CASE REPORT

Creutzfeldt-Jakob Disease with a Codon 210 Mutation: First Pathological Observation in a Japanese Patient

Yasutaka Tajima¹, Chika Satoh¹, Yasunori Mito¹ and Tetsuyuki Kitamoto²

Abstract

We herein report a case of Creutzfeldt-Jakob disease (CJD) with a V210I mutation and discuss the pathological findings. The patient’s clinical course was quite similar to that of patients with sporadic CJD. Diffusion-weighted magnetic resonance imaging (MRI) disclosed a high signal intensity in the basal ganglia and cerebral cortices. Pathologically, spongiform degeneration of neurons and their processes with reactive astrocytosis was observed. Prion protein immunostaining revealed diffuse positive and plaque-type patterns. Only one Japanese case of CJD with this type of mutation has been reported to date, but without any pathological examination results. Therefore, this report is considered to be highly significant for understanding CJD.

Key words: Creutzfeldt-Jakob disease, prion protein gene, mutation, magnetic resonance imaging

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Introduction

Prion disease is a fatal human transmissible spongiform encephalopathy that is classified into sporadic, genetic and acquired forms (1). The most common type is sporadic Creutzfeldt-Jakob disease (CJD), the genetic form of which is defined as a prion disease with causative mutations in the prion protein (PrP) gene in addition to a relevant family history, such as Gerstmann-Sträussler-Scheinker syndrome or familial insomnia (2, 3). Several mutations in the PrP genes and the geographic or ethnic clustering of PrP gene mutations have been reported (4, 5). Only one case has been reported to date in Japan, with the valine-to-isoleucine change at codon 210 (the V210I mutation) (6). This is the first report to describe the clinicopathological features of a Japanese patient with this rare PrP gene mutation.

Case Report

The patient was a 54-year-old woman who had noticed diplopia and distortion of vision two weeks prior to presentation. Her symptoms progressed further and she finally visited our hospital. Her past medical and family histories were unremarkable. She had never undergone surgery or received a blood transfusion. A physical examination showed no abnormalities, while neurological examinations revealed left-sided hemispatial neglect and a slight consciousness disturbance (GCS: E4, V4, M6). The patient’s motor systems were not impaired, and her sensory and cerebellar systems were intact. Diffusion-weighted MRI disclosed a high signal intensity in the right occipital cortex and caudate nucleus (Fig. 1A). The patient refused further examinations. Eight days later, she was hospitalized after being unable to stand up due to dizziness and experiencing irritation with a vague sense of anxiety. Neurological examinations showed no clear differences from the findings observed at her first visit. After admission, she was administered antipsychotic medications and spent all day in bed. She sometimes cried loudly during the night, although she never walked around. Her blood analysis results, including parameters of the thyroid function, were normal. A cerebro-spinal fluid (CSF) examination revealed a protein level of 16 mg/dL and a cell count of 2 cells/mm³. No bacteria or fungi were cultivated from the CSF. Cytology showed no evidence of malignancy, and no significant elevation of the viral antibody titers was ob-
An electroencephalogram (EEG) showed slow background alpha-rhythms with infrequent delta waves, indicating a conscious disturbance. These observations were interpreted to be non-specific changes. Single photon emission computed tomography (SPECT) demonstrated several irregular areas of hypoperfusion in the cerebral cortices, particularly the right occipital lobe (Fig. 1C). By two weeks after admission, the patient had become essentially bedridden, and myoclonus had developed. Tube feeding was therefore necessary. Myoclonic jerks became more apparent in the patient’s face and extremities, then gradually disappeared over the following two months. An EEG showed typical periodic synchronous discharges. Diffusion-weighted MRI demonstrated marked worsening of the cortical atrophy. Furthermore, the areas of abnormal high signal intensity in most regions of cerebral cortices and basal ganglia were more prominent (Fig. 1B). Based on these findings, the patient was considered to be suffering from CJD. An analysis of her PrP genes revealed no specific mutations at either codon 129 or 219. Methionine homozygosity was noted at codon 129, while glutamine homozygosity was observed at codon 219. Intriguingly, an additional mutation at codon 210, quite rare in Japanese CJD patients, was detected. The normal allele at codon 210 encodes valine (GTT); in this case, an additional isoleucine (ATT) sequence was observed (Fig. 2).
The patient remained in a state of akinetic mutism and ultimately died of aspiration pneumonia 19 months after admission. Pathological examinations of her brain demonstrated marked atrophy and thinning of the cerebral cortices, as well as ventricular dilatation (Fig. 3). Microscopically, spongiform degeneration of neurons and their processes, neuronal loss and reactive astrocitosis were observed in the cerebral cortices, thalamus, putamen and caudate nucleus (Fig. 4A-C). Moreover, spongiform degeneration was noted in the posterior horn of the upper cervical spinal cord (Fig. 4D). The hippocampus was relatively preserved. Granular cell loss was marked in the cerebellum (Fig. 4E).

