheritance, as shown by segregation analysis, between families with high or low discrepancy.

However, the difference in AO within sibling pairs was significantly lower when the disease was maternally transmitted. This is important because maternal transmission, in this study and in others,

Figure 5. Apolipoprotein E (APOE) genotype in relation to age at onset of Alzheimer disease in the entire affected population (A) and difference in age at onset in 42 sibling pairs concordant or discordant for the APOE genotype (B). Lines represent mean values. For discordant APOE sibling pairs, a positive value is obtained when dementia appears earlier in the sibling with more ε4 alleles (although mean values are for absolute differences).

do not seem to be a different pattern of inheritance. In these families, there were overwhelming data for a female preponderance in most aspects: substantially more women were affected, and there were more cases of maternal transmission and more mother-daughter transmission. Many studies have analyzed why AD samples always exhibit more affected women than men. Some argue that the explanation may be longer life expectancy in women and that there is not a sex-specific risk for AD

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they can support giving positive expectations when an individual has no symptoms at the age when his or her parent was recognized as having cognitive impairment. Prospective studies should examine further whether the risk of developing dementia decreases significantly once an individual is older than the AO in the parent and whether there may be a tendency to anticipate development of AD.

In summary, AO of AD is a clinical feature probably conditioned by the complex interaction of several genetic factors and a slight influence of extragenetic variables. Although it is difficult to predict an approximate AO in a certain individual with familial AD, maternal inheritance suggests a closer AO among siblings and that children who have no symptoms by the reported AO of dementia in their parents are less prone to develop AD.

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Author Contributions: Dr Gómez-Tortosa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gómez-Tortosa, Barquero, and Jiménez-Escrig. Acquisition of data: Gómez-Tortosa, Barquero, Barón, Sainz, Manzano, Payno, Ros, Almaraz, and Gómez-Garré. Analysis and interpretation of data: Gómez-Tortosa and Barquero. Drafting of the manuscript: Gómez-Tortosa and Barón. Critical revision of the manuscript for important intellectual content: Gómez-Tortosa, Barquero, Sainz, Manzano, Payno, Ros, Almaraz, and Gómez-Garré. Administrative, technical, and material support: Gómez-Tortosa, Barquero, Sainz, Manzano, and Payno. Study supervision: Gómez-Tortosa and Barquero.

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