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Clinical characterization of a presenilin 1 mutation (F177S) in a family with very early-onset Alzheimer's disease in the third decade of life

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Abstract

Background: Early-onset familial Alzheimer disease (AD) is an autosomal dominant disorder caused by mutations in the amyloid precursor protein, presenilin 1 (*PSEN1*), or presenilin 2 gene. The objective of this study was to characterize the phenotype in a large family with a *PSEN1* F177S mutation by performing detailed clinical assessments, neuroimaging, and neuropathological analysis.

Methods: In two subjects, clinical and neuropsychological assessments, structural magnetic resonance imaging, F-18-2-fluoro-2-deoxy-D-glucose positron emission tomographic imaging, AD biomarkers in cerebrospinal fluid and genetic analysis were available. In three deceased affected subjects, medical records were reviewed. In one subject, a complete neuropathological examination was available.

Results: Cognitive impairment and neurological symptoms developed homogeneously around 30 years of age and worsened rapidly. All subjects died about 7 years (range, 6–8 years) after disease onset before 40 years of age. All technical diagnostic information (neuroimaging, cerebrospinal fluid) were typically for AD. Neuropathology showed abundant neuritic plaques and neurofibrillary tangles, typical of severe AD. Antidementia treatment in one subject did not alter the length of survival.

Conclusions: The *PSEN1* F177S mutation leads to typical AD starting at age 30 and a homogeneous phenotype with rapid cognitive decline and prominent neurological symptoms. Excessive amyloid beta 42 production in the brain cortex corresponds well with other *PSEN1* mutations.

Keywords: *PSEN1*; Mutation; Early-onset Alzheimer's disease; Genetics; Neuropathology; Phenotype

1. Introduction

Alzheimer disease (AD) is the most common form of dementia, accounting for 63% to 73% of all cases in dementia [1]. Approximately 25% of cases of AD is familial (i.e., two or more family members have AD) [2], and here, a clinical distinction between early-onset familial Alzheimer's disease (EOFAD; age of onset, <60–65 years) and late-onset familial AD (age of onset, >60–65 years) is made. Approximately 1% to 6% of all cases of AD is early-onset AD, with an onset occurring during the 40s or early 50s, although onset in the 30s and early 60s has been reported. Three autosomal dominant genes were identified to cause EOFAD when mutated: the amyloid precursor protein gene (*APP*) on chromosome 21 [3], the presenilin 1 gene (*PSEN1*) on chromosome 14 [4] and the presenilin 2 gene (*PSEN2*) on chromosome 1 [5,6]. Currently, 197 mutations are identified in *PSEN1*, 25 in *PSEN2*, and 39 in *APP*. *PSEN1* mutations accounts for approximately 70% of EOFAD and cause autosomal

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dominant AD [7–9]. Penetrance of *PSEN1* mutations is complete by 60 to 65 years of age, meaning all mutation carriers develop early-onset AD [10]. *PSEN1* and *PSEN2* mutations alter the proteolytic site of γ-secretase. The mutant enzyme produces more amyloid beta peptide$_{42}$ ($A\beta_{42}$), which is more amyloidogenic and more prone to aggregate than $A\beta_{40}$, and results in a greater amount of neocortical senile plaques and a higher $A\beta_{42}/A\beta_{40}$ ratio than in "sporadic" AD [11]. To date, there are few detailed reports of the clinical phenotypes [12,13], especially across generations. Further examination of the genetic and pathological basis of this AD phenotype with modern clinical and biological assessments helps to identify the underlying disease mechanism, and is likely to improve our understanding and future treatment of AD. The purpose of this study was to characterize the clinical expression of a *PSEN1* mutation with a very early-onset form of AD (age of onset, 30 years). The associated *PSEN1* mutation has been mentioned once as being associated with AD [14]. In the family described here, subjects across six generations were affected.

