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1 *Letter to the Editor*

2 **MM2 cortical form of sporadic Creutzfeldt-Jakob disease without**
3 **progressive dementia and akinetic mutism: A case deviating from current**
4 **diagnostic criteria**

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26 **Keywords** : Sporadic Creutzfeldt-Jakob disease; Corticobasal syndrome; MM2-cortical form.

1 **Dear Editor,**

2 Sporadic Creutzfeldt-Jakob disease (sCJD) is classified into six types based on codon 129 polymorphism in
3 the *PRNP* gene and the protease-resistant prion-related protein, PrP [1,2]. This classification corresponds
4 well with the clinical course and the pathological findings. MM2-cortical type sCJD (MM2C-sCJD) is
5 clinically characterized by slow progressive dementia, increased levels of 14-3-3 protein in the cerebrospinal
6 fluid (CSF), and no periodic synchronous discharge (PSD) in electroencephalography [3]. We report the case
7 of a patient presented with chronic progressive cortical symptoms. Based on the initial clinical findings,
8 corticobasal syndrome (CBS) was suspected although he did not develop akinetic mutism during the lifetime.
9 The postmortem pathological and anatomical findings confirmed MM2C-sCJD. As per the existing
10 diagnostic criteria, our case was difficult to diagnose during the patient's lifetime. Therefore, this is an
11 important case for considering future revisions of the diagnostic criteria for MM2C-sCJD.

12 **1. Case report**

13 We report the case of an 88-year-old male without a family history of any neuromuscular disease but with a
14 history of spinal stenosis and gastric cancer. He was born in Hokkaido and lived in Tokyo for about 40 years
15 before returning to Hokkaido. During 1970-80, he traveled to five European countries including the UK. In
16 May, 2017, he started having difficulty in using the right hand due to tremors. He also complained about
17 instability during walking in October. He visited a local doctor in December, and the brain diffusion-weighted
18 MRI showed high intensity in the left and right parietal cortex (Figure 1A-D). He was referred and admitted
19 to our hospital. At first visit, his neurological findings revealed bradykinesia and upper limbs postural tremor,
20 positive right Barré arm sign, distal muscle weakness of the right leg, mild cogwheel rigidity on both arms,
21 bilateral two points discrimination, graphesthesia, right limb-kinetic apraxia, and right limping and unstable
22 gait. There was no apparent decline in the cognitive functions; the Mini-Mental State Examination (MMSE)
23 and Frontal Assessment Battery (FAB) scores were 29 and 15 respectively. The CSF levels of phosphorylated
24 tau, total tau, and 14-3-3 proteins were normal, and RT-QuIC findings were negative. *PRNP* gene analysis
25 showed no mutations and methionine homozygosity at codon 129. No decrease in the accumulation of the
26 tracer was observed in dopamine transporter scintigraphy and ¹²³I-MIBG myocardial scintigraphy

1 respectively. Levodopa administration had no effect on bradykinesia or walk deficit. The patient was
2 discharged without any improvement and was followed up at the outpatient clinic. In July, 2018, he fell in
3 his home and was re-hospitalized. The neurological findings were not markedly different from the previous
4 ones, bilateral two points discrimination, graphesthesia, limb-kinetic apraxia and Parkinsonism continued,
5 and although the gait worsened, there was an improvement in walking due to rehabilitation and he was able
6 to walk with the help of a walker. His cognitive functions showed slight deterioration, the MMSE score was
7 26 and the FAB score was 13. We performed a second lumbar puncture, although the CSF levels of 14-3-3
8 protein, total tau protein were normal, and RT-QuIC findings were negative. Based on the WHO diagnostic
9 criteria, National CJD Research and Surveillance Unit criteria, and European MRI-CJD Consortium criteria,
10 the patient was negative for prion disease. However, he met the clinical criteria for CBS according to
11 Cambridge criteria and possible CBD as per Armstrong's clinical criteria [4-8]. His right-dominant dystonia
12 exacerbated in September, 2018, and aphasia developed in October. In January, 2019, MRI was re-examined.
13 It was difficult to make a rigorous comparison due to differences of magnetic field strengths, but 1.5T-MRI
14 re-examination showed the possibility of slight extension of the abnormal cortical lesions with swelling
15 (Figure 1E-H). There were no fever or meningeal signs that should be considered for meningoencephalitis at
16 this time. We performed EEG but found no evidence of epileptic seizures. Anxiety was observed in February
17 and expanded hypertonia made oral intake difficult. Sedative was administered in March, and the patient died
18 due to the worsening of aspiration pneumonia in April, 2019. An autopsy was performed with the consent of
19 the family. Before autopsy, one hour after death, a lumbar puncture was performed again and 14-3-3, total
20 tau protein, and RT-QuIC findings in the CSF were positive.

