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Neurol Neuroimmunol Neuroinflamm
2015;2:e53; doi: 10.1212/NXI.0000000000000053

MULTIFOCAL HITS FOR PROPAGATION OF PRION PROTEIN IN SPORADIC CREUTZFELDT-JAKOB DISEASE

OPEN

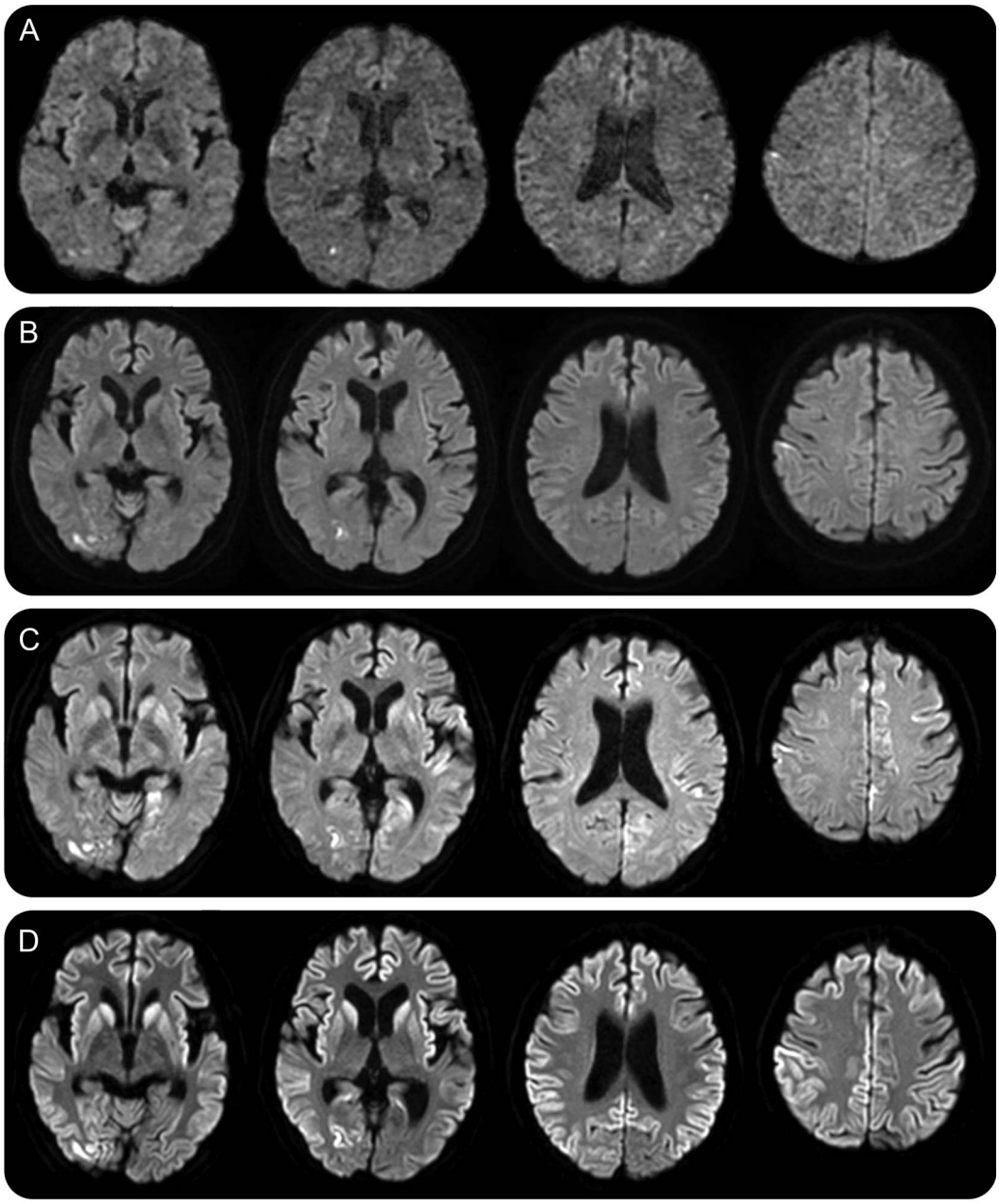
A 60-year-old woman presented with discomfort during respiration and anxiety. One month later, she developed dysarthria and unsteadiness of gait that gradually progressed over 3 months. She was referred to our affiliated hospital. A neurologist noted muscle rigidity, parkinsonian gait, and bradyphrenia, but her general cognitive function was preserved, with a Mini-Mental State Examination (MMSE) score of 29/30. At this time, diffusion-weighted imaging (DWI) demonstrated multifocal spotty hyperintense signals in the cerebral cortex (figure, A). Six months later, she became unable to stand or walk because of limb and truncal ataxia, and she was admitted to our hospital. On admission, she showed marked cognitive decline (MMSE score of 14/30) and apathy. Neurologic examination revealed cerebellar ataxia and parkinsonism such as rigidity and akinesia, but myoclonus was not present. Laboratory findings were all normal except for those of the serologic tests for syphilis (STS) and the *Treponema pallidum* latex agglutination (TPLA) test. Both the STS and the TPLA test showed positivity for syphilis with a low titer, whereas the TPLA test of CSF showed negative results, indicating self-limited syphilis. DWI findings were not significantly different from those 5 months ago (figure, B). EEG showed 5-Hz slow waves but not periodic sharp wave complexes. Two months after admission, she developed urinary tract infection and subsequently severe inspiratory stridor with a high-pitched sound. Laryngeal fiberscope showed that the bilateral vocal cords were fixed in the midline position. After tracheostomy, her stridor disappeared. However, her condition deteriorated rapidly. She became mute and subsequently developed myoclonus. At this time, CSF analysis revealed a total tau protein level of 246 pg/mL (cutoff for the diagnosis of sporadic Creutzfeldt-Jakob disease [CJD] >1,300). The 14-3-3 protein was not detected in the CSF. However, RT-QUIC (real-time quaking-induced conversion) assay, which has a sensitivity of 83.3% for CJD,[1] showed positivity for CJD. EEG showed 1-Hz periodic sharp wave complexes. DWI revealed hyperintense signals slightly spread (figure, C) and extended throughout the cerebral cortex and basal ganglia 4 months later (figure, D). The diagnosis of sporadic CJD was made on the basis of progressive dementia and myoclonus, EEG findings, and hyperintense lesions detected by DWI. Analysis of the prion protein gene *PRNP* showed no mutations. The polymorphic codon 129 was homozygous for methionine and codon 219 was homozygous for glutamate.

