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Novel presenilin-1 mutation with widespread cortical amyloid deposition but limited cerebral amyloid angiopathy

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Abstract

Objective—To clarify the phenotypic heterogeneity in deposition of amyloid beta (Aβ) in the parenchyma and in cerebral vessels of the brains of the patients having presenilin-1 (PS1) mutations. Mutations in PS1 induce increased production of Aβ42(43), resulting in an enhanced overall deposition of Aβ protein within the cerebral cortex.

Methods—Sequence analysis of the PS1 gene of DNA from patients with early onset Alzheimer’s disease, and immunostaining of brain tissues by end specific monoclonal antibodies against Aβ.

Results—Sequence analysis disclosed a novel mutation (N405S) in the PS1 gene in a Japanese patient with early-onset Alzheimer’s disease. Postmortem examination of one patient with N405S showed limited cerebral amyloid angiopathy, whereas postmortem examination of another Japanese patient with Alzheimer’s disease with the E184D mutation disclosed severe cerebral amyloid angiopathy. The brains of both patients showed widespread neuritic plaques, neurofibrillary tangles, and neuronal loss. Immunostaining showed that Aβ42 was predominant over Aβ40 in neuritic plaques in both patients, whereas Aβ40 was found to be predominant over Aβ42 in cerebral amyloid angiopathy in the patient with E184D. However, most cortical vessels of the patient with N405S were not reactive with either of the antibodies.

Conclusion—The N405S mutation of PS1 is a major determinant of cortical Aβ deposition but not cerebral amyloid angiopathy in Alzheimer’s disease.

Keywords: presenilin-1; mutation; Alzheimer’s disease; amyloid angiopathy

Most known early onset familial Alzheimer’s disease pedigrees are linked to mutations in the presenilin-1 (PS1) gene on chromosome 14.1 Mutations in PS1 have been demonstrated to alter the processing of amyloid precursor protein in a manner leading to increased production of amyloid beta (Aβ)42(43) in plasma,2 in brain tissues,3 in transfected cells,4 and in transgenic mice.4 The increase of Aβ42 that is deposited selectively and early in Alzheimer’s disease may result in an enhanced overall deposition of Aβ protein within the cerebral cortex.2 3 Thus, PS1 mutations can cause an aggressive form of early onset Alzheimer’s disease. Postmortem examination of cases with PS1 mutations have been reported to have abundant cerebral amyloid angiopathy as well as many neuritic plaques.7 We also reported that an early onset Alzheimer’s disease pedigree with E184D substitution has severe cerebral amyloid angiopathy.8 However, the extent of the Aβ42 increase did not correlate with PS1 expression levels, and a similar increase was not found in the level of Aβ40.2 3 5 Different PS1 mutations have different effects on Aβ generation, which may induce heterogeneity of clinicopathological features in PS1 associated Alzheimer’s disease. We report in this study the detection of a novel mutation of the PS1 gene, N405S, in a Japanese patient with early onset Alzheimer’s disease. Although postmortem examination of this patient showed widespread neuritic plaques, neurofibrillary tangles, and neuronal loss, there was occasional cerebral amyloid angiopathy. Comparison of the neuropathological features of patients with N405S and E184D emphasises the phenotypic heterogeneity in cerebral amyloid angiopathy.

Materials and methods

SUBJECTS

Early onset sporadic Alzheimer’s disease in Kobe (case HI-1)

A housewife developed memory impairment and was unable to manage housework at the age of 48. The dementia syndrome rapidly progressed over the next year with apparent spasticity to eventually become akinetic mutism. The patient died at 53 years of age, and the diagnosis of Alzheimer’s disease was confirmed at postmortem at Kobe University School of Medicine. She had no known familial background of dementia. Her father had died aged 69 with diabetes mellitus and her mother died in...
at the age of 75, and neither had dementia. Two other siblings, one elder sister and one younger brother, had no dementia.

We compared the pathological findings of the case of HI-1 with those of a patient of the ABCD-1 pedigree to clarify the phenotypic heterogeneity between the patients with PS1 mutations. The patient of the ABCD-1 pedigree was a man who developed memory impairment at the age of 44, myoclonus, and seizure, and died at the age of 51 years. The patient’s mother and her other child had also developed dementia.

Genomic DNA was extracted from a block of brain tissue embedded in paraffin by using the conventional method. The target PS1 gene was sequenced as described previously. Apolipoprotein E (apoE) genotyping was performed according to the method of Wenham et al.

Neuropathological examination
Sections from formalin fixed paraffin embedded brain tissues of the frontal, parietal, and temporal cortices, the hippocampus, amygdala, basal ganglia, thalamus, brainstem, and cerebellum were stained with haematoxylin-eosin, luxol fast blue-cresyl violet, and a modified Bielschowsky method. Selected sections were also immunostained for the two types of carboxyl terminus of Aβ proteins, Aβ42(43) and Aβ40, by using end specific monoclonal antibodies or using end specific affinity purified polyclonal antibodies (Quality Control Biochemicals, Inc, Hopkinton, MA, USA), β40 for Aβ C-term-40, and β42 for Aβ C-term-42, after pretreatment with 99% formic acid for 5 minutes.

Results
MISSENSE MUTATION IN EXON 12 OF THE PS1 GENE (N405S)
The nucleotide and exon numbering described here are according to those of GenBank No L76518–76528. Compete sequencing of the PS1 gene of case HI-1 disclosed a new missense mutation (A to G) at nucleotide 1462 in exon 12, which is predicted to cause an asparagine to serine missense substitution at codon 405 (N405S) in the C terminus of the large loop of PS1. The substitution of A to G in the second position of codon 405 creates a restriction site for BpmI in the PS1 gene. The same substitution was not found in 100 healthy control subjects or in 100 patients with sporadic Alzheimer's disease.

