A Unique Case of Sporadic Creutzfeldt-Jacob Disease Presenting as Progressive Supranuclear Palsy

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Abstract

We report a Japanese case of sporadic Creutzfeldt-Jacob disease (CJD) presenting as progressive supranuclear palsy. For 2 years after onset, neurological deficits had slowly progressed but neither myoclonus nor periodic synchronous discharge was observed. Diffusion-weighted image (DWI) showed unique high signal lesions in the bilateral frontal cortex, left parietooccipital and occipital cortices, but there was nearly no change eight months later. Needle biopsy revealed deposition of prion protein of a patchy/perivacuolar type with spongiform degeneration. Thus, the phenotype of sporadic CJD seems variable and DWI should be performed, even in atypical cases lacking the characteristics of CJD. (Internal Medicine 42: 195–198, 2003)

Key words: Creutzfeldt-Jacob disease, progressive supranuclear palsy, diffusion-weighted image, genetics, pathology, single photon emission computed tomography

Introduction

Sporadic Creutzfeldt-Jacob disease (CJD) is a fatal human transmissible spongiform encephalopathy. The diagnosis of CJD is usually confirmed by the presence of spongiform degeneration with deposition of prion protein (PrP), particularly in the cerebral cortex (1). Approximately, 90% of cases show common features such as subacute dementia, myoclonus, periodic synchronous discharge (PSD) on electroencephalogram (2), and neuronal protein (14-3-3, γ -enolase) in cerebrospinal fluid (CSF)(3), and usually die within a year of onset (2). However, there are various pheno-

types in the disease and the diagnosis of CJD is sometimes difficult. For example, some cases show symptoms like progressive subnuclear palsy (PSP) in the early stage and survive more than 2 years (4–6). To clarify this issue, recently the effectiveness of diffusion-weighted image (DWI) has been suggested(7–9). Some cases of CJD have been reported to show an abnormally high signal lesion on DWI in the initial stage of CJD(7–9).

Here, we describe a Japanese case of sporadic CJD presenting as supranuclear gaze palsy in the initial stage. In particular, this case showed unique abnormal lesions on DWI without any characteristics of CJD during the disease course of more than 2 years.

Case Report

A 56-year-old Japanese woman was in good health until two years before evaluation, when her family noticed that she had difficulty in walking at a normal speed. She gradually developed transient difficulties in initiating movement and postural instability walking in small steps. She had unexplained falls, especially backwards. From age 55, her functional deterioration with respect to speaking and handwriting became progressively more evident. She had no history of blood transfusion, or implanting of corneal or dura matter grafts.

On admission, her mini mental—state examination (MMSE) score was 22/30. She showed a mask-like face, supranuclear gaze palsy in the vertical sides, dysarthria, bradykinesia, and retrocollis. There were rigidities in the neck and right upper arm, dysdiadochokinesis, bradykinesia, freezing phenomenon on gait, postural instability, and reduced arm swings. Sensory examinations and deep tendon reflexes were normal. Cerebrospinal fluid analyses including neuron-specific enolase and 14-3-3 protein were normal. EEG showed diffuse θ wave without PSD. A 1.5 tesla mag-

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Received for publication July 17, 2002; Accepted for publication November 25, 2002

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Figure 1. SPECT using ^{123}I IMP (A) and diffusion-weighted MRI (B, C) at age 56. A: Diffusion-weighted MRI shows high signal lesions in the bilateral frontal cortex and left occipital cortex. B: SPECT image using ^{123}I -IMP shows that hypoperfusion corresponded to the abnormalities detected on diffusion-weighted MRI. C: Diffusion-weighted MRI performed eight months later. High signal lesions extended slightly, but were relatively limited to the cerebral cortex.

netic resonance imaging (MRI) revealed a mild atrophy in the tegmentum of the midbrain. Single photon emission computed tomography (SPECT) using ^{123}I -IMP showed hypoperfusion in the frontal cortex, left parietooccipital cortex and left basal ganglia (Fig. 1B). Although we suspected PSP, we tried treatment with levodopa-carbidopa 200 mg and additional selegiline 10 mg in a day. Her gait disturbance and postural instability improved and she could walk without stumbling. One month later, levodopa-carbidopa and selegiline were withdrawn due to a drug-induced fever. DWI performed two months later revealed high signal lesions in the bilateral frontal cortex, left parietooccipital and occipital cortices (Fig. 1A). Fast fluid attenuated inversion recovery (FLAIR) images showed slightly high signal lesions

corresponding to the abnormalities detected on DWI. Apparent diffusion coefficient (ADC) in the cerebral white matter and cerebral angiography were normal. Eight months later, the degree of parkinsonism and supranuclear gaze palsy became more severe and mental deterioration progressed to severe dementia (MMSE 0/30), but neither myoclonus nor PSD were observed. On DWI, abnormal high-signal lesions in the left cerebral cortex had extended a little (Fig. 1C). After informed consent, we performed needle brain biopsy from the left occipital cortex.