21 Macroscopically, the brain weight was 1,075 g without cerebral cortical atrophy except for mild frontal
22 atrophy. In histological findings, large and small vacuoles (spongiform changes) were observed mainly in
23 the gray matter of the cerebral cortex, basal ganglia, and thalamus (Figure 1I, K, M). Perivacuolar PrP
24 deposits were confirmed by immunostaining and corresponded to large vacuoles (Figure 1 J, L, N). There
25 were synaptic-type deposits around the spongiform changes (Figure 1 J, N). The cerebellum and brainstem
26 were normal, and the number of cells in the inferior olivary nucleus was in the normal range (Figure 1 O, P).

1 A few senile plaques (A β) were also observed. The western blotting result was positive for MM2, which
2 confirmed MM2C-sCJD diagnosis (Figure 1 R, c) [11].

3 **2. Discussion**

4 We reported the case of a patient with MM2C-sCJD, pathologically characterized by slow progressive
5 cortical symptoms without progressive dementia or akinetic mutism within 15 months from onset. There is
6 also a case report of sCJD-CBS who was alert and her orientation was maintained at the first consultation,
7 although no similar long-term dementia-free sCJD is found as far as we are aware [9].

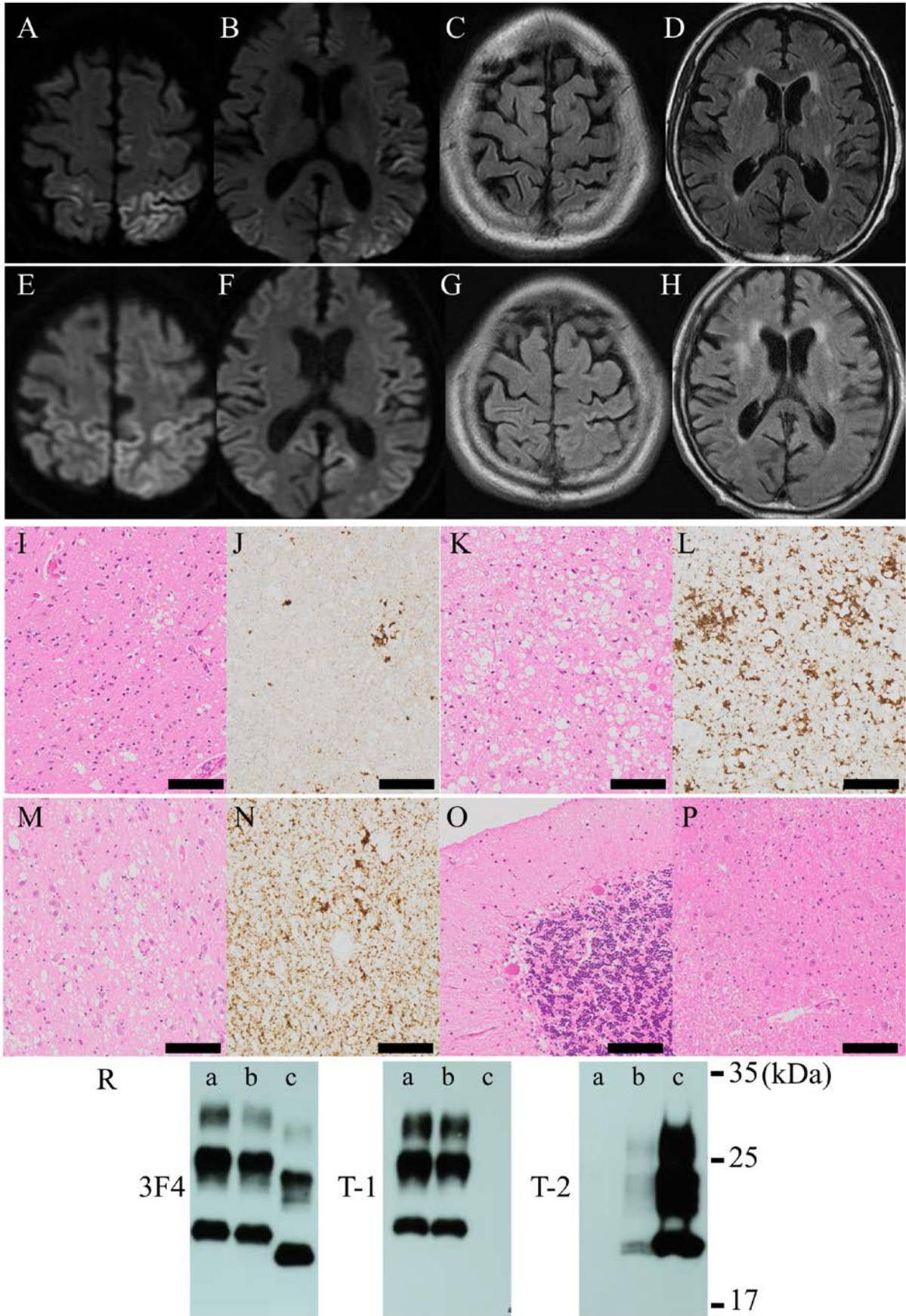
8 Patients showing clinical features of CBS and pathological features of sCJD are defined as sCJD-CBS. Nine
9 cases of sCJD-CBS, which corresponds to 1.8% of the total CJD cases were reported from the Australian
10 CJD registry [9]. Their median disease duration was 5 months, which is shorter than CBD-CBS. Besides, the
11 initial symptom of CBD-CBS is clumsiness, whereas, for sCJD-CBS the initial symptom is the cortical
12 sensory deficit. In the majority of the sCJD-CBS cases, the period from onset of symptoms to death was
13 about six months, but an MV2-CJD case presented with CBS survived for 24 months [10]. In our case, the
14 patient was negative for 14-3-3 protein when alive, but postmortem analysis revealed high levels of total tau
15 protein in the CSF. The patient did not meet any of the sCJD criteria during his lifetime, but MRI
16 abnormalities, which were consistent, and the postmortem CSF findings were compatible with the diagnosis.

