A Case of Familial Prion Disease Diagnosed as Alzheimer’s Disease for 5 Years

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Abstract
Five years prior to visiting our hospital, an 87-year-old woman had been diagnosed as having Alzheimer’s disease, and cognitive symptoms slowly progressed over the course of 4 years. Cortical signal hyperintensities centered on the bilateral temporal and frontal regions on head diffusion-weighted imaging (DWI) and cerebrospinal levels of 14-3-3 protein were high. Prion protein gene testing showed a mutation in codon 180 from Val to Ile, and the genetic prion disease Creutzfeldt-Jakob disease with V180I mutation was diagnosed. In the course of slowly progressive dementia in the elderly, identification of genetic prion diseases may be facilitated by confirmation of changes in cortical signal hyperintensities on DWI over time.

Key Words
Prion disease, Alzheimer’s disease, prion protein gene

Introduction
In Japan, genetic prion disease accounts for approximately 16.7% of all cases of prion disease, and more than 40% of this genetic prion disease involves Creutzfeldt-Jakob disease with V180I mutation (V180I CJD), in which a codon 180 Val→Ile mutation is present in the prion protein gene. V180I CJD occurs in old age and progresses more slowly than sporadic prion disease. In this paper, we discuss genetic prion disease and report a case of a patient with genetic prion disease who was diagnosed as having Alzheimer’s disease (AD) for about 5 years.

Case Report
The patient was an 87-year-old woman with chief complaints of forgetfulness and loss of motivation; she had no subjective symptoms. She had a medical history of knee osteoarthritis, and her family history was unremarkable. She was taking Yokukan-san 5 g/day. She was a graduate of a girls’ high school and had been a full-time homemaker.

Current medical history: At X – 5 years, the patient began living with her son on the occasion of his job transfer. From that time on, she stopped preparing elaborate meals and began showing signs of forgetfulness (asking the same question many times, leaving the gas on, and other episodes). When her family took her to a local mental clinic for examination at X – 4 years, she was diagnosed as having AD. She was prescribed oral medication but strongly refused and decided on her own to stop seeing the doctor. In April of year X, her son was again transferred, and her living environment changed. She began wandering about early in the morning and occasionally soiled herself because she did not know where the toilet was. These lifestyle changes became conspicuous, and she was examined again by the previous doctor, who referred her to our hospital.

Present condition: Height, 148 cm; weight, 39.8 kg, body temperature, 36.7°C; blood pressure, 116/67 mmHg; heart rate, 64 beats/min and rhythmic; no abnormalities in general physical findings.

Neurological findings: Cognitive dysfunction was seen, with a Hasegawa Dementia Rating Scale (HDS-R) score of 10 and Mini-Mental State Examination (MMSE) score of 12. Loss of motivation was also observed, as exemplified by the fact that she...
would not do things unless urged. In interviews with family members, no personality changes were reported. No other higher brain dysfunction was evident, such as the inability to name objects or visual agnosia, and no other abnormal neurological findings were seen.

Laboratory findings: Blood examination showed microcytic hypochromic anemia, with a hemoglobin of 9.2 g/dl; hematocrit, 28.2%; and mean corpuscular volume, 80.3 fl. No obvious abnormalities were seen in other blood count or biochemical tests. Examination of cerebrospinal fluid revealed high values with an initial pressure of 90 mmH₂O; cell count, 1/μl (mononuclear cells:polynuclear cells, 1:0); protein, 42 mg/dl; glucose, 67 mg/dl; Cl, 128 mEq/l; spinal fluid tau protein, >2400 pg/ml; and spinal fluid 14-3-3 protein, 1230 μg/ml. A codon 180 Val/Ile mutation was identified upon prion protein gene examination based on genomic DNA extracted from blood.

Her family members were approached to obtain written consent for a genetic test to determine the accuracy of the diagnosis. Generalized wave slowing was seen on electroencephalography, but no obvious epileptic waves or periodic synchronous discharges were observed.

