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Creutzfeldt-Jakob disease associated with a V203I homozygous mutation in the prion protein gene

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Abbreviations: CJD, Creutzfeldt-Jakob disease; sCJD, sporadic CJD; fCJD, familial CJD; *PRNP*, prion protein gene; PrP, prion protein; PrP^{Sc}, scrapie prion protein; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI, magnetic resonance imaging.

We report a Japanese patient with Creutzfeldt-Jakob disease (CJD) with a V203I homozygous mutation of the prion protein gene (*PRNP*). A 73-year-old woman developed rapidly progressive gait disturbance and cognitive dysfunction. Four months after the onset, she entered a state of an akinetic mutism. Gene analysis revealed a homozygous V203I mutation in the *PRNP*. Familial CJD with a V203I mutation is rare, and all previously reported cases had a heterozygous mutation showing manifestations similar to those of typical sporadic CJD. Although genetic prion diseases with homozygous *PRNP* mutations often present with an earlier onset and more rapid clinical course than those with heterozygous mutations, no difference was found in clinical phenotype between our homozygous case and reported heterozygous cases.

Introduction

Creutzfeldt-Jakob disease (CJD) is a disease of fatal neurodegenerative conditions pathologically characterized by accumulation of the abnormal prion protein (PrP^{Sc}) in the central nervous system. Approximately 85–90 % of CJD cases are sporadic (sCJD) lacking any mutations in the prion protein gene (*PRNP*), while about 10–15% of the disorders are inherited.[1] Familial CJD (fCJD) is associated with at least 20 distinct genetic mutations that are all transmitted as autosomal dominant traits, including point, deletion and insertion mutations.[2] Most of the mutations that cause fCJD, are heterozygous. Pathomechanisms of homozygous mutations in the *PRNP* remain unclear due to the extreme rarity of the disorder. We describe a Japanese fCJD patient with a V203I homozygous point mutation in the *PRNP.*

Case Presentation

A 73-year-old Japanese woman developed gait disturbance and rapidly progressive cognitive dysfunction. She had no family history of the prion diseases or other neurological disorders; however, her parents were first cousins. Three months after the onset, she became bedridden state. On admission to our hospital, neurological examinations revealed severe cognitive impairment and left-sided hemiparesis. Hyperreflexia with positive plantar reflex was evident in the left extremities. No myoclonus or extrapyramidal signs were obvious. No visual disturbance or cerebellar signs were apparent. Routine hematological examinations and blood chemistry were unremarkable. Cerebrospinal fluid (CSF) study revealed an elevation of tau protein (22,528 pg/ml; normal range, <202 pg/ml) and 14–3–3 protein (5,428 μg/ml; normal range, <500 μg/ml); however, there was neither pleocytosis nor an elevation of protein levels. There was no evidence of infectious diseases in the culture from the CSF. Electroencephalography (EEG) revealed diffuse slowing of the waves without apparent periodic synchronous activities. Diffusion weighted brain magnetic resonance imaging (MRI) showed hyperintensity in the right basal ganglia and the right frontal, parietal, and occipital lobes (**Fig. 1**). Single photon emission computed tomography images using ^{99m}Tc-Ethylcysteinate dimer showed mild hypoperfusion in the right frontal lobe and right parietal lobes which were almost consistent with the areas of hyperintensity on the MRI. Four months after the onset, she entered a state of akinetic mutism state accompanied by frequent myoclonus; moreover, periodic synchronous discharges appeared on the EEG.

A genomic study of the *PRNP* approved by the Ethics Committee for Human Genome/Gene Analysis Research at Kanazawa University Graduate School of Medical Sciences was performed after obtaining an informed consent from the family. The gene analysis revealed a homozygous base substitution: c.656G>A (p. V203I) (**Fig. 2**). The polymorphisms of the *PRNP* showed methionine homozygosity at codon 129 and glutamine

