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Genotype-phenotype Analysis in Early-onset Alzheimer's Disease due to Presenilin-1 Mutations at Codon 139

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Abstract: Mutations in the presenilin-1 (PS-1) gene are the main cause of autosomal-dominant early onset Alzheimer's disease (EOAD) and show a high penetrance of symptoms. There are more than 100 mutations in the PS-1 gene. Among them are at present four different missense mutations known at position 139 on exon 5. Lack of genotyping in other family members may lead to the suggestion of sporadic cases.

We present the case of a 46-year old German female with EOAD. Cognitive decline started at the age of 32, while myoclonic and tonic-clonic jerks occurred later. Disease symptoms were present in three generations of her family. Genetic analysis revealed the M139V mutation on exon 5 of the PS-1 gene.

We compared the clinical data of this family with seven previously reported families and two sporadic cases with mutations at the codon 139. The genotype-phenotype analysis showed marked intrafamilial homogeneity, but interfamilial heterogeneity in relation to the onset, duration, and progression of the disease. Onset and duration were not correlated to the amino acid exchanged. Another modifying genetic or environmental factor is probable.

Key words: presenilin-1, autosomal-dominant early-onset Alzheimer's disease, myoclonia

Introduction

Mutations in three genes have been identified as a cause of familial early-onset Alzheimer's disease (EOAD) fulfilling criteria for an autosomal-dominant inheritance: in the PS-1 gene on chromosome 14q24.3 encoding presenilin 1, in the PS-2 gene on chromosome 1q42.1 encoding presenilin 2 and in the APP gene on chromosome 21 encoding the amyloid precursor protein [1].

In a French population the prevalence was reported to be 41.2 / 100 000 for EOAD (< 60 years) and 5.3 / 100 000 for autosomal-dominant EOAD (AD-EOAD) [2, 3]. In this study, mutations in the PS-1 accounted for 56%, in a dutch population–based study for 18% of AD-EOAD families [4]. PS-1 mutations were found in 20% of AD-EOAD in japanese families [5].

More than 100 mutations in the PS-1 have been described. Except one in-frame deletion all other were missense mutations. A high penetrance was seen in most pedigrees. The onset occurs mainly before the sixth decade. One major cluster lies in exon 8, affecting the cleavage site of presenilin 1, a second cluster is situated in exon 5. Up to now four different mutations at the codon 139 in exon 5 of the PS-1 have been reported in at least eight families and two sporadic cases. This mutations leads to an amino acid exchange of methionine to isoleucine, leucin, threonin, and valine [1-4, 6-14].

We report here the clinical course of a female German patient with AD-EOAD caused by the M139V mutation in PS-1 and discuss the genotype-phenotype correlation of the different mutations of codon 139.

Case Report

The patient was admitted to a neurological clinic for the first time at the age of 38 years. Neurological examination of her revealed severe cognitive deficits, diminished competence to judge and responsibility at work and declining ability of daily activities since the age of 32. The patient reached 18/30 points on the MMST (Mini Mental-Status Test). The Hamburg-Wechsler-Intelligence Test for Adults (HAWIE) showed a total IQ of 53. Physical examination and laboratory tests was normal (including Vitamin B12, TSH, TPHA). Her orientation in person and time were fairly accurate, in place and situation inadequate. Her drive was normal, her mood was even. She presented motor aphasia with paraphrasia and agrammatical sentence construction. There was no previous history of chronic or severe illness. The patient had completed secondary school and a training as a skilled worker in electronics, later she was an employee of the municipal administration. She married at the age of 29, and gave birth to one son.

Course of the Disease

At the age of 41 years the patient presented with myoclonic jerks and extrapyramidal signs (choreatic arm movements, upper limb rigidity, hypomimia, parkinsonian gait). Generalized tonic-clonic seizures were observed for the first time. The patient was agitated, not orientated, and had severe motor aphasia. Permanent support in most activities of daily living required admission to an intitutional care.

