Eur Arch Psychiatry Clin Neurosci (1998) 248 : 123–129 © Springer-Verlag 1998

ORIGINAL PAPER

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Early-onset Alzheimer's disease due to mutations of the presenilin-1 gene on chromosome 14: a 7-year follow-up of a patient with a mutation at codon 139

Received: 20 August 1997 / Accepted: 3 March 1998

Abstract Mutations in the presenilin-1 gene (PS-1 gene) on chromosome 14 have recently been identified as a cause of familial early-onset Alzheimer's disease (EOAD). To our knowledge, only two German EOAD patients with mutations in the PS-1 gene have been identified thus far. Herein we report the case of a German EOAD patient with a family history of dementia and a missense mutation at codon 139 (M139V) of the PS-1 gene. The patient came to our clinic for the first time when he was 44 years old. During the following 7 years, his Mini-Mental State Examination (MMSE) score dropped from 24 to 0. Myocloni were an early neurological symptom that was already present during the first consultation. We could demonstrate that myoclonic activity was of cortical origin using a back-averaging method. Magnetic resonance imaging (MRI) revealed only slight changes in the early stage of the disease. Follow-up MRI studies showed progression of bitemporal ventricular enlargement and progressive frontal and temporal cortical atrophy. Although the majority of EOAD patients belong to the sporadic (non-genetic) type of AD, early-onset dementia, early myocloni and a familial history of AD should direct attention to the possibility of a genetic form of AD.

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Key words Early-onset Alzheimer's disease · Presenilin-1 · Chromosome-14 · Myocloni

Introduction

Less than 7% of all Alzheimer's disease (AD) patients have affected first-degree relatives and fulfil formal criteria for an autosomal dominant inheritance (Duara et al. 1993). Mutations in three different genes [amyloid precursor protein (APP) on chromosome-21, presenilin-1 (PS-1) on chromosome-14, presenilin-2 (PS-2) on chromosome-1] are now known to cause autosomal dominant transmission in familial early-onset AD (EOAD). Mutations in the PS-1 gene are responsible for 50–70% of all familial EOAD with an age at onset of 40–45 years (Mullan et al. 1995, Alzheimer's Disease Collaborative Group 1995; Kwok et al. 1997). The PS-1 protein shows a high sequence homology (67%) to the presenilin-2 (PS-2) protein. Mutations in the PS-2 gene on chromosome 1 are the second most frequent form of familial EOAD (age at onset 45–65 years) and have mainly been described in large kindreds of Volga-Germans in the U.S. (Levy-Lahad et al. 1995; Mann et al. 1997). Mutation of the gene for the APP on chromosome 21 is very rare (age at onset 45–60 years) and may cause 5% of familiar EOAD (Hardy 1977).

Up to now only two cases of EOAD due to mutations in the PS-1 gene have been identified in Germany (Sandbrink et al. 1996). Herein we report the clinical course of a patient with a mutation at codon 139 of the PS-1 gene.

Case report

The patient was 44 years old when he contacted our outpatient clinic for the first time. From the age of 43 years he had started to complain about deficits in his short-term memory. His relatives noticed his symptoms even earlier and dated the onset of deficits to his 38th year when he showed increasing interruptions during his speech followed by social withdrawal. There was no previous his-

