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Novel *PSEN1* Mutation in a Bulgarian Patient With Very Early-Onset Alzheimer's Disease, Spastic Paraparesis, and Extrapyramidal Signs

Latchezar Dintchov Traykov, MD, PhD, DSc,
Shima Mehrabian, MD, PhD, Marleen Van den Broeck, MSc,
Margarita Radoslavova Raycheva, PhD, Marc Cruts, PhD,
Albena Kirilova Jordanova, PhD, and
Christine Van Broeckhoven, PhD, DSc

We describe the phenotype of a Bulgarian early-onset Alzheimer's disease (EOAD) family with 3 affected patients in 3 generations. In the proband, a novel L381V mutation in the presenilin1 (*PSEN1*) gene was identified. In this patient, the first symptoms were noticed at the age of 32 years and she died at the age of 37 years. The EOAD phenotype caused by the novel L381V mutation in the *PSEN1* gene presented clinically, by a very early onset in the proband, rapid progression of dementia, spastic paraparesis, and extrapyramidal signs, as atypical clinical signs in Alzheimer's disease patients.

Keywords: early onset Alzheimer's disease; presenilin 1; spastic paraparesis; parkinsonism

Introduction

In the familial cases of early-onset Alzheimer's disease (EOAD), the disease is found to be associated with mutations in 3 genes encoding for the amyloid-β precursor protein (APP),[1] Presenilin1 (PSEN1),[2] and Presenilin2 (PSEN2).[3] Very EOAD is defined as Alzheimer's disease (AD) beginning before the age of 35 years; it is exceedingly rare, and *PSEN1* mutations have been implicated.[4]

We report a family with EOAD caused by a novel *PSEN1* mutation (L381V), where detailed clinical, neuropsychological, and neuroimaging examinations were performed.

From the Departments of Neurology (LDT, SM, MRR), Chemistry and Biochemistry (AKJ), and Molecular Medicine Center (AKJ), Medical University, Sofia, Bulgaria; Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, Antwerpen, Belgium (VdB, MC, AKJ, CVB); and Laboratory of Neurogenetics, Institute Born-Bunge and University of Antwerp, Antwerpen, Belgium (VdB, MC, AKJ, CVB).

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Address correspondence to: Latchezar Traykov, Department of Neurology, University Hospital Alexandrovska, 1, Georgi Sofiiski str, 1431 Sofia, Bulgaria; e-mail: traykov_l@yahoo.fr.

Case Report

The proband is a female, right-handed typist of Caucasian origin. The first symptoms of cognitive decline were noticed at the age of 32 years and she was discharged. At the age of 36 years, neurological examination revealed an apathetic, hypomimic woman. She had spastic paraparesis (SP) in the lower limbs with rigidly increased muscle tone bilateral positive symptom of Negro in the upper limbs, increased tendon reflexes, bilaterally pathologic Babinski signs, and Marinesco-Radovici in the right. The neuropsychological assessment revealed mild dementia (Mini-Mental State Examination [MMSE] = 20). She had moderate-to-severe impairment in episodic memory, moderately impaired visiospatial and constructive abilities, and moderate-to-severe agraphia, and acalculia. Naming and comprehension were not disturbed. Brain computed tomography/magnetic resonance imaging (CT/MRI) revealed severe cortical atrophy with white matter changes.

After 1 year, follow-up neurological examination revealed worsening of spasticity and rigidity in the limbs. Neuropsychological assessment documented

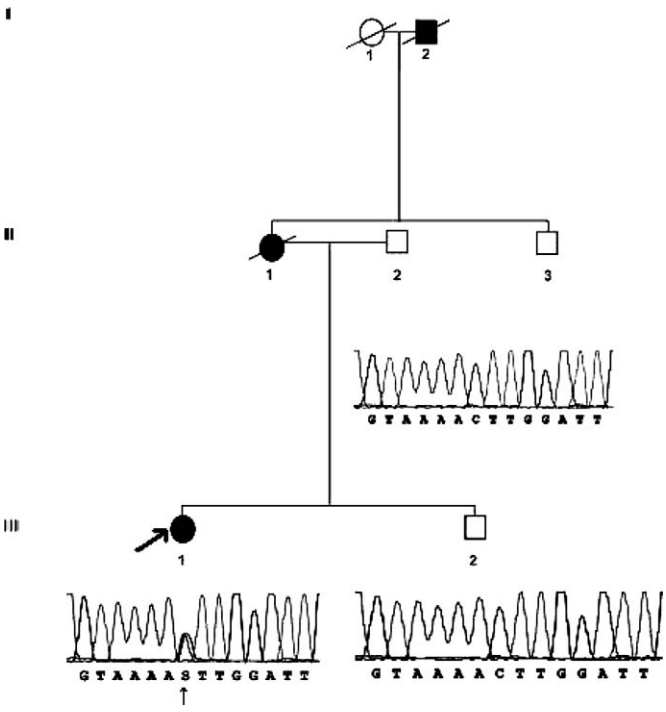

Figure 1. Pedigree of the Bulgarian family with L381V mutation in the *PSEN1* gene. Filled symbols illustrate affected individuals and stricken out symbols indicate deceased individuals. The nucleotide change is indicated by an arrow.

significant cognitive decline (MMSE = 14). Six months later, the neuropsychological assessment showed severe dementia (MMSE = 9). She died at the age of 37 years.

