Short Communication

Novel Mutation (Gly212Val) in the PS2 Gene Associated with Early-Onset Familial Alzheimer’s Disease


Dementia Care Unit, Virgen de la Arrixaca University Hospital, IMIB (Instituto Murciano de Investigación Biosanitaria), Murcia, Spain
Department of Neurology, Fundación Jiménez Díaz, Madrid, Spain
Murcia Brain Bank, Murcia, Spain
Department of Neuropathology and Brain Tissue Bank, Fundación CIEN, Carlos III Health Institute, Madrid, Spain

Handling Associate Editor: Teodorodel Ser

Accepted 1 April 2016

Abstract. Mutations in the presenilin 2 gene (PS2) are an extremely rare cause of early-onset autosomal dominant Alzheimer’s disease (AD), accounting for only 5% of these families. These cases represent a particular model of AD, and the scarcity of reports on their clinical phenotypes makes them of great interest. We report a family with early-onset autosomal dominant AD in four members, where the two living siblings were found to carry the novel PS2 mutation Gly212Val (exon 7, transmembrane domain IV) with highly predicted pathogenicity. Age at onset ranged from 60 to 65 years and three of the cases died between ages 74 and 76 years. Clinical phenotype was quite homogeneous among affected members of the family, and overall features, including cognitive decline, tau/p-tau and amyloid-β cerebrospinal fluid markers, neuroimaging, and neuropathology were consistent with typical AD. Lewy bodies were present but restricted to the amygdala.

Keywords: Early-onset dementia, familial Alzheimer’s disease, neurogenetics, presenilin 2 mutation

INTRODUCTION

Early-onset autosomal dominant Alzheimer’s disease (EOAD) is a rare condition, representing around 0.5% of all Alzheimer’s disease cases. EOAD is known to be associated with mutations in the presenilin 1 (PS1), presenilin 2 (PS2), and amyloid precursor protein (APP) genes [1]. Alterations in these three genes underlie a pathogenic mechanism of enhanced production/deposition of amyloid-β (Aβ) in the cortex. In particular, PS1 and PS2 proteins are core parts of the γ-secretase complex, which is responsible for the intracellular cleavage of APP and the release of Aβ peptides [2, 3].

Families with mutations in these genes represent a unique model of the disease and are of great interest...
for study from different perspectives. The straightforward relationship between the genetic alteration and disease development allows for better understanding of the pathophysiological mechanisms leading to the disease. Comparison of clinical manifestations among affected family members can aid in comprehending the influence of genetic and epigenetic factors in modifying the clinical phenotypes. Presymptomatic diagnosis would allow for the study of AD in preclinical/prodromal stages, would make it possible to begin treatment in these early stages and would also facilitate genetic counseling for carriers of mutations.

PS2 mutations are the least common cause of EOAD, accounting for only 5% of the cases, which translates to under 200 affected subjects reported worldwide [4]. There are fewer than 20 PS2 pathogenic or possibly pathogenic mutations reported in genetic databases (AD&FTD Mutation database: http://www.molgen.vib-ua.be) [5]. Seventy-five percent of the reported cases harbor two more common variants, N141I and M239V, while the other mutations are represented in only one family. Partial clinical information is available for about half of these PS2 mutation carriers, though CSF markers and neuropathological description have been reported for only three mutations [4].

We present an EOAD family with extensive clinical information on two siblings who were found to harbor a novel pathogenic mutation in PS2, a glycine to valine substitution in codon 212 (G212V).

MATERIALS AND METHODS

Family report

This family was studied as part of a Spanish cohort of patients with dementia followed at the Dementia Care Unit of Hospital Virgen de Arrixaca (Murcia). The family tree appears in Fig. 1 and includes four affected members: three siblings and their maternal uncle. The mother was assumed to be the carrier of the

Fig. 1. Family tree and neuroimaging studies of proband 1 (CT scan and SPECT) and proband 2 (MRI and SPECT). AO, age at onset; AD, age at death.
Table 1

