Probable Sporadic Creutzfeldt-Jakob Disease with Valine Homozygosity at Codon 129 and Bilateral Middle Cerebellar Peduncle Lesions

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Abstract

We describe a 67-year-old Japanese man with probable sporadic Creutzfeldt-Jakob disease (CJD) who had valine homozygosity at codon 129, a rarity in the Japanese. T2-weighted magnetic resonance imaging (MRI) detected high-intensity lesions in the bilateral middle cerebellar peduncles and basal ganglia as well as cerebellar and cortical atrophy. He developed cerebellar ataxia and subsequent mental deterioration, myoclonus, and periodic synchronous discharge as shown in an electroencephalogram. Cerebrospinal fluid examination showed a high level of neuron-specific enolase and a positive immunoenzyme assay for the 14-3-3 protein. He died of pneumonia 10 months after the initial symptoms appeared. Whether or not the genetic polymorphism increased his susceptibility to sporadic CJD is not clear because valine homozygosity at codon 129 is less than 1% in the normal Japanese population. Although there is no convincing evidence in the present case, the MRI findings of cerebellar peduncle changes, which are rare in CJD, suggest a kind of degeneration, demyelination, or both.

Key words: cerebellar ataxia, codon 129 polymorphism, susceptibility

Case Report

A 67-year-old retired pharmacist was admitted to our hospital in January 1998 because of slowly progressive cerebellar symptoms of double vision, ataxic speech, and unsteady gait of 6 months duration. Just before admission, he became confined to a wheelchair due to severe gait disturbance. His past history showed he had Wallenberg’s syndrome in March 1996. External hemorrhoidectomy and appendectomy had been performed under spinal anesthesia respectively about 20 and 30 years earlier. He had had hypertension since age 50. He had no past history of blood transfusions or acupuncture. His father had died of heart failure, and his mother of myocardial infarction.

Physical examination at admission yielded the following data: blood pressure, 182/118 mmHg; temperature, 37.1°C; pulse rate, 88 beats/minute. No anemia, jaundice, or swollen lymph nodes were observed, nor abnormal findings for the lungs, heart and abdomen. His score on the Revised Version of Hasegawa’s dementia scale was 23 (full score 30), but evaluation was difficult due to severe ataxic dysarthria.

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Neurological examination revealed ataxic speech, truncal ataxia, severe limb ataxia, and normoreflexia in the lower extremities, but no pathological reflexes. There were no signs of limb muscle weakness or sensory disturbance. He was unable to stand or walk because of severe ataxia. Laboratory test findings were total bilirubin, 1.0 mg/dl (normal; 0.2–1.2); aspartate aminotransferase (AST), 33 IU/l (normal; 8–30); alanine aminotransferase (ALT), 30 IU/l (normal; 5–35); lactate dehydrogenase (LDH), 208 IU/l (normal; 100–225); blood urea nitrogen, 12 mg/dl; serum creatinine, 1.0 mg/dl; Na, 142 mEq/l; K, 3.8 mEq/l; Cl, 104 mEq/l; Ca, 9.4 mg/dl. Cerebrospinal fluid (CSF) findings showed a normal cell count, 61 mg/dl total protein (normal, 10–40); 67 mg/dl glucose (normal, 50–75); 88 ng/ml neuron-specific enolase (NSE) (normal, ≤10); and a positive immunoassay for the 14-3-3 protein. CSF cytology was class 2. Analysis of the PrP gene showed valine homozygosity at codon 129. He had no mutations at PrP codons 102, 105, 117, 145, 178, 180, 200, 210, 219, or 232. Single photon emission computed tomography detected diffusely decreased regional cerebral blood flow of 30–36 ml/100 g/minute with no perfusional defect.

Repeated MRI and angiography done before admission did not find any abnormalities, including in the cerebellum and basal ganglia, although his severe cerebellar symptoms slowly worsened. Cranial MRI on admission, 6 months after the initial symptoms appeared, showed bilateral hyperintensity in the caudate nuclei and putamina on T2-weighted images for the first time and isointensity on T1-weighted images without contrast enhancement (Fig. 1). Moreover, mild cerebellar atrophy had first been pointed out by the radiologist. However, cortical atrophy had not been noted at that time. Bilateral chronic subdural hematomas also were present. As his mental status had deteriorated slowly, we made the tentative diagnosis of possible prion disease based on clinical findings of progressive consciousness disturbance, ataxia of cerebellar origin, high NSE in the CSF, the absence of a family history, and MRI features. Intravenous hyperalimentation was started at the end of January due to worsening of his dysphagia and consciousness disturbance. A follow-up MRI study on the 42nd hospital day showed progressive atrophic changes in the cerebellum and basal ganglia, particularly in the caudate nuclei heads. In addition, the frontotemporal region of the cerebrum appeared atrophic. Clonazepam was administered to control myoclonus in his upper extremities, which developed in February. A follow-up EEG in April detected PSD (Fig. 2). The last MRI examination on the 114th day showed bilateral lesions in middle cerebellar peduncles (Fig. 3). Cortical atrophy, predominantly of the fronto-temporal region, was present, and his severe cerebellar atrophy had worsened. In addition, the putamina showed a high signal intensity on the T1-weighted images and isointensity on the T2-weighted sequences, probably because of the administration of total parenteral nutrition. He died of pneumonia in May 1998.