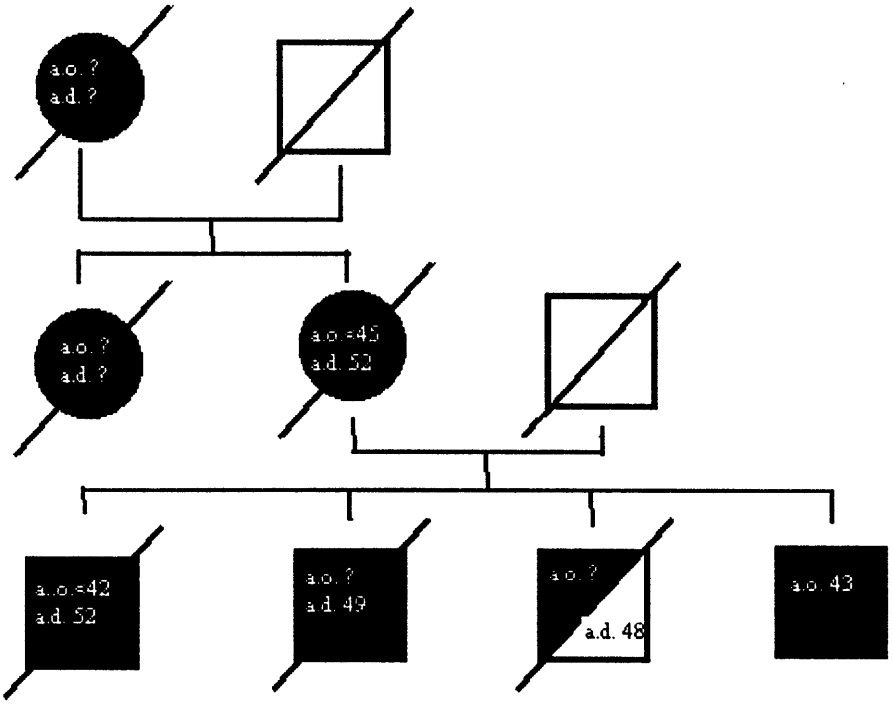


Fig. 1 Family tree for the patient. *Squares* male; *circles* female; *filled symbols* affected subjects; *diagonal line* deceased subjects; *a. o.* age at onset of dementia; *a. d.* age at death

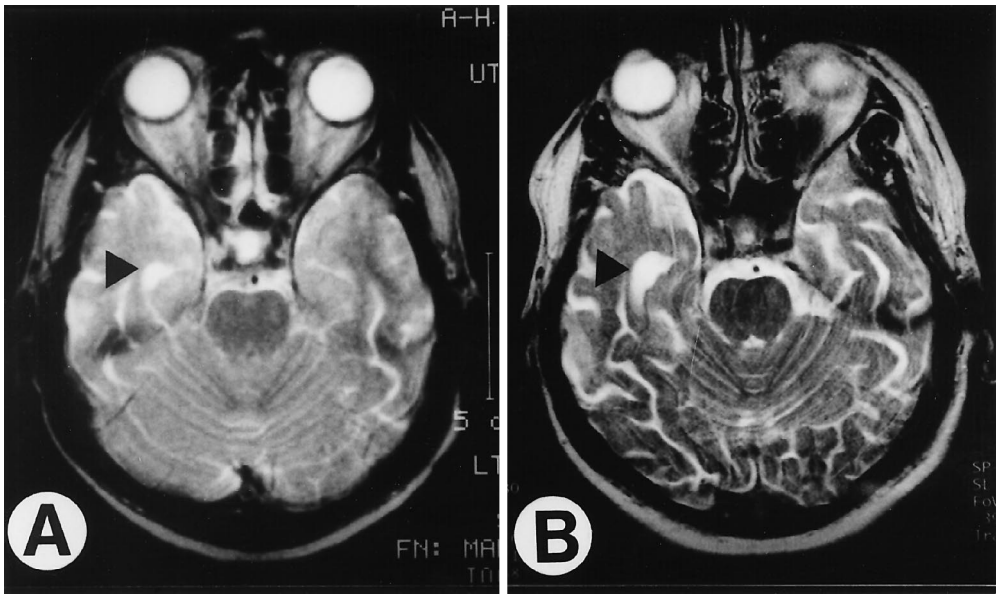


Fig. 2 A, B T2-weighted MRI scan of the patient. **A** At the age of 44 years; **B** at the age of 49 years. Note the enlargement of the lateral ventricle *(black arrowhead)* due to progradient hippocampal atrophy

