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LETTER TO THE EDITOR

Familial Creutzfeldt-Jakob Disease with M232R Mutation Progressed Slowly like Alzheimer's Disease

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Dear Editor,

Creutzfeldt-Jakob disease (CJD) is a typically fatal neurodegenerative disease, and 90% of CJD patients die within 1 year of diagnosis. Of all CJD cases, 10−15% are autosomal dominant disorders of the prion protein gene (*PRNP*) in chromosome 20, classified as genetic or familial CJD.

Familial CJD has an younger onset and has a lengthier disease progression than sporadic CJD.[1] In the past, clinical patterns of CJD with M232R mutation (CJD232) were like sporadic CJD. However, CJD232 cases that reveal longer clinical courses and periodic sharp and wave complexes distinctively found in an eletroencephalography (EEG) are not observed have been recently reported.[2] The authors report cases of patients diagnosed with familial CJD revealed slow progress like Alzheimer's disease.

A 62-year-old male patient visited our hospital because he had gait disturbance 2 years ago and symptoms of memory deterioration, etc. occurred 1 year ago. In his medical history,

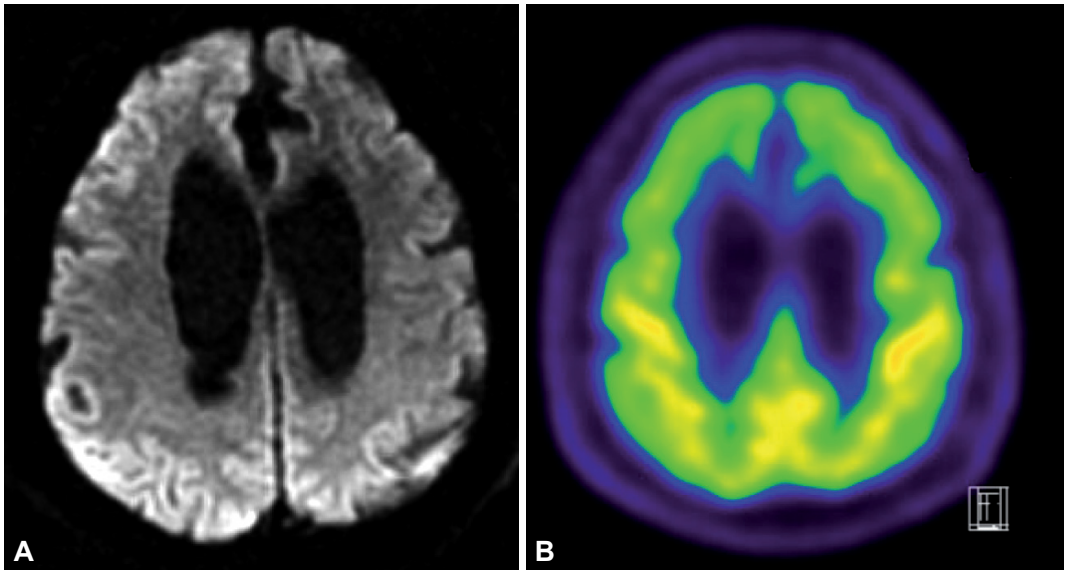

Fig. 1. Initial DWI and 18F-fluorodeoxyglucose PET CT. A: DWI demonstrates cortical high-signals. B: PET study shows diffuse hypometabolism of bilateral frontoparietal lobes. DWI: diffusion weighted image, PET: positron emission tomography.

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he had hemorrhagic brain contusion in the left frontal lobe due to injury 5 years ago. Besides that, no particulars and other family history were found.

When the patient visited the hospital, he had alert consciousness, and no focal neurologic deficit was observed. Spontaneuos speech deteriorated, and he scored 23 points in Mini-Mental Stage Examination (MMSE) and 1 point in Clinical Dementia Rating (CDR). Education duration was 6 years. Disorientation of time, cathexis dysfunction and memory retrieval deterioration were found. In an EEG, background activity was reduced, but a sharp wave was not observed. In terms of T1- and T2-weighted brain magnetic resonance images, the frontal lobe and temporal lobe revealed cortical atrophy, and in the diffusion-weighted MRI, a lesion with high-signal intensity was observed in the overall cortex (Fig. 1A). 18F-fluorodeoxyglucose positron emission tomography in the (FDG PET) CT, diffuse hypometabolism findings were observed in the frontal, parietal and temporal lobes in both sides (Fig. 1B). With the clinical aspect, Alzheimer's disease was considered, but in the cerebrospinal fluid examination that was performed because the lesion with high-signal intensity was observed in the diffusion-weighted image. 14-3-3 protein test was weakly positive, and *PRNP* genetic test revealed Met232Arg mutation (Fig. 2). In *PRNP* genetic test conducted in son and daughter of the patient, the same mutation was identified as well.