Family History

The family tree is shown in Figure 1. In 1988, her mother aged 45 was hospitalized with a 5-year history of memory impairment and decline in her daily living activities. Neurological examination revealed mild pyramidal and extrapyramidal signs. Computed tomography showed moderate generalized atrophy and enlargement of ventricles. Electroencephalogram (EEG) revealed diffuse unspecific changes. Neuropsyhological assessment documented moderate dementia with severe impairment in episodic memory, acalculia, dysgraphia, and construction apraxia. A diagnosis of probable AD was made. Two years later, follow-up examinations revealed rapid progression of dementia, worsening of pyramidal and extrapyramidal signs. The patient died at the age of 48 years. The grandfather was reported to have evidence of memory and psychotic manifestations with onset at the age of 65 years and died at the age of 69 years. No brain tissue from any of the diseased family members was available for pathologic study.

The proband's sibling (III-2), a 31-year-old man, has no memory problems. He was normal at clinical and neuropsychological investigations.

Molecular Genetic Investigations

In the proband, a single nucleotide g.69055C->G transversion, leading to a novel L381V mutation in exon 11 of the *PSEN1* gene, was identified. The mutation was not present in the healthy father and brother of the patient. Sequencing analysis of 200 randomly selected and ethnically matched, non-AD Bulgarian control individuals ruled out a rare polymorphism.

Discussions

Here, we have reported a Bulgarian family with very early-onset AD, associated with SP and extrapyramidal signs and caused by a novel L381V mutation in the *PSEN1* gene.

Monogenic diseases typically exhibit variations in biological features, such as age of onset, severity, and multiple clinical and cellular phenotypes. These variations can be due to specific alleles of the disease-causing gene, environmental effects, or modifier genes. Most of the *PSEN1* defects are missense mutations predominantly located in the highly conserved transmembrane domains. L381V mutation lies in the VIIth transmembrane domain of the PSEN1 protein, where about 6% of mutations are identified. *PSEN1* mutations, compared to the defects in the other AD-associated genes, are usually the most malignant. They have a mean age of onset in the early 40s and complete penetrance.[5] The youngest documented patients have the onset of AD recorded in their early 20s. All reported cases of very early onset AD with conclusive genetic analysis seem to be associated with *PSEN1* mutations.[4] In the reported family, the L381V mutation caused AD at the age of 32 years in the proband (very early age at onset), 40 years in the parent, and 65 years in the grandfather, respectively. This is a phenomena known as genetic anticipation characterized by a reduction in the age at disease onset and also by an increase in both the severity and proportion of affected individuals in successive generations. *PSEN1* mutations are typically associated with a

narrow, mutation-specific onset age range.[6] Although wider onset age ranges have occasionally been reported,[7] genetic anticipation has to our knowledge never been described in familial AD. The apolipoprotein E (APOE) genotype cannot explain the very early onset age in the proband, since she was homozygous for the protective ε3 allele.[8] No genetic information was obtained from the mother or maternal grandfather. Although diagnostic bias might explain the observed genetic anticipation to some extent, possibly other modifying factors might also be involved.

A striking variation in clinical presentation occurs in some AD pedigrees in which some individuals have SP, either preceding, concurrent with, or instead of dementia, and with brain pathology characterized by Aβ-positive cotton-wool plaques. Spastic paraparesis is present in the very earliest reports of patients with AD. The first such report was by Barrett[9] who described a patient with AD in her 30s with unusual neurological disturbances that included SP. Later on, Van Bogaert et al[10] reported a Belgian pedigree with familial AD and SP. In 1997, the first definitive association of SP with *PSEN1* mutations was reported, thereby defining a potential genetic etiology to this neurological variant of familial AD.[11]

This study provides further evidence of clinical heterogeneity in phenotype associated with *PSEN* mutations. The combination of SP and parkinsonism with dementia as the clinical feature of familial AD caused by *PSEN* mutation has not been reported previously. There are 21 reports of clinical pictures of AD/SP and 4 AD/extrapyramidal signs (http://www.molgen.ua.ac.be/ADMutations/). Lewy bodies (LB) and neurites containing aggregates of insoluble α-synuclein are found in the amygdale in about 20% of patients with *PSEN* or *APP* mutations.[12] It is not clear whether they contribute to the clinical picture, because they are usually restricted to the amygdala. Patients with *PSEN* or *APP* mutations sometimes show clinical features of prominent parkinsonism or visual hallucinations, which can be associated with more widespread LB formation.[13,14]

In conclusion, we describe a novel *PSEN1* mutation (L381V) resulting in familial EOAD with affected members in 3 generations. The phenotype is clinically characterized by very early onset (32 years of age in the proband) and rapid progression of dementia proceeded by spastic paraparesis and extrapyramidal signs, as atypical clinical signs in patients with AD.

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