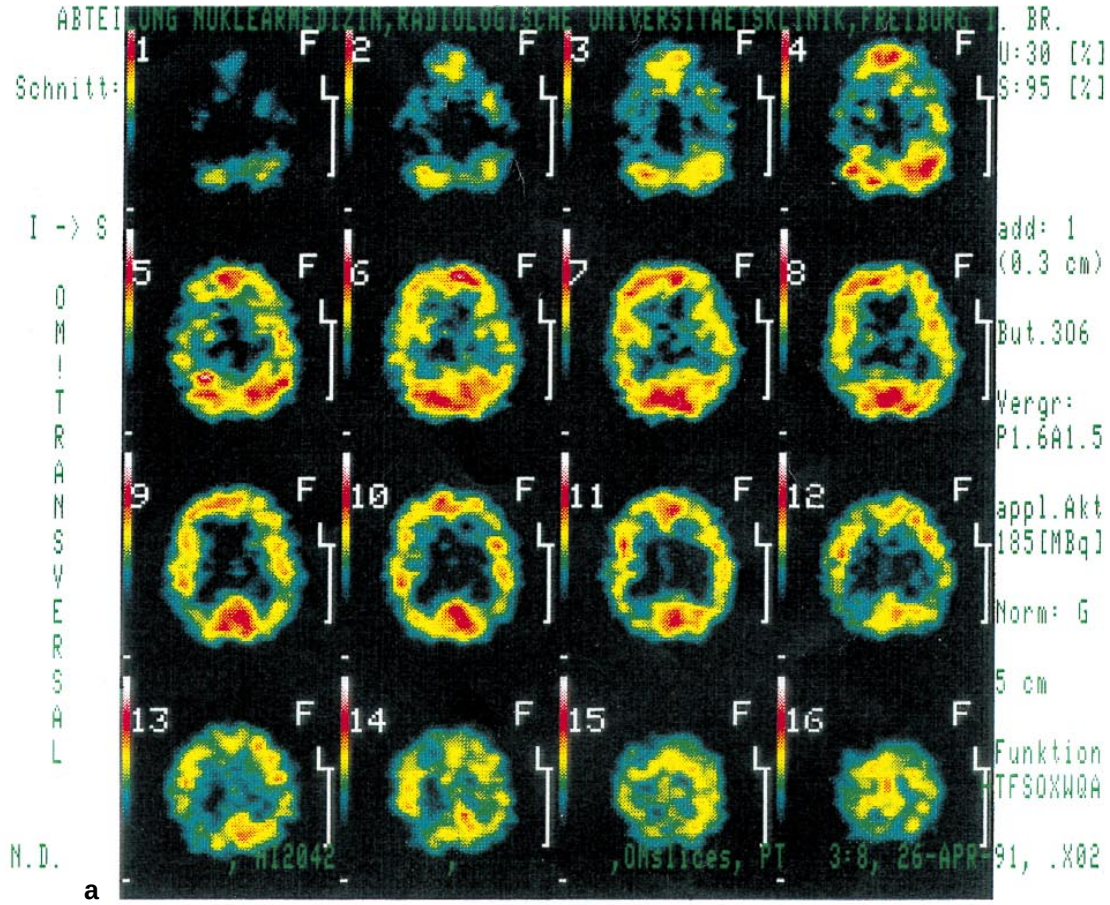
tory of severe or chronic illnesses. However, there was a strong familial history of dementia (Fig. 1) with an affected grandmother, an affected mother and two affected brothers. A third brother died at 48 years, but there is no information on his last years of life. The age of onset of dementia in this family was between 42 and 45 years.

Mental status

At the first presentation of the patient his orientation in time, place and person were accurate. His autobiographical memories were vague, he was unable to date biographical events of the past few years and he was aware of his cognitive deficits. His mood was well and tended to be slightly euphoric. The patient needed no help in performing activities of daily living.

Physical and neurological examination at the first presentation were normal except for the observation of rarely occurring single generalized myoclonic contractions of the upper extremities. Blood and cerebral spinal fluid chemistry revealed no abnormalities.