Discussion. CJD is caused by the propagation of the pathologic prion protein. However, it is unclear whether it starts from a single site in sporadic cases. The present case showed a few remote, spotty lesions on DWI early in the course, suggesting that lesions emerge simultaneously from multiple sites and not from a single seed in sporadic CJD cases.

The national surveillance in Japan showed that the annual incidence rate of sporadic CJD is less than 1 per million population.[2] Hence, it is extremely rare to take MRIs incidentally early in the course of sporadic CJD. One sporadic case has been described as showing hyperintense lesions on DWI before the onset of symptoms. These lesions appeared ribbonlike, not spotty as in our case[3]; however, the sensitivity of MRI in that case might have been lower than in our case. It has been suggested that the mechanisms underlying hyperintense signals on DWI in CJD are spongiform changes and neuronal loss,[4] although others pointed out that CJD-related pathologic changes correlated with only apparent diffusion coefficient but not DWI hyperintense signals.[5] Hence, our case might show that CJD-related pathologic changes emerge spontaneously from multifocal sites and subsequently propagate locally in sporadic CJD.

Our patient developed bilateral vocal cord paralysis 1 year after she felt discomfort during respiration. It is uncertain whether this symptom was due to a subtle paresis of the vocal cords. In 2 previous cases, the patients developed bilateral vocal cord paralysis during the course of CJD, which was confirmed by laryngeal fiberscope.[6,7] Findings on autopsy[6] and EMG of the intrinsic laryngeal muscles[7] suggest that the vocal cord paralysis in those patients was induced by upper lesions of the motor nucleus of ambiguus, which was preserved in both patients. Our patient showed predominantly extrapyramidal and cerebellar symptoms early in the course. However, she was aware of a subtle discomfort during respiration, which might be caused by lesions of the respiratory

Figure Serial diffusion-weighted imaging of patient



Diffusion-weighted imaging (DWI) carried out 4 months after disease onset (A) and 6 months later (B) showed spotty hyperintense signals in the right occipital and right parietal cortices. Follow-up DWI 1 year after disease onset demonstrated the spread of the hyperintense signals (C). Four months later, DWI demonstrated hyperintense signals extending throughout the cerebral cortex and basal ganglia (D).

center. This implies that lesions were multifocal initially, which is consistent with the DWI findings of multiple lesions. Our case supports multifocal hits and local propagation as the mechanism of sporadic CJD progression.

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Acknowledgment: The authors thank Dr. Kitamoto for genotyping and Dr. Satoh for analyses of CSF biomarkers.

Study funding: This work was supported from the Research Committee on Surveillance and Infection Control of Prion Disease, funded by the Ministry of Health, Labor and Welfare, Japan.

Disclosure: K. Kasuga has received research support from Japan Society of Promotion of Science. R. Takeuchi, T. Takahashi, N. Matsubara, R. Koike, and A. Yokoseki report no disclosures. M. Nishizawa has received research support from Takeda; Eisai;

Kissei; Dainihon-Sumitomo; Ono; Tanabe-Mitsubishi; MSD; Ministry of Health, Labor and Welfare, Japan; and Japan Society for the Promotion of Science. Go to Neurology.org/nn for full disclosures. The Article Processing Charge was paid by the authors.

Received August 29, 2014. Accepted in final form November 4, 2014.

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