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Probands 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General data:</strong></td>
<td></td>
</tr>
<tr>
<td>Age at onset: symptoms</td>
<td>65 y: memory deficits</td>
</tr>
<tr>
<td>First assessment: age, MMSE</td>
<td>70 y, MMSE 14/30</td>
</tr>
<tr>
<td>Functional scales (first study)</td>
<td>IDDD 49/99, Blessed 8.5, CDR 2, GDS 5</td>
</tr>
<tr>
<td>Time of follow-up</td>
<td>70 to 76 y</td>
</tr>
<tr>
<td><strong>Cognitive profile:</strong></td>
<td></td>
</tr>
<tr>
<td>At 70 y (5 y evolution)</td>
<td>Direct 4, Inverse 3</td>
</tr>
<tr>
<td>At 65 y (2 y evolution)</td>
<td>Learning trials 2/1/3</td>
</tr>
<tr>
<td>Free recall 0/10; recognition 11/20</td>
<td></td>
</tr>
<tr>
<td><strong>Complementary studies:</strong></td>
<td></td>
</tr>
<tr>
<td>ApoE genotype</td>
<td>3/3</td>
</tr>
<tr>
<td>Neuroimaging (CT/MRI)</td>
<td>Bilateral medial temporal atrophy</td>
</tr>
<tr>
<td>HMPAO-SPECT</td>
<td>Bilateral temp-parietal hypoperfusion</td>
</tr>
<tr>
<td>CSF markers</td>
<td>---</td>
</tr>
<tr>
<td>Neuropathology</td>
<td>High probability AD (Reagan)</td>
</tr>
</tbody>
</table>

CDR, Clinical Dementia Rating scale; GDS, Global Deterioration Scale; IDDD, Interview for Deterioration in Daily living activities in Dementia; MMSE, Mini-Mental State Examination.

**PS2** mutation, although she was cognitively asymptomatic when she died at the age of 54 years from leukemia-related causes. Retrospective information was obtained on the uncle (P4) and elder sister (P3), while another two siblings (P1 and P2) were clinically studied and followed-up, one until her death and subsequent brain donation.

**Clinical studies**

P1 and P2 underwent cognitive assessments with extensive neuropsychological batteries, structural neuroimaging (brain CT or MRI studies), and HMPAO single photon emission tomography (SPECT) imaging. AD biomarkers were analyzed in the CSF of P2 using commercially available sandwich enzyme-linked immunosorbent assay (ELISA). Brain necropsy of P1 was performed after informed consent, and a neuropathological study was carried out by the Brain Bank of Carlos III Health Institute (Madrid).

**Genetic analyses**

The family history of P1 prompted a genetic analysis including the **PS1**, **PS2**, **APP**, **APOE**, **PGRN**, and **TAU** genes. After informed consent, a DNA sample of P1 was amplified by PCR for genetic analysis of the whole coding regions of the genes, with the exception of **APP** in which only exons 16 and 17 were examined.

**RESULTS**

A summary of the clinical information for the two probands is presented in Table 1.

**Proband 1 (P1)**

This man was first evaluated at 70 years of age, after 5 years of slow, progressive memory decline. His cognitive assessment showed deficits in temporal orientation, attention, executive and memory tasks, and mild anemia and visuomotoric apraxia, altogether consistent with probable AD according to NIA criteria [6]. Neuroimaging revealed medial temporal atrophy in CT scan and bilateral temporoparietal hypoperfusion in SPECT (Fig. 1).

He was treated with donepezil and he had transient improvement during one year. Then he deteriorated progressively, with increasing functional depen-
J. Marín-Muñoz et al. / Novel PS2 Mutation

Fig. 2. Autopsy Proband 1. 1) Macroscopic image of hippocampal atrophy; 2) amyloid-beta immunohistochemistry (×100): high density of amyloid plaques in frontal cortex; 3) tau immunohistochemistry (×100): high density of neurofibrillary tangles in hippocampus; 4) alpha-synuclein immunohistochemistry (×200) Lewy bodies and Lewy neurites restricted to the amygdala.

dence. He did not develop parkinsonism, significant behavioral or psychiatric problems, seizures, or myoclonus. He died at 76 years of age in a status of complete dependence. His brain study was consistent with high probability of AD according to consensus criteria [7], associated with mild amyloid angiopathy. Lewy bodies were found only in the amygdala (Fig. 2).

Proband 2 (P2)

The sister of P1 was examined for the first time at 64 years of age. She had begun to have memory complaints one year earlier, though she had exhibited anxiety and depressive symptoms since age 61 years. A cognitive examination revealed a Mini-Mental State Examination (MMSE) score of 18/30 and deficits consistent with dysfunction of the frontal, medial temporal, and parietal lobes. MRI showed prominent parietal-lobe atrophy with milder temporal-lobe involvement. Brain SPECT showed bilateral (left predominant) temporoparietal hypoperfusion (Fig. 1). A CSF biomarker study supported high probability of AD [6]: decreased Aβ (539 pg/mL, cut-off point for normal >700) and increased tau (987 pg/mL, normal <400), and p-tau (115 pg/mL, normal <60).