Fig. 3 a, b J-123 Iomazenil and HM-PAO SPECT scan of the patient at the age of 44 years. There is a bitemporal reduction in **a** benzodiazepine binding sites (Iomazenil SPECT), and only a slight reduction in **b** rCBF (HM-PAO SPECT) ▶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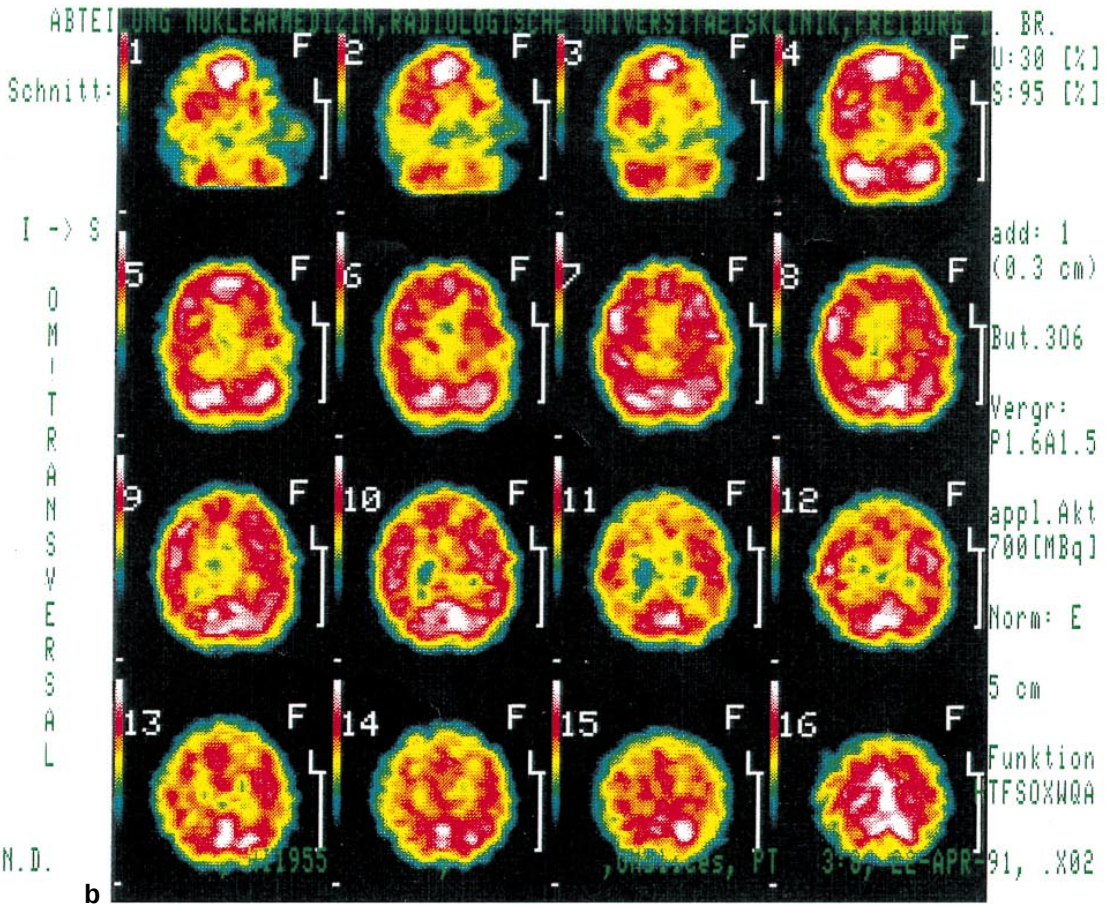
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Neuropsychological tests

The Mini-Mental-State-Examination (MMSE), the Hamburg-Wechsler Intelligence Test for Adults (HAWIE) and the Hooper Visual Organization Ability Test (H-VOT) were used to determine the patient's cognitive abilities. At the first presentation the patient reached a score of 24 points on the MMSE. The HAWIE showed a total IQ of 93 with a relevant discrepancy between the verbal IQ of 101 and the performance IQ of 84. This was mainly due to the inability of the patient to distinguish between important and less important aspects of the serial picture stories used in these IQ subtests. The H-VOT showed a reduced ability to structure visual information with a score of 13 points of 30 possible points.

Electrophysiological tests

At the first presentation the electroencephalogram (EEG) showed a slow alpha rhythm (8.5/s) with a paroxysmal activation of irregular frontal sharp and slow waves. Using a back-averaging method it was possible to consistently demonstrate a positive wave at the C4 electrode 15 ms before the EMG onset of the left biceps. There was a typical pattern of successive arm muscle activation with burst-like innervation in the biceps shorter than 50 ms. These findings demonstrate a cortical origin of the myoclonus.

Cerebral imaging

At the first presentation magnetic resonance imaging (MRI) scanning showed slightly enlarged ventricular spaces (Fig. 2). Tc-99m-HM-PAO single positron emission computed tomography (SPECT) showed a reduction in the regional cerebral blood flow (rCBF) in the left temporal region. In constrast to the slight reduction in the rCBF as measured with HM-PAO, the measurement of benzodiazepine receptors applying J-123-iomazenil-SPECT showed severe abnormalities with a reduction in benzodiazepine receptors in both temporal areas with a stronger reduction on the right side (Fig. 3).

