Wide Range of Disease Onset in a Family With Alzheimer Disease and a His163Tyr Mutation in the Presenilin-1 Gene

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Objectives: To describe clinical and genealogical data of a Swedish family with a His163Tyr mutation in the presenilin-1 gene (PS1) and to study the Alzheimer disease (AD) penetrance in this family.

Design: Interviews with relatives, studies of medical records, analysis of pedigree, physician examination of the affected individuals, and comparison with other families affected by AD with PS1 mutations.

Setting: Large university-affiliated hospital.

Patients and Other Participants: Individuals with a His163Tyr mutation in PS1 and their relatives.

Results: A study of this family with a history of very early AD onset (mean age, 47 years) has been previously published, but an investigation of the extended family revealed a new pattern of onset, with a mean age at onset of 54 years (range, 44-65 years). In general, families with AD show a tight cluster of age at onset with high penetrance of the disease. However, in this family, an individual whose child carries the PS1 mutation died at age 67 years free from cognitive symptoms, indicating a very late age at onset or nonpenetration of the disease. No association between age at onset and disease duration was found. Furthermore, the disease duration did not differ between those having an early onset compared with those having a late onset. The earliest clinical manifestations were deficits in memory function and disorientation in time and place. Myoclonic jerks and epileptic seizures were common symptoms later in the disease.

Conclusion: The large range in age at onset in this family with a uniform genetic basis for the disease, a His163Tyr mutation in PS1, supports the existence of other unknown genetic or environmental factors of importance for the expression of the AD phenotype.

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Genetic factors are of importance in the cause of Alzheimer disease (AD), a progressive neurodegenerative disorder of the central nervous system, leading to dementia. Families with AD in which there is a pattern of autosomal dominant inheritance with affected members in several generations have been investigated. Three dominant acting genes have been identified: the amyloid precursor protein (APP) gene on chromosome 21, and the presenilin-1 (PS1) and presenilin-2 genes on chromosomes 14 and 1, respectively. The apolipoprotein E (APOE) gene on chromosome 19 is a susceptibility gene, which affects risk and age at onset of AD, originally identified in late-onset familial AD. Variance in the age at onset has generally been attributed to genetic heterogeneity. However, a wide range of disease onset was observed in families with APP mutations, while the APOE genotype does not appear to influence age at onset in chromosome 14–linked familial AD.

The clinical picture in early onset chromosome 14–linked AD families has been described by Haltia et al and Mullan et al. In these pedigrees, the disease has an autosomal dominant mode of inheritance, a very early disease onset, and a rapid course of the disease. Furthermore, seizures and myoclonic jerks were
PATIENTS AND METHODS

The family in this study contacted us because of their concerns about the hereditary nature of dementia in the family. Since there had been a very early age at onset in the still-living affected individuals, they were screened for mutations in the PS1 gene. The family extends over 6 generations and originates from a small town in the middle of Sweden. Some of the family members have remained in that area, while others have moved to other parts of Sweden. Men worked in steel and chemical factories, and women worked in the home. Information about as many prior generations as possible was obtained and data concerning the affected person’s date and place of birth, occupation, prior illnesses and hospitalizations, and cause and date of death were obtained by interviewing 18 family members and by collecting information from parish registers and historical archives. For all affected individuals, detailed data on family history of dementia, age at onset of disease (defined as the age when the first signs of cognitive impairment appeared), and its course were registered. In 16 of the 18 affected individuals, we had reliable information regarding age at onset, symptoms, and their order of appearance both by medical records and by the information obtained from the interviews. The age at onset and the clinical course in subjects II:5 and II:8 were difficult to determine as information only was based on interviews. Affected and unaffected family members (n=24) had blood samples taken, and DNA was prepared. The APOE genotype was determined using a microsequencing method on microtiter plates (AffiGen APOE, Sangtec Medical, Bromma, Sweden).30

Four subjects (II:1, II:2, III:27, and IV:8) in the pedigree were defined as obligate carriers of the disease-causing mutation, as they had demented offspring (Figure). There was no information as to whether subject II:1 and subject II:2 were demented or not when they died at age 66 years and 75 years, respectively, while subject III:27 and subject IV:8 died not demented at age 44 years of tuberculosis and at age 67 years of gastric cancer, respectively.