Immunohistochemical examinations demonstrated diffuse positive PrP immunostaining in the frontal and temporal lobes (synaptic pattern) (Fig. 5A). In addition, a plaque type immunostaining pattern was prominent in the occipital lobes (Fig. 5B). The deposits were also positive for thioflavin-T, suggesting a possible relationship with amyloid formation (Fig. 5C). The protease-resistant PrP was demonstrated to be type 1 (MM1) on a protein analysis.

**Discussion**

CJD is a neurodegenerative disorder caused by the accumulation of abnormal PrP in the brain that is characterized by specific clinical and neuropathological features. An estimated 10-15% of CJD cases are attributable to mutated PrP genes and are thus designated as genetic CJD.

Several mutations in PrP genes and the geographic or ethnic clustering of PrP gene mutations have been reported. According to Kovacs et al., the mutation changing valine to isoleucine at codon 180 (V180I) is the most common in Japan, although it is very rare in Europe (4). The most common mutation in Europe causes a switch from glutamine to lysine at codon 200 (E200K); this is the third most common mutation in Japan (5). As to the V210I mutation, its frequency is 16.2% according to the EuroCJD; however, only one case has been reported to date in Japan, and the patient was not autopsied (6). This mutation would presumably be among the most representative of ethnic differences in the occurrence of CJD.

Therefore, our present clinicoradiological investigations accompanied by pathological observations are highly significant for understanding this type of genetic CJD.

The patient’s initial manifestations included visual problems and dizziness followed by psychotic symptoms. She became bedridden a few weeks later, and ultimately exhibited akinetic mutism. During the course of her illness, myoclonus appeared and persisted for two months. Our patient’s clinical course strongly resembled that of patients with sporadic CJD.

The present patient’s initial MRI examinations showed areas of faint high signal intensity in the posterior cortex and caudate nucleus. The signal alterations observed on diffusion-weighted MRI subsequently spread, such that brain atrophy became more apparent two months later. Among the genetic forms of CJD, that involving a substitution from methionine to arginine at codon 232 (the M232R mutation) has been shown to exhibit two different clinical phenotypes, i.e., rapid and slow progression (7, 8). In patients with the M232R mutation, high-signal intensity lesions in the medial thalamus depicted on diffusion-weighted imaging are assumed to be a common finding of the slowly progressive type of the disorder. In addition, high signal alterations in the cerebral cortex, with sparing of the medial occipital and cerebellar cortices, are considered to be characteristic features of CJD associated with the V180I mutation (9). Our patient had no unusual or unique lesions not seen in other types of CJD. The signal alterations on diffusion-weighted imaging of the basal ganglia and cerebral cortices observed in our case were not specific; these findings are, in fact, common in CJD patients (10-12).

The molecular type of PrP is another factor closely associated with the clinical and pathological phenotypes of CJD. The present case was proven to be type I (MM1) and this genotype correlated well with the patient’s disease progression. Immunohistochemical staining of PrP revealed diffuse synaptic type deposits in the frontal and temporal lobes.
Figure 4. Histological examinations of V210I CJD. Spongiform degeneration and reactive astrocytosis were observed in the caudate nucleus (A). Myelinated fiber loss and neuronal cell loss were highly evident (B) (A: Hematoxylin and Eosin staining, ×40; B: K-B staining, ×200). Spongiform degeneration was also seen in the cerebral peduncle (C) and spinal posterior horn (D) (C: D). Granular cells were markedly decreased in the cerebellum (E).

Figure 5. Immunohistochemical staining of PrP. (A): Synaptic-type PrP deposits were diffusely observed in the temporal lobes. (B): Plaque-type immunostaining was recognized in the occipital lobes. (C): The deposits were also positive for thioflavin-T staining.
similar to those observed in sporadic CJD cases associated with MM1. In addition to these synaptic patterns, we also identified a plaque staining pattern in the occipital lobes that was positive for thioflavin-T as well as MM1. Whether these pathological findings are specific to this type of mutation remains to be determined, as pathological investigations of the V210I mutation are currently insufficient (13-15). Mastrianni et al. summarized the histopathological data of three patients with this type of mutation, and reported nerve cell loss, vacuolation and reactive astrogliosis to be characteristic features resembling those of sporadic CJD. The authors also evaluated histopathological changes using transgenic mice carrying the V201I mutation and concluded that the immunohistochemical patterns of PrP are similar to those of the sporadic form of CJD. Our immunohistochemical investigations indicated the coexistence of a diffuse synaptic pattern and a plaque pattern, suggesting positive PrP immunoreactivity to be a possible characteristic feature of the V210I mutation.

The authors state that they have no Conflict of Interest (COI).

References