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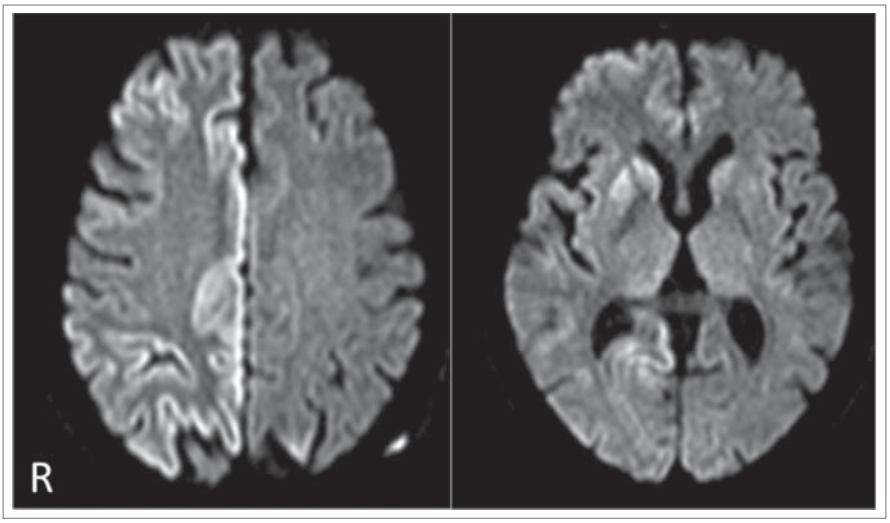

Figure 1. Diffusion-weighted magnetic resonance images showing increased signal intensity in the right basal ganglia and the right frontal, parietal, and occipital cortices.

homozygosity at codon 219. The V203I mutation was not observed in any of the 100 healthy Japanese control subjects. We thus made a diagnosis of fCJD with a V203I homozygous mutation. The patient died 24 months after the onset. An autopsy was not performed.

Discussion

In this report, we have described a Japanese fCJD patient with a V203I homozygous mutation in the *PRNP*. Although no histopathological examinations were performed, the clinical course to akinetic mutism, findings of the brain MRI and EEG, and elevation of tau and 14–3–3 proteins in the CSF were consistent with those typical of CJD patients.[3] The genotype frequency of the V203I mutation in the genetic prion diseases has been reported as 0.9% in the Japanese (2/216 cases)[4] and 1.2% in Europeans (5/425 cases).[5]

There have been 3 case reports of fCJD associated with the V203I heterozygous mutation so far;[6-8] however, there have been no reports of fCJD with the V203I homozygous mutation. The clinical characteristics and laboratory features of 3 reported cases and our patient are summarized in **Table 1**. All the reported cases with this mutation lacked a family history of the prion diseases.[6-8] The clinical manifestations of the patients with fCJD who have a V203I heterozygous mutation are consistent with those of patients with typical sCJD. This includes rapidly progressive dementia, ataxia, tremor, and myoclonus.[6–8] All patients died within 2 months of onset. An elevation of 14–3–3 protein in the CSF was seen in all the reported cases. Two out of the 3 patients showed typical periodic sharp waves on the EEG. Brain MRI also showed gyriform hyper intensity in the cerebral cortex in T2-weighted and diffusion-weighted images.[6] As regards of polymorphisms at codon 129 in the *PRNP*, one patient presented both methionine and valine heterozygosity, while, 2 patients were methionine homozygous only. Histopathological investigation was performed in only one case (the Korean female).[6] This patient showed astrogliosis, vacuolization with spongiform changes and large vacuoles, neuronal loss and PrP^{Sc} deposition in the cerebrum, basal ganglia and cerebellum;[6] Western blot analysis of proteinase K-treated brain samples of the case showed a typical PrP type 1 pattern in addition to a band at 17 kDa.[6]