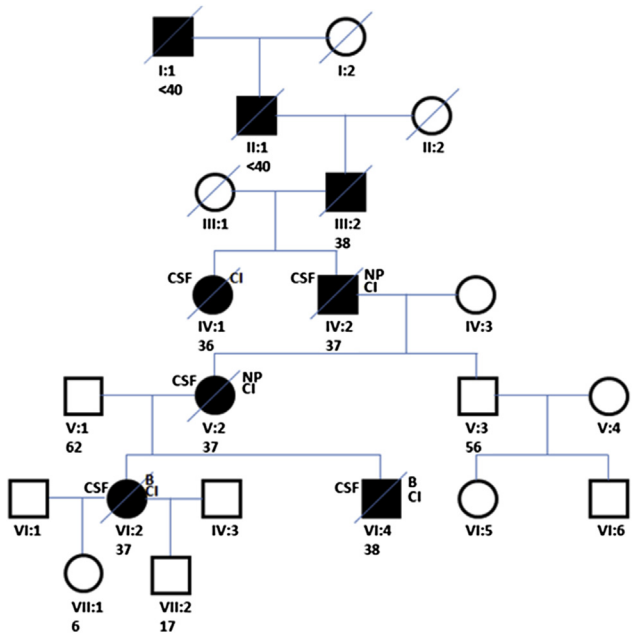

Fig. 1. Pedigree of the family. Circle, female; square, male; slash, deceased; filled shape, affected siblings. Numbers indicate the age of death or age at the time of writing. CSF, cerebrospinal fluid; CI, clinical information; NP, neuropathological examination; B, blood samples available for genotyping.

2. Methods

2.1. Patients

Eight subjects (five male and three female) from one family distributed across six generations diagnosed with probable EOFAD (two according National Institute of Neurological and Communicable Diseases and Stroke–Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria [15] in the fourth decade of life (Fig. 1).

2.2. Clinical assessments

Clinical data were acquired at the Departments of Psychiatry or Neurology at the Universities Frankfurt/Main or Heidelberg, respectively, and the Central Institute of Mental Health, Mannheim. All clinical information was obtained by personal interviews with the affected subjects, the relatives of deceased subjects, and/or detailed medical records.

The two youngest patients were examined by standardized neuropsychiatric assessments for a diagnosis of AD: the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery, the Mini-Mental State Examination (MMSE), and the activities of daily living and instrumental activities of daily living (IADLs) scales.

2.3. Neuroimaging

Structural neuroimaging was performed by structural cranial magnetic resonance imaging (MRI: subjects VI:4 and VI:2), cranial computer tomography (CT; subject V:2), cranial ventriculography and arteriography (subjects IV:2 and IV:1), or pneumoencephalography (subject VI:2). All structural ratings were performed by visual analysis by an experienced neuroradiologist. Cranial CT was assessed with a Volume Zoom CT (Siemens Somatom DR3, Erlangen, Germany). Cranial MRI was performed at 1.5 T (Siemens) using the standard head coil and a gradient Echo-planar imaging (EPI) sequence. Routine high-resolution T1- and T2-weighted sequences were recorded. Functional neuroimaging was done by F-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in subjects VI:4 and VI:2. Cerebral glucose metabolism at rest was assessed using a Siemens ECAT-47 PET tomograph. PET images (47 slices; slice thickness, 3.3 mm; scan duration, 30 minutes) were acquired 30 minutes after an intravenous injection of 252 MBq ^{18}F-desoxyglucose. At follow up, a PET scan in subject VI:4 was acquired with a Siemens ART ECAT PET tomograph (34 slices; slice thickness, 5 mm; scan duration, 30 min; acquired 30 minutes after intravenous injection of 169 MBq ^{18}F-desoxyglucose). In addition to visual analysis, the scans were analyzed quantitatively using the metabolic index [16].

2.4. Cerebrospinal fluid (CSF) analysis

Routine CSF cell count, protein, glucose, and protein electrophoresis assessments were performed by standard laboratory techniques. Classic enzyme-linked immunosorbent assays were performed to measure the concentration of $A\beta_{42}$, $A\beta_{40}$, total tau, and phosphorylated tau$_{181P}$ according to the manufacturer's protocols (done in subject VI:4 only).