One year after the first admission she was wheelchair bound, incontinent, and showed no adequate reaction to verbal demand. A few months later she was bedridden und showed no visual contact.

At the age of 45 years she was admitted for the first time to our institution with exacerbation of tonic clonic seizures and in an apallic state. She was tetraspastic and had flexion contractures. Myoclonic jerks in face and extremities occurred spontanously and could be induced by physical contact as well.

EEG

Electroencephalogram (EEG) at the age of 38 and 41 years showed a slow alpha rhythm (8.5/s) with paroxysmal activation of irregular frontotemporal theta wave activity. EEG at the age of 45 years showed delta-theta wave activity and once paroxysmal (partly 1/sec) triphasic potentials with no correlation to acustic and sensoric stimuli.

Cerebrospinal Fluid

At the age of 45 years CSF revealed normal cell count and protein content. There were no oligoclonal bands. NSE and protein 14-3-3 were within the normal range. Protein S 100 was elevated 3.03 μg/l (normal range <0.12)

Cerebral Imaging

MRI at the age of 38 years showed slight bilateral temporoparietooccipital cortical atrophy and seven years later severe enlarged ventricular system and severe temporal accentuated cortical atrophy.

Family History

The patient's paternal grandfather died at the age of 46 years (in 1936) and her father at the age of 40 years after a clinical course of approximately 5 years on the sequelae of a pneumonia. Histopathological examination revealed abundant senile plaques and Alzheimer fibrils in the cortex of both cases. The macroscopic brain examination of the father's brain showed symmetrical frontoparietal accentuated cortical atrophy and internal hydrocephalus.

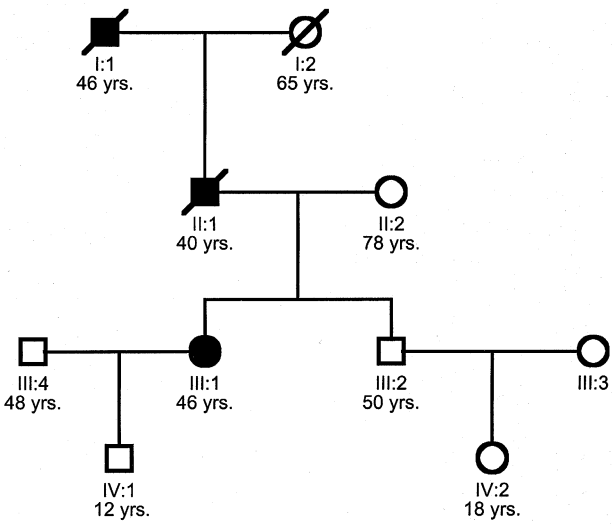

Fig. 1. Pedigree of the family over four generations. Numbers indicate the age (filled symbols - symptomatic family members, crossed out - deceased, circle - female, square - male).

The 78-year old mother of the patient, her 12-year old son, the 50-year old brother and his 16 year old daughter are asymptomatic and mutational analysis was not performed (Fig. 1).

Results

Mutational analysis in our patient was done on genomic DNA from peripheral blood leucocytes by direct sequencing of both strands of PCR-amplified coding exons of PS-1 gene as previously reported [9]. Informed consent for the mutational analysis was obtained by the patient's carer.

A heterozygote missense mutation resulting in a replacement of methionine at position 139 on exon 5 with valine (M139V) in the PS-1 gene was detected in this patient.

The comparison of our familial case and previously reported cases are summarised in Table 1 according to the type of amino acid and nucleotide change respectively, age of onset, ethnic origin, age at death, duration of illness, and the occurrence of myoclonic and generalized tonic-clonic seizures. SPECT examination in two patients showed bilateral temporal/ temporoparietal hypoperfusion [11, 13].

