

## SHORT REPORT

MRI characteristics of sporadic CJD with valine homozygosity at codon 129 of the prion protein gene and PrP<sup>Sc</sup> type 2 in Japan

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Two Japanese sporadic Creutzfeldt-Jakob disease (sCJD) patients with valine homozygosity at codon 129 of the prion protein gene and protease-resistant prion protein (PrP<sup>Sc</sup>) type 2 (VV2) are described. In contrast with Western countries, this type of sCJD is very rare in Japan. In 123 sCJD cases, only two were recognised as VV2 by the Japanese CJD surveillance committee. The clinical symptoms and pathological findings of the patients were similar to those of European and US patients. The noteworthy finding of diffusion weighted MRI (DWI) was that an abnormal high intensity covered a wide range of the thalamus including the dorsomedial nucleus, the pulvinar, and the ventral anterior, lateral, and posterolateral nuclei. This thalamic pattern has not been recognised in sCJD with methionine homozygosity and PrP<sup>Sc</sup> type 1 (MM1) or methionine/valine heterozygosity and PrP<sup>Sc</sup> type 1 (MV1) which comprises the vast majority of sCJD. This finding may be characteristic to VV2 and may distinguish it from MM1, MV1, and variant CJD. DWI can provide a very important clue for the antemortem diagnosis of VV2 subjects.

Since the discovery of the relationship between bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom,<sup>1</sup> nationwide surveillance for CJD including vCJD has begun in many countries. It has been found that the major differential diagnosis of vCJD is sporadic CJD (sCJD).<sup>2</sup> The classical triad of progressive dementia, generalised myoclonus, and periodic sharp and slow wave complexes (PSWCs) in electroencephalogram (EEG) are important clues for sCJD. Periodic sharp and slow wave complexes in EEG are a useful marker for distinguishing sCJD from vCJD because vCJD never shows PSWCs.<sup>2</sup> However, both the differentiation of sCJD without PSWCs from vCJD and the diagnosis of such an uncommon sCJD are difficult.

In 1999, Parchi, *et al* proposed a classification of sCJD based on a polymorphism at codon 129 of the prion protein gene (PRNP) and the types of protease-resistant prion protein (PrP<sup>Sc</sup>).<sup>3</sup> Sporadic CJD with type 2 PrP<sup>Sc</sup> and valine homozygosity at codon 129 of PRNP (VV2) is a representative sCJD without PSWCs and the second most common type of sCJD in Western countries.<sup>3</sup> On the other hand, reflecting the fact that valine homozygosity at codon 129 (VV) in the normal Japanese population is very rare,<sup>4</sup> only one Japanese sCJD with VV has been reported.<sup>5</sup> We report two cases of Japanese sCJD with VV2 and their characteristic diffusion weighted MRI (DWI) findings which are useful for distinguishing sCJD with VV2 from sCJD with methionine homozygosity (MM) and type 1 PrP<sup>Sc</sup> (MM1), methionine/

valine heterozygosity (MV) and type 1 PrP<sup>Sc</sup> (MV1), and vCJD.

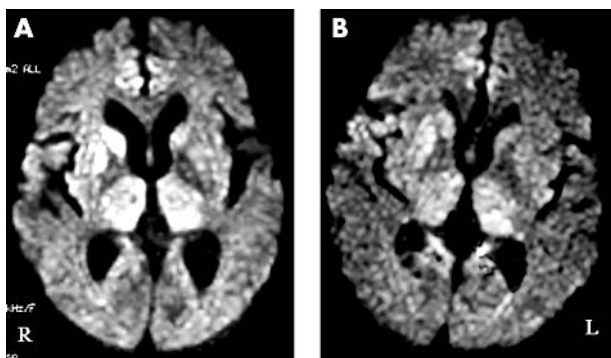
## CASE REPORT

Patient 1 was a 75 year old woman without a family history of prion disease or personal history of neurological disease. She had never received cadaveric growth hormone, dura mater, or cornea. She noticed unsteadiness of gait in February 1999. She visited our outpatient clinic in March 1999 because of this progressive unsteadiness. Neurological examination showed only cerebellar ataxia. The cerebellar ataxia progressed and mild cognitive dysfunctions appeared. In May 1999, she was unable to walk because of advanced cerebellar ataxia, and dementia rapidly progressed. In July 1999, slight myoclonic jerks appeared and she became akinetic and mute thereafter. She died of pneumonia on 4 January 2000.