17 **3. Conclusions**

18 In our case, the patient did not show progressive dementia, and no muteness was observed at least 15 months
19 from onset. Besides, no electroencephalographic PSD was confirmed during the course, and the PrP tests
20 were positive only in the postmortem cerebrospinal fluid. On the other hand, brain MRI recognized cortical
21 abnormalities throughout the course. Moreover, in our case, the current prion disease diagnostic criteria failed
22 to diagnose the disease during the patient's lifetime. Establishment of specific clinical diagnostic criteria for
23 MM2C-type sCJD is required.

24

1 **Figure 1**



1 **Brain MRI and histological findings.** (A-D) Brain 3T MRI acquired 7 months after the onset of initial
2 disease symptoms. Diffusion-weighted MRI revealed high-intensity lesion in the parieto-occipital cortex (A,
3 B), and relatively weak intensity lesion was observed in the fluid-attenuated inversion recovery images (C,
4 D). (E-H) Brain 1.5T MRI acquired 21 months after the onset of initial symptoms. Compared to the previous
5 images, these images show extended high-intensity lesions (E, F), and swelling of the parieto-occipital cortex
6 (G, H). (I-P) Microscopic findings of frontal cortex (I, J), occipital cortex (K, L), thalamus (M, N), cerebellar
7 cortex (O) and inferior olivary nucleus (P) with Hematoxylin & eosin staining (I, K, M, O, and P) and anti-
8 PrP immunostaining using 3F4 antibodies (J, L, N). Scale bar = 100 μ m. In frontal cortex and thalamus, small
9 vacuoles are mainly observed and large vacuoles are interspersed at several places (I, M). There are diffuse
10 synaptic-type deposits and a few perivacuolar PrP deposits around the large vacuoles (J, N). In the occipital
11 lobe, large vacuoles and small vacuoles are markedly observed with a tendency to fuse (K), and there are
12 perivacuolar PrP deposits around the fusing vacuoles (L). The cerebellum was well maintained with little
13 damage (O) and the number of cells in the inferior olivary nucleus was normal (P). (R) Western blot analysis
14 using 3F4 antibodies, Tohoku-1 (T-1), and Tohoku-2 (T-2) [11]. Brain homogenate sample from MM1
15 patients (a) and MM1 + 2 patients (b), and the current patient (c). Panels showed type 2 PrP^{sc}, with 19kDa
16 unglycosylated band in the current patient.

17

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21 and Welfare of Japan.

22

23 **Ethics approval and consent to participate**

24 This study was conducted with the approval of the Ethics Committee of Hokkaido University Hospital and
25 Nishimaruyama Hospital. The study was performed in accordance with the ethical standards laid down in

1 the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the
2 patients' families prior to their inclusion in the study.

3

4 **Declaration of Competing Interest**

5 The authors declare that they have no competing interests.

6

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