Discussion

Mutations at codon 139 in exon 5 are missense mutations leading to a substitution of methionine to isoleucine, leucine, threonine, or valine. They belong to a cluster of mutations (codon 135, 139, 143, 146) affecting the transmembrane region 2, where these amino acid residues are used to form an a-helical array. A toxic gain of function of this mutations is proposed [1, 6]. The actual effect of this mutations on the PS-1 gene has not been elucidated yet. The detection of heterozygote mutations at codon 139 in at least eight independent families and two sporadic cases with EOAD and different ethnic origin supports their pathogenicity. Furthermore, these mutations were not found in a substantial number of controls indicating that they are not polymorphisms [3, 8, 9]. Lack of genotyping in other family members may have led to the suggestion of sporadic cases.

Mutations at codon 139 are only reported in EOAD patients of caucasian origin. The age of symptom onset ranges between 32 and 50 years (mean: 41.6 years). Death, which was mainly caused by the sequelae of the disease occurred in the course of the fifth decade (mean: 47.4; range: 42-52 years), including the afflicted cases of our family. There seem to be substantial interfamilial, but not intrafamilial differences in onset and duration of the disease. The differences in the onset could probably not be accounted for by the different amino acid exchange or the APOE status. This suggests the involvement of other, still unknown, genetic or environmental factors that modulate the clinical expression of the disease. The duration of the illness of the deceased patients ranged from 4 to 12 years (mean: 5.9 yrs). However, a substantial longer

Table 1. Comparison of our familial case and previously reported cases.

	Campion et al. 1995	Boteva et al. 1996	ADCG 1995 Hardy et al. 1997 Fox et al. 1997	Dumanchin et al. 1998	Sandbrink et al. 1996 Hüll et al. 1998	Finckh et al. 2000 Present patient	Queralt et al. 2001	Larner et al. 2003
Mutation	M139T	M139V M139I	M139V	M139L	M139V	M139V	M139T	M139V
Familial/sporadic	1 FAD	2 FAD	2 FAD 2 families	1 spo	1 FAD	1 FAD	1 FAD	1 spo
Number of affected individuals	2	n.r.	16 (7 in 2 generations and 9 in 4 generations)	1 sporadic	7 (3 generations)	3 (3 generations)	2 (1 generation)	1
Age of onset (range)	48-50	n.r.	n = 7 44.3 (42-48) n=9 37.7 (36-40)	37	43.3 (42-45)	midthirties 32 (index)	47 48	46
Ethnic origin	Caucasian french	n.r.	Caucasian british	Caucasian french	Caucasian german	Caucasian german	Caucasian spain	n.r.
Age of death	n.r.	n.r.	n = 4 49.7 (49-52) n = 7 44.2 (42-49)	n.r.	n=4 50.3 (48-52)	41 46	-	50 (myocardial infarction
Duration of observation	n.r.	n.r.	6-10 yrs	n.r.	8 yrs index	Index 14 yrs	12/18 yrs	4 yrs
Generalized seizures	n.r.	n.r.	n = 7 43 (41-47)	n.r.	index after 1 year	index patient after 8 yrs	no	no
myoclonus	n.r.	n.r.	n = 10	n.r.	index after 1 yr	index patient after 8 yrs	no	no
APOE	ε3/ε3	n.r.	4 x ε3/e4 4 x ε4/e4 1 x ε2/e3	ε3/ε3	-	-	ε3/ε3	-

Hardy et al. (1997) reported about a further M139I and M139T mutation. whether sporadic or familial was not reported.

course of the illness as in our index patient is possible (>12 years, Table 1) [1-4, 6-14].

Myoclonic jerks are a prominent feature in EOAD due to PS-1 mutations. They were observed in a substantial number of patients with mutations at codon 139, mainly in the later course of the disease. Generalized tonic-clonic seizures were also common in severely affected patients. In our index patient, generalized tonic-clonic seizures and myocloni appeared after eight years.

The identification of further genetic and nongenetic factors in addition to a defined PS-1 mutation remains a challenge in AD-EOAD families.

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