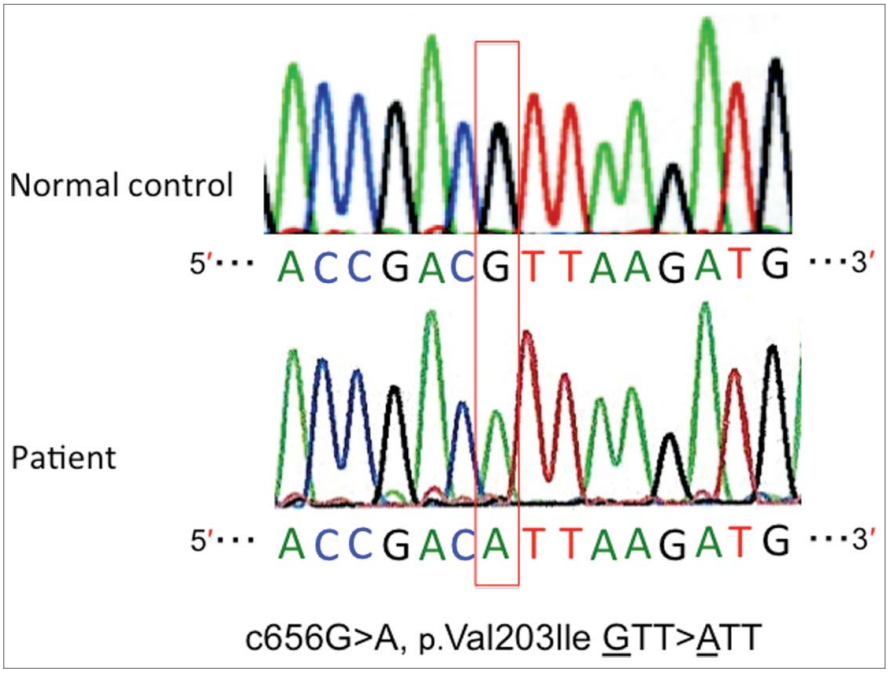

Figure 2. Sequence chromatogram of the homozygous c.656G>A (p.V203I) mutation in the prion protein gene (*PRNP*).

Our patient presented similar neurological and laboratory findings to those of patients with typical sCJD and fCJD with a V203I heterozygous mutation.[6-8] The influence of a homozygous mutation in the *PRNP* on the disease phenotype is uncertain. The substitution of lysine for glutamate at codon 200 (E200K) is the only mutation which has been reported to be homozygous in some cases.[9] E200K homozygous patients showed earlier development of the diseases in comparison to those with a heterozygous E200K mutation; however, there were no distinguishing clinical

Table 1 Clinical and investigational features of patients with the V203I mutation in *PRNP*

Author, year, country	Age at onset (years), sex	V203I mutation	Codon 129	Initial clinical manifestation	Hyperintensity on DWI (MRI)	PSD in EEG	CSF		Histopathology	Disease duration, (months)
							14–3–3 protein	Total tau (pg/ml)		
Peoc'h et al, 2000, Italy[7]	69 M	Heterozygote	M/M	Diplopia, dizziness	N/A	+	+	N/A	N/A	1
Jeong et al, 2010, Korea[6]	66 M	Heterozygote	M/V	Gait disturbance, cognitive dysfunction	Cerebral cortex	N/A	+	N/A	Large vacuoles, spongiform changes, synaptic-type PrP^{Sc} deposition	2
Shi et al, 2013, China[8]	80 M	Heterozygote	M/M	Memory loss, slow response	Cerebral cortex	+	+	N/A	N/A	2
Present patient, Japan	72 F	Homozygote	M/M	Gait disturbance, cognitive dysfunction	Basal ganglia, cerebral cortex	+	+	22,528	N/A	24

Key: CSF, cerebrospinal fluid; DWI, diffusion-weighted images; EEG, electroencephalogram; PSD, periodic synchronous discharges; N/A, not available

symptoms between the homozygous and heterozygous patients.[9] The lack of wild type prion protein in patients with homozygous mutations in the *PRNP* might be susceptible to the generation of PrP^{Sc} and subsequent propagation of the protein. Our patient presented with a long disease history compared to patients with a V203I heterozygous mutation; [6-8] however, the longer survival after akinetic mutism in Japanese patients with CJD could be attributable to careful nutritional and medical support.[10] Although the amino acid residue of codon 203 is located in the hydrophobic core of PrP,[11] details of the pathomechanisms underlying this point mutation remain unknown. Further comprehensive studies are essential to clarify the influence of this mutation on disease phenotype.

Conclusion

We report the first case of fCJD with a V203I homozygous mutation in the *PRNP*. The onset age and neurological and laboratory findings were similar to those reported in patients with V203I heterozygous mutation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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