Comparisons between female and male family members were analyzed with the Mann-Whitney U test. Pearson correlation coefficients were used to study the relationship between age at onset and duration of illness. Significance levels were set at P<.05.

RESULTS

An extended genealogical and clinical investigation (Figure) revealed a wide range of ages at onset (Table 1) and a mean onset age of 54 years. This family history had been previously reported9 as having an earlier age at onset (mean, 47 years). The mean (±SD) age at onset was 55.2 years (±7.1 years; range, 43-65 years) for male family members and 53.0 years (±7.8 years; range, 44-65 years) for female members. The mean (±SD) age at death was 65.4 years (±6.5 years; range, 55-75 years) for men (n=9) and 70.7 years (±8.5 years; range, 59-83 years) for women (n=6). These differences between men and women were not statistically significant. However, we found a longer disease duration in women (mean±SD, 15.0±4.9 years; range, 11-23 years) compared with men (mean±SD, 9.3±2.6 years; range, 5-12 years) (P=.01). There was no association between age at onset and disease duration in this family. The duration did not differ between those having an early age at onset compared with those having a late age at onset. Three affected individuals are still alive (Figure).

A similar pattern and progression of the disease were observed in all affected individuals (Table 2). The first cognitive feature in 15 of 16 patients was an insidious loss of memory for recently acquired information. Symptoms before the clinical manifestation of AD were depression, seen in 5 patients and expressed as anxiety, decreased power of concentration, and headache. Disorientation for time and place, dysphasia, and dyspraxia occurred early in the disease. In 9 patients, psychiatric symptoms such as depression, aggressiveness, anxiety, jealousy, and suspiciousness were observed. When the disease progressed, myoclonus and seizures occurred in 9 patients (Table 2). The still-living affected individuals were at an advanced stage and exhibited total apraxia, aphasia, incontinence, gait disturbances, rigidity, and myoclonia. The Mini-Mental State Examination was not possible to perform due to their stage of severe dementia.

The family descended from ancestors I:1 and I:2, who were born in the middle of the 19th century. Ancestor I:1 died at age 47 years of an unintentional injury, and ancestor I:2 died of an unknown cause and at an unknown age. The mode of inheritance in this family was compatible with an autosomal dominant disorder (Figure). Three affected individuals—IV:18, IV:19, and V:3—were directly shown to have the PS1 mutation by single-strand confirmation polymorphism tests, followed by direct DNA sequencing. Subject IV:16 was an obligate carrier of the mutation as the offspring were mutation carriers. One of the obligate mutation carriers (subject IV:8) died at age 67 years not demented (Figure). Whether there was an incomplete penetrance or a very late age at onset in this individual remains uncertain.

The APOE genotype was possible to confirm in 3 affected individuals and to deduce in 1 individual. Three individuals with AD onset at ages 44, 45 (deduced), and...
Our hypothesis was that there was a uniform genetic basis, a His163Tyr mutation in the PS1 gene, for AD in this Swedish family. However, a wide range of ages at onset, from 44 to 65 years, was found. Defining the earliest signs of a disease with an insidious onset can prove to be a most elusive task, particularly a disease whose very nature renders the patients’ self-reports unreliable. To investigate the earliest perceived signs of illness in the patients, 18 family members were interviewed and medical records of affected individuals (available in 16 patients) were carefully studied. Variance in the age at onset has generally been attributable to genetic heterogeneity. A similar variability in the age at onset in PS1-mutation families was recently reported by Rossor et al and Lopera et al, suggesting an important role for genetic modifiers or environmental factors in determining the age at onset. In contrast to our results, families with chromosome 14–linked AD have been previously reported to have a characteristic early onset with a narrow range. There are limitations in our study as the inherent methodological difficulties of any retrospective, informant-centered study are obvious. Our aim in this study was to define the earliest signs of change as perceived by family members. Families with the disease in prior generations may be more observant of early symptoms, which may account for an earlier age at onset in the present generation. However, the duration of disease in affected individuals did not differ between those having an early age at onset as compared with those having a late age at onset, indicating that the age at onset is variable in this PS1 family. Furthermore, the assumption that subject IV:8 was a mutation carrier with a very late age at onset (died at age 67 years not demented) corroborates a strong evidence for a wide age range of disease onset in this family.