Cerebrospinal fluid analysis was normal except for an increased concentration of neuron specific enolase (NSE) (77 ng/ml) and the presence of 14-3-3 protein (+). Four sequential EEGs showed no PSWCs during her illness. Diffusion weighted MRI showed an abnormal high intensity in the head of the caudate nucleus, putamen, cingulate gyrus, and insular cortex. A wide range of the thalamus was also involved in the lesion (fig 1A). Genetic analysis of codon 129 of PRNP revealed VV and no point mutation was found. Postmortem examination revealed diffuse spongiform changes, gliosis, and neuronal loss in the cortical ribbon except for the calcarine gyrus where these features were limited to the deep layers. These features were also present in the striatum and thalamus, and marked in the cerebellar granular layer with preserved Purkinje cells. PrP deposition occurred in a plaque-like pattern. Western blot analysis revealed type 2 PrP<sup>Sc</sup>.

Patient 2 was a 69 year old man with no family history of prion disease or personal history of neurological disease. He had never received cadaveric growth hormone, dura mater, or cornea. He noticed unsteadiness of gait in June 2001. He could not continue his accounting work from July 2001. Unsteadiness and intellectual deterioration progressed and dysphagia then appeared. He was admitted to our hospital in September 2001. Neurological examination showed mild dementia, frontal release signs, and cerebellar ataxia. He could walk with the aid of a handrail. Soon after admission, he could not remain sitting. Less prominent myoclonic jerks were evoked by extrinsic stimulation from November 2001.

**Abbreviations:** DWI, diffusion weighted MRI; EEG, electroencephalogram; PRNP, prion protein gene; PrP, prion protein; PSWC, periodic sharp and slow wave complexes; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease



**Figure 1** Diffusion weighted MRI (DWI) was performed with single shot spin-echo echo-planar imaging using 1.5-T MR unit (Signa, GE Medical System, Milwaukee, WI, USA). Imaging parameters were as follows: 4999/104/1 (TR/TE/NEX), 5 mm section thickness with a 1 mm intersection gap, 128×128 matrix, 230 mm field of view, and a diffusion encoding strength (b value) of 1000 s/mm<sup>2</sup>. (A) Axial brain DWI of patient 1 showed abnormal high intensity in the head of the caudate nucleus, the putamen, the cingulate gyrus, and the insular cortex. Note that a wide range of the thalamus including the dorsomedial nucleus, the pulvinar, the ventral anterior nucleus, the ventral lateral nucleus, and the posterolateral nucleus were affected by the lesion. (B) Axial brain DWI of patient 2 showed abnormal high intensity in the head of the caudate nucleus, the putamen, and the cortical ribbon similar to patient 1. Note that a wide range of the thalamus including the dorsomedial nucleus, the pulvinar, the ventral anterior nucleus, the ventral lateral nucleus, and the ventral posterolateral nucleus were affected by the lesion.

He became akinetic and mute in December 2001. He died of pneumonia on 24 January 2002.

Cerebrospinal fluid analysis was normal except for an increased concentration of NSE (110 ng/ml) and the presence of 14-3-3 protein (++) . Three sequential EEGs showed no PSWCs during his illness. Diffusion weighted MRI showed an abnormal high intensity in the head of the caudate nucleus, putamen, and cortical ribbon (prominent in the cingulate gyrus, and insular cortex). Like patient 1, a wide range of the thalamus was also affected by the lesion (fig 1B). Genetic analysis of codon 129 of PRNP revealed VV and no point mutation was found. In the postmortem examination, spongiform changes, gliosis, and neuronal loss in the cortical ribbon were limited to deep layers and the laminar cortical structure was preserved except for the frontal lobe. These features were also present in the striatum, thalamus, and brainstem nuclei, and marked in the cerebellar granular layer with preserved Purkinje cells. PrP staining mainly showed plaque-like structures. No amyloid plaques were visible. Western blot analysis revealed type 2 PrP<sup>Sc</sup>.