Imaging findings: No abnormalities were evident on electrocardiography or chest radiography. Brain MRI showed diffuse hyperintensity in the cerebral cortex, with right dominance on diffusion-weighted imaging (DWI) (Fig. 1A). Fluid-attenuated inversion recovery (FLAIR) imaging revealed abnormal areas that matched those seen on DWI (Fig. 1B). Coronal FLAIR and T₁-weighted imaging showed generalized brain atrophy and mild hippocampal atrophy (Fig. 1C). Single photon emission computed tomography (SPECT) of the brain using 123I-IMP quantitative determination revealed diffuse decreases in blood flow, but no obvious differences in asymmetry were

![Figure 1](image-url)  
**Figure 1.** Brain MRI on admission  
A) Axial diffusion-weighted imaging shows hyperintense regions in the cerebral cortex.  
B) Axial FLAIR images show hyperintense regions in the cerebral cortex.  
C) Coronal T₁-weighted images show diffuse brain atrophy and mild hippocampal atrophy.
seen. Images processed using three-dimensional stereotactic surface projection (3D-SSP) analysis showed regions of decreased blood flow in the bilateral temporal lobes, posterior cingulate gyrus, and the precuneus, and SPECT showed characteristic findings of AD (Fig. 2).

**Course:** Only cognitive dysfunction was seen during the patient’s first admission to our hospital. With respect to activities of daily living (ADL), she was still able to walk and eat meals independently. The family members were provided mental health care through a multidisciplinary team, and we explained in detail that this disease can be refractory. In July of year X, black emesis was observed several times, and she was admitted to the gastrointestinal ward of our hospital with suspected gastrointestinal bleeding. At that time, cognitive function had deteriorated to the point that she could only follow moving points. ADL had also deteriorated to the point where she was unable to walk and had to use a wheelchair.

As her general condition improved, she was readmitted to a group home. She became bedridden naturally because of lying in bed for long periods to control her gastric problem.

In October of year X, her food consumption in the group home decreased, and she became difficult to manage due to deteriorating cognitive function. She was then readmitted to our hospital. Her HDS-R score at the time was 0, and in terms of ADL, she was considered to be bedridden. The patient was subsequently transferred to a convalescent hospital.

**Discussion**

V180I CJD is a genetic prion disease caused by a mutation resulting in codon 180 of the prion protein gene coding isoleucine (I) rather than valine (V). This disease is generally identified in older individuals, with a mean age at symptom onset of 76 years.\(^3\) Onset in this patient was also in old age. Prion disease occurs with slowly progressive cognitive dysfunction.
that needs to be differentiated from AD, as in this case, and cases are separated into patients with concurrent AD and patients with slowly progressive prion disease only. The form of prion disease in patients with concurrent AD and prion disease is reported to involve codons 129MM and 219GG\(^4\)\(^5\). Progression is rapid, with sudden exacerbation of clinical symptoms during the course of slowly progressive dementia and a short survival period of 3 to 4 months after this exacerbation\(^4\)\(^6\). Among the pathological findings, \(\alpha\beta\) protein and the characteristic spongy degeneration of prion disease are seen\(^4\)\(^–\)\(^6\). Nearly all cases of slowly progressive prion disease only, without clinical symptoms of AD, involve V180I. In previously reported cases\(^7\)\(^–\)\(^9\), the predominant symptom was uniformly cognitive dysfunction, as in the present case, and no sudden worsening of cognitive function was seen. Among the pathological symptoms of slowly progressing cases of V180I CJD, senile plaque is sparse if present at all, and the mean time until development of akinesia is 13.9 ± 3.6 months\(^3\). The present patient was characterized by slow progression even in comparison with past reports. Because this patient showed high blood flow distribution specific to AD on cerebral blood flow SPECT, the existence of Alzheimer pathology cannot be completely ruled out. However, other clinical images were considered to be consistent with the course of slowly progressive prion disease; therefore, this patient was diagnosed clinically as having V180I CJD alone.

Prion disease is characterized by cortical ribbon-like high-signal intensity changes on DWI. In sporadic CJD, diffuse cortical high-signal intensity lesions on DWI develop within several weeks after onset. Therefore, the detection of DWI MRI abnormalities in patients with suspected prion disease should be included in the early stage of this disease. Increased DWI signal lesions in prion disease correspond to fewer water molecules in tissues, and this phenomenon suggests the severity of the spongiform changes\(^10\)\(^–\)\(^13\). Because the DWI sequences differ at every facility, abnormal findings on DWI might not be detected in the early stage immediately after onset. We recommend that patients with slowly progressive dementia such as this case are suitable for evaluation by long-term DWI follow-up study.

From the above, genetic prion disease, particularly V180I CJD, is thought to be a slowly progressing cognitive dysfunction with onset in old age, but sometimes cases such as the present are seen in which the correct diagnosis is only made after a long course. In cases of mild dementia in elderly individuals with a slowly progressive course, brain MRI including DWI should be performed with genetic prion disease kept in mind.

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