The duration of disease in this family had a similar wide span as reported in 2 other studies. However, in previously described families with chromosome 14–linked AD, the disease duration appears to be short, reflecting the severity of PS1-associated familial AD. We did not observe a correlation between disease duration and age at onset; others have reported that patients with late onset had shorter duration of disease than those with early onset. Other studies reported that patients with early onset AD had a more rapid course than patients with late onset AD, consistent with a more aggressive course of disease in the early onset cases.

Table 1. Clinical Data of 18 Patients With Alzheimer Disease (AD)

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age at AD Onset, y</th>
<th>Age at Death, y</th>
<th>Duration of AD, y</th>
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</thead>
<tbody>
<tr>
<td>II:5†</td>
<td>~50</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>II:6</td>
<td>65</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>II:8†</td>
<td>~50</td>
<td>73</td>
<td>23</td>
</tr>
<tr>
<td>III:5</td>
<td>56</td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td>III:6</td>
<td>62</td>
<td>73</td>
<td>11</td>
</tr>
<tr>
<td>III:12</td>
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<td>72</td>
<td>12</td>
</tr>
<tr>
<td>III:13</td>
<td>59</td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>III:29†</td>
<td>64</td>
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<td>19</td>
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<tr>
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<td>11</td>
</tr>
<tr>
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<tr>
<td>V:3</td>
<td>46</td>
<td>NA</td>
<td>7</td>
</tr>
</tbody>
</table>

* NA indicates not applicable; individual is still alive. The roman numeral in the “Subject No.” column indicates generation (see Figure).
† Data for these family members were previously published without age at onset.
‡ Data for these family members were previously published with age at onset.

47 years had the genotype 3/4, and 1 individual with AD onset at age 46 years had the genotype 3/3.
The disease usually started insidiously with loss of memory for recently acquired information, and, as the disease progressed, psychiatric symptoms, such as anxiety, suspiciousness, aggressiveness, and depression, often were noticed. However, defining the earliest signs of a disease with an insidious onset can be difficult. In this family, before the clinical manifestation of AD, 5 patients had depression, expressed as anxiety, decreased power of concentration, and headache (Table 2). As AD progressed, the patients developed impairments of language comprehension and verbal fluency and developed difficulty in naming. Disorientation for time and place and dyspraxia were commonly observed symptoms. Most of the patients did not have neurologic problems other than impairment of mental status until late in the disease course. Myoclonic jerks and epileptic seizure were observed later in 10 of 16 patients. The clinical picture of this family is in accordance with the findings in 2 other families with PS1 mutations, but differed from the families previously described by Haltia et al and Mullan et al where myoclonus and epileptic seizure were early and prominent signs.

Large families with inherited AD offer a unique opportunity to study the mode of inheritance through many generations. The disease in this Swedish family is caused by a His163Tyr mutation in the PS1 gene inherited as an autosomal dominant trait. However, within this pedigree, clinical features show phenotypic variability, for example, the wide range of age of onset among patients carrying the same mutation. In 1 subject (subject IV:8), we could not determine whether there was a nonpenetration of the disease or if there was a very late age at onset that made this individual free from cognitive symptoms until death at age 67 years. One genetic determinant believed to affect age at onset is the number of APOE e4 alleles. Since there was APOE genotype information only for 4 affected individuals, it was not possible to draw any conclusions about the influence of the APOE genotype on the age at onset in this family. However, the APOE genotype does not appear to influence age at onset in chromosome 14-linked familial AD and may not explain the absence or delay of disease expression in this individual. Although penetrance is high in this family, it may not be complete and the expression is highly variable in terms of age at onset. This fact has important implications for genetic counseling of those at risk and, potentially, for understanding the pathophysioologic workings of AD and the opportunities for delaying the age at onset. The large range of age at onset in this family supports the existence of unknown genetic or environmental factors of importance for the expression of AD phenotype. These factors remain to be clarified.

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REFERENCES


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