Clinical Features of Early-Onset Alzheimer Disease in a Large Kindred With an E280A Presenilin-1 Mutation

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Objectives.—To characterize clinical features of a very large pedigree with early-onset Alzheimer disease (AD) in which all affected individuals carry the identical glutamic acid-to-alanine mutation at codon 280 in the presenilin-1 gene.

Design.—Clinical histories were obtained by patient and family interviews and through medical or civil records. Using standard diagnostic criteria, a case series of 128 individuals was identified, of which 6 have definitive (autopsy-proven) early-onset AD, 93 have probable early-onset AD, and 29 have possible early-onset AD.

Setting.—Community-based in Antioquia, Colombia.

Patients.—A population-based sample in which all members of 5 extended families (nearly 3000 individuals) were surveyed. Criteria for inclusion required obtaining sufficient information to categorize the individual as affected.

Main Outcome Measures.—Age at onset, neuropsychological profile, neurologic history, and examination.

Results.—The patients had a mean age at onset of 46.8 years (range, 34-62 years). The average interval until death was 8 years. Headache was noted in affected individuals significantly more frequently than in those not affected. The most frequent presentation was memory loss followed by behavior and personality changes and progressive loss of language ability. In the final stages, gait disturbances, seizures, and myoclonus were frequent.

Conclusions.—Other than the early onset, this clinical phenotype is indistinguishable from sporadic AD except that affected individuals frequently complained of headache preceding and during the disease. Despite the uniform genetic basis for the disease, there was significant variability in the age at onset, suggesting an important role for environmental factors or genetic modifiers in determining the age at onset.

THE GENETIC basis for many cases of early-onset familial Alzheimer disease (AD) has now been established. Remarkably, mutations in at least 3 different genes lead to a disease similar both clinically and neuropathologically. The mutated genes are the amyloid precursor protein (APP) gene on chromosome 21,1 presenilin-1 (PS1) on chromosome 14, and presenilin-2 (PS2) on chromosome 1.2,3 Most of the described mutations occur at various loci within the PS1 gene.2,6,7 One aim in genetically defining the many mutated loci capable of causing AD is to understand how different mutations give rise to the disease phenotype. A detailed description of the phenotype is a prerequisite to tracing the mechanism by which specific mutations lead to the pathology and the clinical picture of the disease. In some cases, small differences in the specific mutated codon of a single gene can lead to significant phenotypic differences. For example, mutations within APP lie on either side of the sequence that corresponds to the excised β-amyloid (or Aβ) peptide, the major protein found in senile plaques. These mutations lead to a phenotype that is typical of AD, except for the early onset. However, a mutation within the Aβ sequence gives rise to a distinct phenotype—designated hereditary cerebral hemorrhage with amyloidosis—Dutch type.4 This single-base modification, which causes a glutamic acid-to-glutamine substitution in codon 693, shifts the most prominent site of amyloid deposition from the neuropil to the cerebral vasculature and shifts the clinical presentation from dementia to cerebral hemorrhage. Families with a mutation at the adjacent codon, 692, have a phenotype with features of both presenile dementia and cerebral hemorrhage attributable to cerebral amyloid angiopathy.5

In the case of the presenilins, patients with mutations at various loci develop a slowly progressive dementia that begins in the third to fifth decade. Several pedigrees with PS1 or PS2 mutations have been reported, and some of the reports have described distinctive clinical features. Haltia and colleagues6,7 described...
scribed a family with an M146V mutation in PS1 that has an unusually early onset, ranging from age 35 to 39 years. Although early myoclonus was noted, only 1 patient is described in detail, and the myoclonus was present at a late stage of the disease when that patient became bedridden. Lampe and colleagues described the “L family” in whom they noted early myoclonus, seizures, and progressive aphasia. Of the 16 reported cases, the mean ± SD age at onset was 41.6 ± 4.7 years, and the mean ± SD age at death was 47.2 ± 3.8 years. In only 6 patients was a mean ± SD age documented for the onset of myoclonus (44.7 ± 2.8 years); likewise the mean ± SD age for the onset of seizures (44.8 ± 2.9 years) was documented in 6 patients. From these ages, it seems that, relative to the rapid course of the disease in this pedigree, the onset of myoclonus and seizures occurred well after the onset of cognitive symptoms when the disease was advanced. Kennedy and colleagues also noted myoclonus in the affected members of the pedigree they reported, but no details are given regarding the onset of the myoclonus relative to the disease course. Among 50 individuals from the Volga German families who harbor a PS2 mutation, myoclonus was noted in 12%, and seizures were noted in 24%. Findings did not occur early in the disease course for any of those cases. Myoclonus and seizures were also a late but frequent occurrence in a large family aggregate from Normandy in whom the disease was linked to chromosome 14.