**Discussion**

Our Japanese patient presented cerebellar symptoms at onset followed by consciousness disturbance and myoclonus after 7 months and PSD after 9 months during a clinical course of about 10 months. In addition, none of the PrP gene mutations already reported were found. According to the recently established molecular basis for phenotypic heterogeneity of sporadic CJD, six different phenotypes are characterized by the size of the protease-resistant fragment of the pathological PrP (types 1 and 2) and homozygosity or heterozygosity for methionine or valine at codon 129 of the PrP gene (designated by MM1, MM2, MV1, MV2, VV1, and VV2). Zerr et al (8) reported 2 cases of VV1 patients and 15 cases of VV2 patients; VV1 patients differed from VV2 patients by younger age at onset (range of 23–31 years vs median of 62 years and range of 40–76 years) and by longer disease duration (range of 20–31 months vs median of 7.5 months and range of 2.9–15.7 years). Regarding this point, the present patient’s age at onset and disease duration was similar to those of VV2 patients. A necropsy, however, could not be performed on our patient because of hospital policy. Cerebellar ataxia at onset and hyperintensities in the basal ganglia, which were also seen in our case, were observed in 47% and 70% of VV2 patients, respectively. However, no VV2 patients had myoclonus or PSD in the EEG. On the other hand, Miyazono et al (9) reported that in Japanese sporadic CJD, the change in the PrP codon 129 affects the...
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Figure 2. EEG detected PSD at intervals of about 3.0–4.0 seconds.

Clinical course. They examined one CJD patient who had valine homozygosity and six CJD patients who had valine heterozygosity at PrP codon 129 (Val/Val and Met/Val CJD patients). For comparison, they also examined 13 sporadic CJD patients with methionine homozygosity at codon 129 (Met/Met CJD patients) and 7 GSS patients who had leucine instead of proline at PrP codon 102. In comparison to Met/Met CJD patients, Val/Val and Met/Val CJD patients had a relatively long clinical duration (a mean of 33 months) and ataxia at onset, but rarely PSD on their EEGs. The clinicopathological findings for Val/Val and Met/Val CJD were similar to those for GSS, but immunohistochemistry findings showed different PrP deposit distributions and morphologies.

There are significant differences regarding genetic polymorphism at PrP codon 129 in the populations of Japan, England, and Germany (1-4). In England and Germany where normal subjects with valine homozygotes make up more than 10% of the populations (3, 4), valine homozygosity at codon 129 may increase susceptibility to sporadic CJD. The frequency of valine homozygosity at codon 129 found for 179 normal, unrelated Japanese is much lower (no Val/Val, 15 Met/Val and 164 Met/Met) (1). Any predisposition to sporadic CJD therefore would be masked in Japan if a patient has valine homozygosity at PrP codon 129 (1), as did our patient. Whether his genetic polymorphism increased the risk of probable sporadic CJD remains a matter of speculation.

MRI findings for CJD are lesions such as cortical atrophy, cerebellar atrophy, and hyperintensity at the basal ganglia as seen on T2-weighted images (10–12). In the present case, cranial MR T2-weighted images already had revealed high signal intensities in the bilateral caudate nuclei and putamina before definite cognitive impairment developed. Moreover, brain MRI showed abnormal signal intensities in the bilateral middle cerebellar peduncles late in the course of the illness. To our knowledge, similar findings have never been reported for sporadic CJD. On the other hand, similar lesions in the

Figure 3. Cranial MRI showing bilateral lesions of the middle cerebellar peduncles as a high signal intensity on the T2-weighted image (arrowheads).
middle cerebellar peduncles are reported to be a radiological feature in chronic toluene intoxication, multiple system atrophy, portal-systemic shunt encephalopathy, and citrullinemia (5–7). In the case of chronic toluene intoxication, similar MRI findings are presumed to be demyelinating lesions (6). Regarding multiple system atrophy, the high intensity areas on the T2-weighted images, including the middle cerebellar peduncles, suggest degeneration and demyelination (7). Although there was no pathological evidence, the MRI features in this case suggest a kind of degeneration, demyelination, or both at the middle cerebellar peduncles.

We presented the case of a Japanese man with probable sporadic CJD who had a rare polymorphism of codon 129 Val/Val, and an additional rare finding of high intensity in the cerebellar peduncle on T2-weighted MR images.

References