NEUROPATHOLOGY IN N405S MUTATION IN THE PS1 GENE
The clinical diagnosis of Alzheimer's disease was confirmed by the presence of many neuritic plaques and neurofibrillary tangles in the postmortem neuropathological study (fig 2 A). In addition, microscopic examination of brain tissues from HI-1 showed a considerable loss of nerve cells in the hippocampus (fig 2 A), entorhinal cortex, and amygdala. Neuronal loss was also evident in the cerebral neocortex. A modified Bielschowsky silver impregnation technique identified numerous neuritic plaques, neurofibrillary tangles with severe gliosis in the hippocampus, entorhinal cortex, amygdala, and neocortical areas examined. Cerebral amyloid angiopathy was not as remarkable in the brain parenchyma of this case as it was in the affected brain tissues of the ABCD-1 family with the E184D mutation (fig 2 B).

The two Aβ40 antibodies or the two Aβ42 antibodies exhibited a similar pattern of immunostainings, respectively. Immunohistochemistry of temporal cortices from the HI-1 and the ABCD-1 cases for Aβ40 or Aβ42(43) disclosed that BC05 or β42 positive neuritic plaques containing Aβ42(43) peptide were predominant over BA27 or β40 positive plaques containing Aβ40 peptide in the case of the patient with sporadic Alzheimer's disease, but the predominance was not as remarkable as that reported in the familial Alzheimer's disease cases with the amyloid precursor protein 717 mutation (fig 2 C-F). In the hippocampus of the patient with familial Alzheimer's disease, there was a prominent cerebral amyloid angio-pathy (fig 2 E-H), which was preferentially immunoreactive for Aβ40 (fig 2 F and H). By contrast, immunolabelling of cerebral vessels was not found either for Aβ42(43) or for Aβ40 (fig 2 C and D) in the affected brain tissues of the HI-1 case. Thus, the immunohistochemistry showed that Aβ42(43) was predominant.
over Aβ40 in the neuritic plaques in both patients, and that Aβ40 was predominant over Aβ42 in cerebral amyloid angiopathy in the patient with E184D, whereas most cerebral vessels in the patient with N405S were not reactive with either of the antibodies.

ApoE genotypes of the HI-1 and the ABCD-1 cases were both ε3/ε4.

Discussion
As the N405S mutation was found in a single patient without a known familial background
of dementia, we cannot exclude the possibility that this substitution corresponds to rare variants. However, the phenotype was an early onset and aggressive form of Alzheimer's disease, and the N405S substitution was not found in 100 controls and 100 patients with sporadic Alzheimer's disease. These facts may indicate that the substitution is not polymorphism and is also involved in early onset Alzheimer's disease.

The patient with the N405S mutation had numerous neuritic plaques and neurofibrillary tangles in the temporal cortex, with only occasional areas of cerebral amyloid angiopathy (fig 2). The identified risks for cerebral amyloid angiopathy are advancing age and accompanying Alzheimer's disease. Recently, the apoE ε4 allele has also been associated with the presence of cerebral amyloid angiopathy and an earlier onset of haemorrhage in cerebral amyloid angiopathy.\(^{15}\) The mild cerebral amyloid angiopathy in the patient with N405S is unlikely to represent an unusually short duration of illness, an earlier age at onset, an earlier age at death, or apoE genotype, because the patient with the N405S mutation shared a similar age, duration of the disease, and one ε4 allele with the patient with the E184D mutation who had abundant cerebral amyloid angiopathy.

The second feature to be noted in the patient with N405S mutation is early manifestation of spasticity, suggesting involvement of the upper motor neurons at some level. A combination of PS1 mutant associated Alzheimer's disease and spastic paraparesis has been reported in five other pedigrees, one of which had the R278T mutation,\(^ {14}\) and the rest were associated with the A9 deletion of the PS1 gene.\(^ {16}\) The neuropathology of the R278T mutation was not described.\(^ {14}\) The families with the A9 deletion were characterized by the occurrence of cotton wool plaques and severe cerebral amyloid angiopathy.\(^ {15}\) These unusual features seem to be different from the pathology of the patient with the N405S mutation.

The clinical characteristics of PS1 mutant associated Alzheimer's disease cases are early manifestation of myoclonus and seizure, whereas the main pathological feature may be severe deposition of amyloid in the parenchyma and in cerebral vessels. Less cerebral amyloid angiopathy was reported in a patient with a frame shift mutation in PS1.\(^ {17}\) Hayashi \( et \ al\) reported that PS1 antibodies stained cerebral amyloid angiopathy in Alzheimer's disease affected brains, suggesting that the PS1 protein plays a part in the formation of cerebral amyloid angiopathy. However, the extent of cerebral amyloid angiopathy is variable in PS1 mutant associated Alzheimer's disease cases, regardless of the age at onset, age at death, and duration of the disease. Variations among the patients in the amount of Aβ deposited as plaques seem to occur together with a variable presence and extent of cerebral amyloid angiopathy. This is compatible with the in vitro finding that different PS1 mutations are associated with significant different degrees of increase in Aβ.\(^ {18}\) Previous studies indicate that the seeding peptide in plaques seems to be Aβ(42),\(^ {19}\) and that the amyloid within the vessels is primarily Aβ(40),\(^ {20}\) which is consistent with our immunostaining results. Although it remains possible that the severity of cerebral amyloid angiopathy depends on the specific type of PS1 mutation, our data suggest that the N405S mutation is not associated with cerebral amyloid angiopathy in Alzheimer's disease.


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