## DISCUSSION

Our two patients exhibited the uncommon variant of sCJD with VV2. They started with cerebellar ataxia followed by dementia and became akinetic and mute five and six months respectively after the onset. Compared with the mean duration of 3.5 months from onset to becoming akinetic and mute of 116 Japanese typical sCJD with MM (calculated by the authors based on the data reported to Japanese CJD surveillance committee), the five and six months of our patients were relatively longer, but the difference was not statistically significant. Myoclonic jerk was less prominent, and no PSWCs were detected during their illness. These clinical characteristics coincided with those of sCJD with VV2 in Western countries,<sup>3</sup> the previous ataxic variant.<sup>6</sup> The pathological features of our patients also coincided with those of Western sCJD with VV2.<sup>3</sup> According to a report by Parchi *et al*, 16% of their sCJD subjects had VV2 and they

represented the second most common subtype. However, in Japan, sCJD with VV2 is extremely rare and only one sCJD with VV has been reported.<sup>5</sup> Of the 123 sCJD subjects with the genotype at codon 129 reported to the Japanese CJD surveillance committee, 116 subjects had MM, five had MV, and two (the present patients) had VV. These differences relate to the difference of the genotype at codon 129 in the normal population between Japan and Western countries; 92% for MM, 8% for MV, and 0% for VV in Japanese<sup>4</sup> v 37% for MM, 51% for MV, and 12% for VV in Westerners.<sup>3</sup>

Another characteristic of our patients was the DWI finding. Diffusion weighted MRI is sufficiently sensitive to show the lesions of CJD<sup>7,8</sup> and helped us diagnose our patients. Usually, hyper-intense lesions are shown in the cortical ribbon and the basal ganglia. “Pulvinar sign” and “Hockey stick sign” are famous MRI findings demonstrating thalamic lesions in vCJD,<sup>10</sup> and are included in the diagnostic criteria of vCJD.<sup>2</sup> In our patients, however, DWI showed hyper-intense lesions in the cortical ribbon, basal ganglia, and a wide range of the thalamus. These thalamic lesions involved the dorsomedial nucleus, the pulvinar, the ventral anterior nucleus, the ventral lateral nucleus, and the ventral posterolateral nucleus. This thalamic pattern is apparently different from that of vCJD. Various lesions in CJD are depicted on MRI; however, the thalamic lesion is rare. Only 7.4% of CJD patients demonstrated thalamic lesion and the changes were only mild.<sup>11</sup> We reviewed the DWI findings of our 24 CJD patients comprising 17 sporadic (including one MM2-thalamic based on Parchi’s classification<sup>3</sup> and one MV as uncommon variants), six familial (one substitution of arginine for methionine at codon 232, one substitution of lysine for glutamine at codon 200, and four substitutions of isoleucine for valine at codon 180), and one iatrogenic CJD (a recipient of cadaveric dura mater) in addition to the present two patients. We found basal ganglia lesions in three, cerebral cortical lesions in six, and both lesions in 15 patients, but could not find thalamic lesions. Including the present two patients, two of 26 (7.7%) CJD patients in our series had thalamic lesions on DWI. Schröter *et al*,<sup>11</sup> Finkenstaedt *et al*,<sup>12</sup> and Samman *et al*<sup>13</sup> described thalamic lesions but they were restricted to the dorsomedial nucleus and pulvinar. Bahn *et al*<sup>14</sup> and Collie *et al*<sup>15</sup> also described thalamic lesions in the dorsomedial nucleus and the pulvinar, respectively. The thalamic lesions that we demonstrated in our two patients involved a wider range of the thalamus than those described in previous reports.<sup>11–15</sup> Thalamic lesions that involved almost the entire thalamus were in both our patients and may be a characteristic of sCJD with VV2 rather than merely a coincidence, because such thalamic lesions have not been described before and sCJD with VV2 is extremely rare in Japanese.

Diffusion weighted MRI findings are not included among the major diagnostic criteria,<sup>16</sup> although DWI is more sensitive than EEG and can detect lesions at an early stage.<sup>17</sup> Even in cases of sCJD without the classical triad, we can make a correct diagnosis more easily if we know the specific imaging finding for a specific subtype. In the case of sCJD with VV2, which does not show prominent myoclonic jerks or PSWCs in the EEG, the characteristic thalamic lesions demonstrated in DWI may lead to an exact diagnosis. These characteristic thalamic lesions can also be an important clue to distinguish sCJD with VV2 from vCJD, because the major differential diagnosis of vCJD is sCJD without PSWCs.

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