Genetic diagnosis

Deoxyribonucleic acid was extracted from white blood cells. PS-1 gene fragments were amplified with primers specific for human PS-1 and sequenced (Sandbrink 1996). A missense mutation resulting in a replacement of a methionine at position 139 with valine (M139V) in the PS-1 gene (see Table 1) was detected in this patient.

Follow-up and course of disease

The patient showed progressive mental decline. The results of further neuropsychological tests, EEG and MRI data are summarized in Table 2. Occasional drop attacks occurred during the first year after presentation. Since they were considered to be due to seizure-like cerebral activity, treatment with valproat was started and reduced the frequency of drop attacks. When the patient was 47 years old he was no longer able to take care of himself. He became dependent with activities such as shopping and housekeeping. Despite continued valproat treatment, generalized, myoclonic seizures associated with loss of con-

Table 1 Known mutations of the PS-1 gene on chromosome 14 associated with early-onset Alzheimer's disease (EOAD). * Mutation present in our patient

Mutations causing dementia in the PS-1 gene on chromosome 14

Position	Wild type	Mutation	Reference
79	A	V	4
82	V	L	4
96	V	F	4
115	Y	C	4
115	Y	H	4
120	E	D	4
120	E	K	4
139*	M	V	1
139	M	T	4
143	I	F	4
143	I	T	4
146	M	V	1
146	M	L	2
163	H	Y	1
163	H	R	2
209	G	V	4
213	I	T	4
231	A	V	4
231	A	T	4
233	M	T	3
235	L	P	4
246	A	E	2
250	L	S	4
260	A	V	4
263	C	R	4
264	P	L	4
267	P	S	1
269	R	G	4
269	R	H	4
278	R	T	3
280	E	G	5
280	E	A	5
285	A	V	4
286	L	V	2
290	S	C	4
318	E	G	4
384	G	A	4
392	L	V	1
410	C	Y	2
426	A	P	4
436	P	S	4

References: 1 Alzheimer's Disease Collaborative Group (1995), 2 Tanahasi et al. (1995); 3 Kwok et al. (1997); 4 Hardy (1997); 5 Lopera et al. (1997)

Table 2 Clinical course of the patient with EOAD with a mutation of the PS-1 gene (M139V). *MMSE* Mini-Mental State Examination; *SPECT* single positron emission computed tomography; MRI magnetic resonance imaging

Age (years)	MMSE	EEG	MRI[a]	Further investigations
44	24	8–9/s Left frontal dysrhythm, EEG back averaging of myocloni show cortical source	Slight bitemporal ventricular enlargement	HM-PAO-SPECT: slight reduction in left temporal rCBF Iomazenil-SPECT: bitemporal reduction in benzodiazepine receptors
46	16	8–9/s No focal abnormality	Asymmetrical progression of ventricular enlargement right > left	
49	9	7–7.5/s No focal abnormality	Further ventricular enlargement temporal and frontal cortical atrophy	
50	4	6–7/s		
51	0	20–30/s induced by benzodiazepine treatment		

[a] See Fig. 1

sciousness occurred. When he was 49 years old he started to lose orientation in his neighbourhood. He moved to an institutional home the same year. At this point he was disoriented with regard to the year and the season of the year. When he was 50 years old the frequency of myocloni increased despite therapy with valproat and showed only limited response to additional treatment with clonazepam. During this year three seizures were associated with a prolonged loss of consciousness. The patient developed gait disturbances and was confined to a wheelchair. At the age of 51 years, the patient was unable to repeat words or to follow instructions. He spoke only single words which were remotely connected to the actual situation.

Discussion

Herein we document clinical and apperative findings in a patient with early-onset dementia and with a mutation at codon 139 (M139V) in the PS-1 gene. The same mutation has been shown to cosegregate in an autosomal dominant way with EOAD in British pedigrees (Fox et al. 1997). Cognitive deficits became obvious when he was 43 years old with an average age of onset of dementia in his family at 42–45 years. Although we were not able to analyse the PS-1 gene in the other four affected relatives, the detected PS-1 mutation strongly suggests a genetic origin of EOAD in the deceased members of this family.