The first suggestion that an early-onset dementing disorder was present in a large kindred from the Colombian state of Antioquia was presented by Cornejo et al and was followed by the identification of several additional families from the same geographical region. Members of the 5 Colombian kindreds described in this article all have a point mutation in codon 280 that results in a glutamic acid-to-alanine substitution in PS1. A haplotype analysis demonstrates that the families are likely to have a common founder. The large size of these kindreds allows a detailed study of the range of disease phenotypes associated with this mutation.

METHODS

Ascertainment of the Pedigrees

Five pedigrees from Antioquia with an index case of early-onset AD were assembled from extensive community-based searches for affected families. The index cases for each family were selected from the Neurology Department, University Hospital San Vincente de Paul, Medellín, Antioquia. These cases were evaluated by neurologic and neuropsychological testing. The clinical diagnostic criteria used were the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; 6 cases had autopsy confirmation of their diagnosis and met the established criteria for AD. At least 1 case in each family was analyzed for the presence of a mutation in the PS1 gene. The diagnosis of probable AD required that the patient be examined by 1 of the participating neurologists. When it was not possible to evaluate an individual directly, the case was considered as probable AD if histories obtained from 2 family members both fulfilled the diagnostic criteria. The case was considered as possible AD if it was not possible to obtain more than 1 reliable history, and it was considered definite AD if there was postmortem confirmation.

Beginning with the index cases, we assembled a pedigree for each extended family. To construct the family tree and to determine the status of individual cases, several strategies were used: door-to-door search for all family members and examination of baptismal records, notary registries, and clinical records of the Mental Hospital of Antioquia and the University Hospital San Vincente de Paul. Consent for evaluation was obtained from all subjects according to a protocol approved by the human subjects committee of the University of Antioquia.

Clinical and Neuropsychological Analysis

In addition to routine neurologic examination, a random subset of 15 individuals mildly to moderately affected by AD and 34 normal controls underwent neuropsychological testing. Controls were relatives taken from the same families as the familial AD patients and were therefore at risk, but they matched the familial AD group in sociocultural conditions, including educational level. At the time of the examination, they were active, functionally normal, and with no significant complaints or memory impairments.

The neuropsychological test battery included Spanish-language versions of instruments used by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) and several additional tests adapted to the cultural and linguistic idiosyncrasies of the target population. The battery included the following sections: verbal fluency, naming, Mini-Mental State Examination (MMSE), memory of words, constructional praxis, recall of words, recognition of words, recall of line drawings, and trail-making tests. Some additional neuropsychological tests were also administered: the Raven Test, the Wechsler Memory Scale, the praxis ability test, the Boston Naming Test, Spanish version, the Boston Diagnostic Aphasia Examination, Spanish version, the Rey-Osterrieth Complex Figure with the scoring system proposed by Taylor, and Serial Verbal Learning. The Wechsler Memory Scale, Boston Diagnostic Aphasia Examination, Rey-Osterrieth Complex Figure, and Serial Verbal Learning tests have been previously normalized in Colombia in different age and educational groups.

Analysis of Postmortem Tissue

Autopsy material was available from 6 individuals in 2 pedigrees. The brain was fixed with formalin, and sections were taken from the frontal, parietal, temporal, and occipital cortices, and the hippocampus, caudate, thalamus, midbrain, pons, medulla, and cerebellum. Sections were stained with hematoxylin-eosin, a modified Bielschowsky method, and antibodies to the Aβ peptide, glial fibrillary acidic protein, and tau. The neuropathological diagnosis of AD was based on quantitative criteria suggested by CERAD and by Khachaturian. Some specific aspects of the neuropathology were presented as part of an immunocytochemical study.

RESULTS

Pedigrees and Sample Characteristics

Five extended families with early-onset AD were identified in Antioquia. The families live in towns located in a relatively small altiplano area within a radius centered at 6°33.04' N, 75°20.13' W at a mean altitude of 1700 m above sea level. These families trace their genealogies over 5 to 7 generations (Figure 1). A common origin of all 5 families is likely based on the presence of the same PS1 mutation (E280A) in all of the affected patients, the presence of a rare haplotype, the limited geographic distribution of the family members, and the sharing of 4 last names among a high proportion of the family members. The most common of these last names can be traced to 1783, when the name was registered for the first time in the town of Yarumal, Colombia (founded in 1780). The combined sample size among all of the pedigrees, including healthy and at-risk individuals, is approximately 3000 individuals. From this sample, a diagnosis of probable AD was made in 93