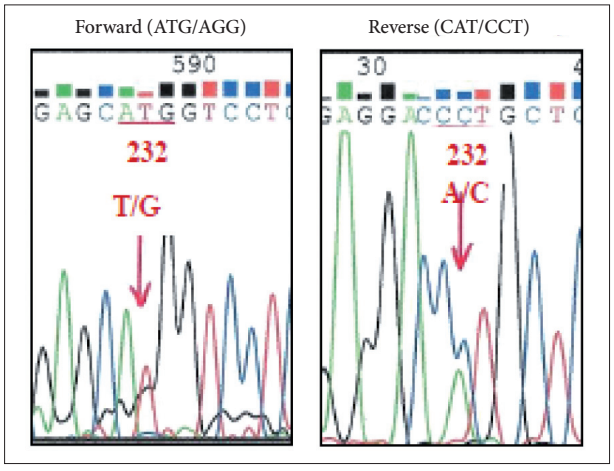

Fig. 2. DNA sequence at codon 232 of the prion protein gene. There is a point mutation causing a substitution of ATG (Methionine) by AGC (Arginine) at codon 232.

After 2 years, the patient was hospitalized again, mainly complaining of intermittent myoclonus. After discharge from the hospital, he did not walk at all, and focal neurologic deficit was not noticeable except atrophy in both lower extremities. He scored 20 points in MMSE and 1 point in CDR, which did not reveal significant difference in cognitive function compared to previous tests. Regarding an EEG, no sharp wave was observed, and in the diffusion-weighted MRI, the lesion with high-signal intensity in the overall cortex as it was 2 years ago (Fig. 3A). T1- and T2-weighted MRI and 18F-FDG PET CT did not reveal significant change compared to those in the past (Fig. 3B).

According to literature that analyzed clinical phenotypes of 20 CJD232 patients, 15 patients progressed in rapid type, and 5 patients progressed in slow type. Mean time from ini-

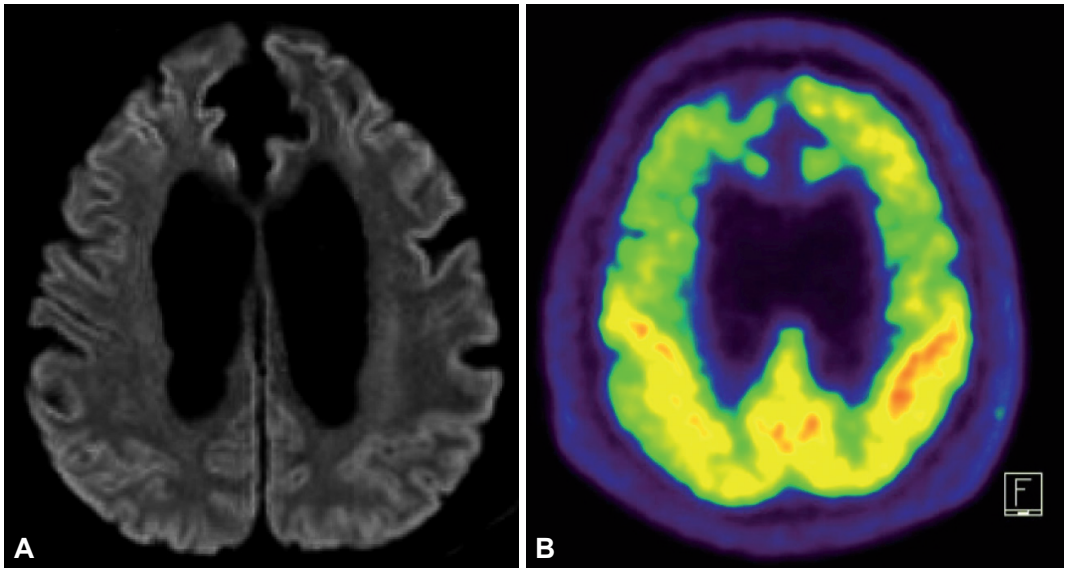

Fig. 3. DWI (A) and 18F-fluorodeoxyglucose PET CT (B) obtained 26 months later. Compared with previous DWI and PET CT, there are no interval change. DWI: diffusion weighted image, PET: positron emission tomography.

tial symptom to akinetic mutism was 3.1±1.5 months in the former type and 20.6±4.4 months in the latter type. Regarding mean time to reveal myoclonus, it took 2.4±1.8 months in the rapid type and 15.3±12.3 months in the slow type. Two different phenotypes were revealed in patients with accurately identical genotype. There were some cases that dementia with Lewy bodies was identified in the result of the final pathological autopsy of patients suspected of CJD with M232R mutation.[2]

The patient in the current case was assumed as Alzheimer's disease because he was 65 years old with cognitive deterioration that progressed 1 year ago at the first hospitalization and the patient did not have abnormal findings in psychataxia, myoclonus, and EEG. As CJD was suspected due to the lesion with high-signal intensity in the diffusion-weighted MRI, identified accidentally, he received cerebrospinal fluid examination and was finally diagnosed with familial CJD. However, he is now revealing slower clinical progress than the slow type of patients with CJD232 reported so far, and his image findings revealed no changes for 26 months, that is exceptional compared to the progress period published in other literature. In the future, it will be necessary to conduct more studies to identify if M232R mutation contributes to familial CJD, or studies on variation factors of Alzheimer's disease.

Conflicts of Interest

The authors have no financial conflicts of interest.

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