Microscopic examination disclosed marked spongiform degeneration consisting of mild gliosis and neuronal loss in areas with no physiological change of needle biopsy. In particular, there were massive patchy/perivacuolar PrP-type

Figure 2. Light micrographs of biopsied tissue from the patient at age 56 (A: HE stain, magnification $\times 400$, B: PrP immunostain, magnification $\times 400$). A: Marked spongiform change accompanied with neuronal loss and mild gliosis is shown. B: Perivacuolar type-PrP deposits are present.

deposits without florid plaque (Fig. 2). Molecular genetic analysis for prion protein gene (*PRNP*) revealed no mutation or methionine/methionine homozygosity (MM) at codon 129. We could not perform an immunoblot profile of PrP^{sc} due to there being too little material from the needle brain biopsy. Although she became bedridden three years from onset, she could still talk and eat by herself.

Discussion

The diagnosis of sporadic CJD in the present case was established by the presence of spongiform degeneration with patchy/perivacuolar-type PrP deposition in the cerebral cortex. The neuropathological features were identical to sporadic cases of CJD, but the clinical phenotypes and findings on DWI were quite unusual. Recently, signal-intensity changes on DWI were reported to reflect the histologic changes of CJD (7), and show the change in the early stage without any change on conventional MRI (9). The high signal lesion on DWI in the present study was seen in the initial stage without any clinical hallmarks of CJD. Interestingly, the slow extension of the lesion on DWI seems consistent with the slow progression of the clinical course. Compared with other cases, which showed rapid progression of clinical manifestation (7), the extension on DWI is much slower.

Thus, DWI might be effective in the diagnosis and the evaluation of the progression in CJD.

Although disturbance of vertical gaze occurs in 3–5% cases of CJD (10), a case showing clear L-dopa responsive parkinsonism and supranuclear gaze palsy at the clinical onset is uncommon. Kawasaki et al (5) reported a similar case that showed symptoms like PSP in the early stage and survived more than 4 years. They speculated that their case was the sporadic form of fatal insomnia because the pathology was similar to that of fatal insomnia, which showed a severely affected thalamus and a mutation in codon 178 of the *PRNP*. It is not clear whether the present case could be classified as sporadic form of fatal insomnia or not, because the thalamus was not investigated pathologically. However, we speculate that the thalamus may not be involved in the present case because there were no clinical manifestations such as sensory impairment or intractable pain and no lesion on DWI and SPECT. Vingerhoets et al (6) also reported a similar case of sporadic CJD that presented L-dopa responsive parkinsonism and diplopia. In that case, apoptosis in the substantia nigra without PrP deposit was revealed, and they speculated that L-dopa responsive parkinsonism was an early involvement of the nigrostriatal dopaminergic pathway. From that viewpoint, the initial clinical signs in the present study could not be explained without the involvement of nigrostriatal

dopaminergic pathway, and we speculate that there were subtle histological changes in that lesion.

A classification of sporadic CJD was proposed on the basis of the genotype at polymorphic codon 129 of *PRNP*, and the physiochemical properties of the protease-resistant core of the pathological PrP^{sc} (3, 11). The distinct PrP^{sc} isoforms are associated with different patterns of PrP deposition: type 1 is found in areas with diffuse PrP immunoreactivity and type 2 is associated with perivacuolar and plaque-like deposits (12). The present case revealed MM at codon 129 of *PRNP* that is seen in 96% of the normal Japanese population. Although it was difficult to identify the type of PrP^{sc}, we speculate that PrP^{sc} in the cortex in the present case might be that of type 2 because of the presence of perivacuolar and plaque-like deposits. However, the classification should be determined by Western blot analysis in other areas, because there are some cases with the co-occurrence of different types of PrP^{sc} in the same brain (12).

The present case showed typical signs of PSP at clinical onset. The high signal signs on DWI made us reconsider the diagnosis, which was subsequently proved to be sporadic CJD. Thus, the phenotype of sporadic CJD seems to be more variable and DWI should be performed, even in atypical cases presenting as L-dopa responsive PSP or lacking the characteristics of CJD.

Acknowledgements: The authors are indebted to Katsumi Douura (Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University) for screening 14-3-3 protein.

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