Downloaded from jama.ama-assn.org at Oregon Health & Science University on February 12, 2011
individuals, possible AD in 29 individuals, and definite AD (autopsy-confirmed) in 6 individuals. The sex distribution among the cases was 66 men (52%) and 62 women (48%). Nearly all of the patients live in a rural setting, except for a few who live in the city of Medellin, Colombia. The mean educational level attained was the second grade. The majority of the male patients were coffee farmers, and the majority of the female patients were housewives. The mean ± SD age at onset among 88 individuals for whom this information was available and considered reliable (41 women and 47 men) was 46.8±6.4 years (range, 34-62 years). There was no significant difference in the age at onset between men and women. Among the patients for whom there was an adequate history, 27% were smokers, 12% consumed alcohol excessively, and 7% had a history of head trauma that resulted in unconsciousness. At the time of the analysis, 69 of the 98 probable AD patients and 14 of the 29 possible AD patients had died. The mean ± SD age of death, based on 54 observations, was 54.8±7.3 years (range, 38-65 years), with no significant differences between men and women. When possible AD patients were excluded, the mean age at onset was 47.7 years (range, 34-62 years), and the mean age at death was 60 years (range, 40-65 years). The average interval between onset and death was 8 years (range, 3-18 years). All of the patients were taken care of in their homes throughout the duration of the disease, and none received nursing home care.

Clinical Symptoms and Neurologic Examination

The most common initial complaints were progressive memory loss and changes in personality and behavior. Every history included the complaint of memory disturbance. Language difficulties such as naming were also frequent in the early stage of the disease. Most of the patients did not have neurologic problems other than impairment of mental status until late in the disease course. Gait difficulty, seizures, and myoclonus were among the latest changes observed. A total of 73% of those affected complained of severe headache, often as a prodromal feature, up to several years before the onset of dementia. Only 2 (17%) of 12 nonaffected subjects from the largest families reported headache. Table 1 presents the frequency of neurologic findings among the sample of affected patients for whom complete neurologic information was available (118 patients).

Neuropsychological Evaluation

Patients with a diagnosis of possible AD and severely demented patients were excluded from the compiled mental status data. Two subjects in the control group (1 man, 1 woman), and 3 subjects in the affected group (1 man, 2 women) were completely illiterate, and the rest had a
Results in the Wechsler Memory Scale were particularly notable. Logical memory and associative learning (both verbal memory tests) were significantly impaired in the AD patients, whereas visual reproduction (nonverbal memory) scores were remarkably similar in both groups. The memory quotient, using Colombian norms, was more than 2 SDs lower in the familial AD group. In the praxis ability test, difficulties in performing movements under verbal command were impaired for both hands. Buccofacial movement scores, although decreased in the affected patients, were better preserved than hand movements. In the Boston Naming Test, scores in the familial AD group were roughly half of the scores observed in the controls; however, the control group performance was also low, as expected because of the limited education level of the population. Naming difficulties were observed in the confrontation naming subtest, but not in responsive naming and body-part naming. High-probability repetition (but not low-probability repetition), word reading (but not oral reading), and writing (mechanics but not primer-level writing) were relatively well preserved in the dementia patients. Those with dementia had extremely low scores in the Rey-Osterrieth Complex Figure—copy condition, a constructional ability, and the score for the Rey-Osterrieth Complex Figure recall condition, a test using nonverbal memory, was only 1 point of 36. The Serial Verbal Learning test was especially difficult for the patients with AD, and statistically significant differences were observed in delayed recall.

**Neuropathological Features**

In the 6 autopsies performed, the brain was atrophic. Three of the cases were genotyped and had the expected glutamic acid-to-alanine substitution at position 250 in the PS1 gene. Histologically, all the cases met the criteria for AD in terms of plaque and tangle density. A description of the pathologic characteristics in 1 case is representative. The brain weighed 700 g, and there was severe and extensive cortical atrophy and symmetrical central atrophy. Atrophy of the frontal and temporal lobes was most severe, with the gyriform thin projections into the subarachnoid space. The hippocampus was markedly shrunken bilaterally, and the striatum, particularly the head of the caudate, was atrophic. The substantia nigra was depigmented.