Linkage of PS-1 mutations with the autosomal transmission of familial EOAD has been shown for 43 different positions in the PS-1 gene including the mutation at codon 139 (Table 1). Estimations of the frequency of occurrence of mutations in the PS-1 gene in pedigrees with suspected familial EOAD vary between 50 and 70% (Sherrington et al. 1995; Alzheimer's Disease Collaborative Group 1995; Van Broeckhoven 1995; Mullan et al. 1993). Thus, mutations of the PS-1 gene appear to be the most important cause of familial AD.

The cDNA sequence of the PS-1 gene suggests a protein with 467 amino acid residues and seven or eight transmembrane regions (Van Broeckhoven 1995). The PS-1 protein is located mainly in the endoplasmic reticulum and might physiologically influence the function of the Notch protein which is important for neurogenesis (Walter et al. 1996; Wong et al. 1997). Regarding its potential role in AD, studies with transfected cell lines and transgenic animals expressing mutant PS-1 showed an alteration in amyloid processing leading to a higher production of β-amyloid peptid 1-42/43 (Citron et al. 1997; Borchelt et al. 1996; Tomita et al. 1997; Xia et al. 1997). Brains of AD patients with a PS-1 mutation display the typical hallmarks of AD such as amyloid plaques and tangle-bearing neurons. Antibodies against the PS-1 protein showed staining of tangle-bearing neurons and of a subfraction of amyloid plaques not only in the brain of patients with a PS-1 mutation, but also in brains of sporadic AD patients (Murphy et al. 1996; Levey et al. 1997).

Whether there are significant differences in clinical symptomatology between different mutations of the PS-1 gene awaits further investigation. Slight differences in the age of onset of patients with different mutations (M233T before 35 years, M139V and M146V around 40 years, E280 and C410Y between 45 and 50 years) have been noted (Alzheimer's Disease Collaborative Group 1995; Van Broeckhoven 1995; Sherrington et al. 1995; Kwok et al. 1997)

Several studies reported a high incidence of myocloni and seizures in AD patients with PS-1 mutations. In the U.S. Lampe et al. (1994) documented the clinical course of a large pedigree of familiar EOAD with linkage to chromosome 14. In 16 affected individuals the age of onset was 41.6 ± 4.7 years and early myocloni were present in 13 of these 16 individuals. The age of onset of myoclonus was 44.7 ± 3.8 years. Generalized seizures were present in 11 of the 16 individuals. In Great Britain, Mullan et al. (1995) investigated a similar pedigree of chromosome 14

linked EOAD with seven affected members. The age of onset was 41.3 ± 4.4 years, myocloni were present in 2 and seizures in 1 affected individual. Hannequin et al. (1995) obtained retrospective information for 15 EOAD patients in a large French family. The age of onset was 46 ± 3.5 years, early myocloni were present in 9 patients (starting 3–9 years after the beginning of cognitive deficits) and seizures were present in 13 of 15 cases. In South America several patients with EOAD due to a mutation of codon 280 (E–A) of the PS-1 gene were investigated (Lopera et al. 1997). In this study the onset of disease showed a broad range (34–62 years). Myocloni and seizures were only found late in the course of the disease.

At the first presentation we observed myocloni in our patient. The patient himself did not complain about myocloni. Given the value of 24 points in MMSE we consider myocloni a very early element in EOAD in our patient. The observation of early myocloni has also recently been reported in two British families with familial EOAD due to a PS-1 mutation at codon 139 (Fox et al. 1997). Differences to other reports, especially the late appearance of myocloni in the above-mentioned South American study (Lopera et al. 1997), might be due either to the retrospective determination of onset of myocloni by exploring relatives, or might point to a real difference in clinical symptomatology between mutations at codon 139 (our patient) and codon 280 (South American patients).

Conclusion

Although mutations in the genes for PS-1, PS-2 and APP cause familial EOAD, it must be remembered that the majority of EOAD is not genetically determined but belongs to the sporadic type of AD. Early-onset Alzheimer's disease due to a mutation in the PS-1, PS-2 or APP gene seems to be rare in Germany. In our patient with a PS-1 mutation, myocloni were early symptoms of the disease. Myocloni in an early stage of familial EOAD should therefore direct attention to the possibility of AD on a genetic basis.

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