The patient is currently 67 years of age. Her MMSE score is 10/30, mainly due to deterioration in temporal-spatial orientation, and she is more dependent for activities of daily living (IDDD 48/99, Blessed 6/28). She has not developed any motor or behavioral problems, delusions, seizures, or myoclonus. She continues to have some degree of anxiety, but depressive symptoms are decreasing as anosognosia increases.

Probands 3 (P3) and 4 (P4)

According to information provided by relatives, an elder sister (P3) had died at 74 years of age after approximately 15 years of dementia syndrome. Memory problems were reported to be the most relevant symptoms. The same timeframe was reported for the maternal uncle, whose first symptoms appeared around 60 years of age and who died at 75 years.

Genetic results

The study of P1 revealed a glycine to valine substitution (G212V) in codon 212 (exon 7) of PS2,
representing a novel change—not reported in genome databases—predicted to be pathogenic by Polymorphism Phenotyping v2 (PolyPhen 2), obtaining the highest score (Hum Div score of 1.0, sensitivity 0.0, specificity 1.0). Five years later, an analysis of P2 revealed the same G212V mutation, consistent with segregation. According to the algorithm of Guerreiro et al. for grading pathogenicity of AD mutations [8], this change can be considered definitely pathogenic for the following reasons: a) segregation in two affected siblings, b) it alters a conserved residue between PS1 and PS2 located in transmembrane domain IV (TM IV), and c) a pathogenic mutation has been described in the PS1 homologue site [9].

**DISCUSSION**

We describe a family with early-onset AD associated with the novel PS2 mutation Gly212Val, in which two affected siblings have undergone a complete study, including CSF biomarkers in one and neuropathology in the other, deceased case. This family represents a homogeneous model of AD where the clinical phenotype of the affected members was quite similar and overall features, including cognitive decline, tau/p-tau and Aβ CSF markers, neuroimaging, and neuropathology, were consistent with typical AD.

Age at death was almost the same in the three deceased cases (75 years). Age at onset (60 to 65 years) was also quite homogeneous, considering that preliminary symptoms such as anxiety/depression may have been noticed with differing accuracy. Though most cases with PS1 mutations have presenile onset, some cases with PS2 mutations develop the disease at a relatively later age. Particularly, reports of exon-7 PS2 mutations describe an age of onset between 45 and 85 years, thus conflating early- and late-onset AD [10–12]. The typical AD profile of this family, which includes initial mood symptoms, resembles what has been described in a majority of cases with PS2 mutations, although there have also been isolated mutations associated with clinical phenotypes of Lewy body dementia [13] or frontotemporal dementia [11].

According to current criteria [8], definite pathogenicity of the novel G212V mutation is supported by G212 being a conserved residue across species, a previous report of a pathogenic mutation in the homologue PS1 site [9], and segregation in two affected siblings. Location in a transmembrane domain coupled with a high pathogenic score revealed by prediction programs further supports pathogenicity. This family report can therefore help to interpret future cases in which the G212V change is found. Previous exon-7 PS2 mutations have only been described in TM V, though recently the change V214L was reported to be probably pathogenic in a Korean woman with dementia of the Alzheimer type starting at 69 years of age [14]. Structural prediction of the mutant PS2 V214L revealed important structural changes affecting adjacent aminoacids.

Considering their rarity, it is of interest that this is the third PS2 mutation found after genetic study of AD-related genes of 79 cases within our dementia cohort (Hospital Virgen Arrixaca, Murcia, Spain), which was selected based on early-onset age and/or strong family history. The other two cases (unpublished data) include the S130L—classified as unclear pathogenic nature in databases [5]— and the undescribed T380M mutation, which we can only consider as possibly pathogenic (one case affected, conserved residue, not present in controls). Furthermore, G212V is already the fifth different PS2 mutation reported in Spanish families [8, 15–17]. Currently, half of the reported PS2-related EOAD cases are present in Italian or Spanish families [4], therefore distributed throughout the Mediterranean area.

**ACKNOWLEDGMENTS**

Dr. Gómez-Tortosa’s research activity is supported by grant FIS 14/00099 and FEDER funds.

Thank you to Oliver Shaw for editing the manuscript.

Authors’ disclosures available online (http://j-alz.com/manuscript-disclosures/16-0050r2).

**REFERENCES**