Histologically the case satisfied the criteria for AD. In the cerebral cortex the neuritic plaque density often exceeded 30/mm². By digital image quantitation of the inferior frontal gyrus, there was a total plaque density of 150/mm² on cross section; however, only a portion of these plaques had adjacent neurites or dense amyloid cores at the center. Of interest was the presence of neuritic plaques and dense core plaques in the cerebellum as well as abundant diffuse plaques often located within the depths of the tertiary cerebellar folia. Within the hippocampus...
and cerebral cortex, there were prominent neurofibrillary tangles and “ghost tangles.” The neurofibrillary tangles stained with tau antibodies and the diffuse and compact plaques stained with Aβ antibodies (Figure 2, top and bottom). The detailed characteristics of the Aβ staining with antibodies against various forms of the Aβ peptide have been reported. Other stigmata of AD such as granulovacuolar degeneration were observed in the hippocampus, but Hirano bodies were not observed. The entire cerebro cortex showed a prominent vacuolation of the neuropil in the superficial layers, accompanied by severe gliosis often seen in Creutzfeldt-Jakob disease (Figure 2, middle); however, the tissue tested negative with antibodies against prion protein. There was significant pallor within the central region of the centrum semiovale.

Clinical Cases

Case 1.—A 47-year-old man presented with the chief complaint of gradual progressive memory loss beginning 1½ years earlier. He had run a farm for many years, but had gone bankrupt 4 years earlier. From that time onward he worked irregularly. When he was seen in the clinic, his family reported that he often forgot their names. He had reduced verbal fluency, did not initiate conversation, and had difficulty following the thread of a conversation. Most recently he had lost interest in his work and in his family responsibilities. He began to wander and sometimes did not seem to recognize his own house. However, he remained competent to care for himself in his daily living activities. His MMSE score was 4. He could not recall any digits or recall a sentence. In categories, he named 8 animals in 1 minute, 2 fruits in 1 minute, and 1 body part in

Table 3.—Additional Neuropsychological Tests*

<table>
<thead>
<tr>
<th>Test</th>
<th>Controls (n=34)</th>
<th>AD Patients (n=15)</th>
<th>P†</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<td>Digits</td>
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<td>Forward</td>
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<td>Visual reproduction</td>
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<td>Right hand</td>
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<td>Word order</td>
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<tr>
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<tr>
<td>Delayed recall</td>
<td>7.4</td>
<td>1.7</td>
<td>1.5</td>
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*AD indicates Alzheimer disease. Data presented as scores.
†Two-tailed t tests.
families falls within the ages of 18-37 and live with the collected members of the An¬

Among the largest familial AD kindred in the literature, this family set is the number of patients who carried the E280A mutation, and autopsy confirmation, they were classified as familial AD. Familial AD have been documented in the Iberian peninsula, and the clinical phenotypic features described for other PS1 mutations, including early myoclonus and seizures, may reflect the effects of a mutation at sites other than position 280. In this regard, a clinical description of the family with the Glu280Gly mutation would be of particular interest because they have a mutation in the identical codon as the Antioquian families. Alternatively, as the sample size grows for families with other PS1 mutations, the clinical phenotype may appear increasingly similar to sporadic AD.

The postmortem findings were diagnostic of AD—senile plaques and neurofibrillary tangles were abundant. The cerebellum was also significantly affected with diffuse plaques as well as neuritic plaques and dense core plaques. Although cerebellar senile plaques are well recognized to occur in sporadic AD, their presence is variable, and only rarely are they associated with neuropsychological or do they form cores. The changes around plaques were positive with ubiquitin antibodies and negative with tau antibodies. Despite the significant cerebellar involvement, gait difficulty was a late occurrence.

Within this very large pedigree, a number of commonly assessed clinical features show phenotypic variability. For example, the age at onset ranged from 34 to 62 years. If the 2 patients at the extreme of each range were discarded as outliers, the onset would still span 21 years (ages 39 to 60 years). Although both of the outliers were categorized as probable AD because they lack autopsy confirmation, they both carry the E280A mutation and, therefore, provide strong evidence for a wide age range at disease onset. The age range of disease onsets reported with various mutations in PS1 is from 35 to 55 years, a range that falls within the ages observed in our pedigrees. The wide age range of disease onsets among patients that carry an identical mutation strongly suggests an effect of genetic or environmental modifiers. One genetic determinant believed to affect age at onset is the number of apolipoprotein E
(APOE) e4 alleles; however, the APOE e4 allele distribution in this population does not correlate with age at onset. 17 Besides APOE e4, other possible genetic disease modifiers include the CYP2D6 allele, 18 and polymorphisms in NACP or synuclein, 19 possibly a-antichymotrypsin, 20,21 and the intron 3' to exon 8 of PS1. 22 Environmental exposures, which may affect the incidence of AD, 23 are also a possible explanation for the wide range of age at onset; however, at this juncture, there are no obvious clues concerning the identity of such a factor. Clearly, these families provide an ideal clinical setting in which to search for genetic and environmental modifiers of disease expression.

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