Dementia and Delirium in 4 Patients With Machado-Joseph Disease
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Background: Machado-Joseph disease (MJD; spinocerebellar ataxia type 3) is a hereditary neurodegenerative disease caused by mutation of the MJD1 gene. Patients with MJD usually present with cerebellar ataxia, external ophthalmoplegia, pyramidal and extrapyramidal signs, and muscle wasting. However, it has been reported that these patients do not demonstrate dementia.

Case Description: We noticed symptoms of dementia and delirium in 4 patients with MJD. The symptoms included abnormal behavior, excitement, an uncooperative attitude, crying, disorientation, slow thought processes, hallucinations, and delusions. These symptoms were observed in patients with a relatively young onset age, and after a long clinical course. In these patients, the CAG repeat length in the MJD1 gene was much longer compared with the mean repeat length found in patients with MJD. On electroencephalographical examination, they showed slow background activity, but computed tomography and magnetic resonance imaging scans showed no cerebrocortical atrophy. Neuropathological findings in 2 patients revealed a normal cortical structure on conventional morphological examination, but at immunohistochemical examination, we found abnormal staining by an antipolyglutamine antibody in the cerebrocortical neuronal nuclei.

Conclusions: Symptoms of dementia and delirium in patients with MJD could occur in the late stages, and they might be caused not by loss of cerebrocortical neurons, but by their dysfunction.

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MACHADO-JOSEPH disease (MJD; spinocerebellar ataxia type 3) is the most common form of hereditary spinocerebellar degeneration in Japan,1 Germany,2 and the United States.3 The abnormal expansion of CAG repeats in the MJD1 gene on chromosome 14q32.1 has been identified as the causative mutation.4 The cardinal symptoms of MJD are cerebellar ataxia, external ophthalmoplegia, pyramidal signs, dystonia, rigidity, bradykinesia, fasciculation, and muscle wasting.5-9 The neuropathological findings of MJD consisted of degenerations in the substantia nigra, dentate nucleus, pontine nuclei, cranial nerve nuclei, spinal anterior horns, Clarke columns, globus pallidus, and subthalamic nucleus.6,10,11 With regard to mental activity in patients with MJD, it can be said to be preserved.8,9

We recently examined 4 patients with MJD revealing similar characteristic symptoms of dementia and delirium, and 2 of these patients had a neuropathological examination. Here we describe details of the dementia and delirium observed in the patients with MJD, brain computed tomography (CT) and magnetic resonance imaging (MRI) findings, electroencephalography (EEG) findings, and neuropathological findings.

In the affected regions of the MJD brain, we found intranuclear inclusions,12 similar to those in other polyglutamine diseases,13-15 that were due to elongated CAG repeats in the abnormal gene. Even in the cerebral cortex, which was reported as spared by conventional microscopic examination, immunohistochemical examination using antipolyglutamine antibodies of the MJD brain showed intranuclear stainings.16

We discuss the relevance of these mental symptoms in patients with MJD, and the mechanism causing these symptoms based on immunohistochemical examination of the MJD brain.

REPORT OF CASES

CASE 1

In 1976, a 26-year-old woman reported experiencing ataxic gait and a speech disturbance subsequently developed. In 1988, she was admitted to Niigata University Hospital, Kashiwazaki, Japan. Her mental state was normal (Wechsler Adult Intelligence Scale [WAIS] score: verbal IQ, 93; performance IQ, 74; and total IQ, 84). Ocular movement...
was limited to upward motion, with horizontal gaze nystagmus. Muscle power was normal, but muscle atrophy and fasciculation were noted in her face and tongue. Limb and truncal ataxia were obvious. She could not walk without assistance. Dystonia was observed in her face and right big toe. Her tendon reflexes were exaggerated, and Babinski sign examination was positive. A brain MRI showed atrophy of the pons and cerebellum.

In March 1991, she was admitted to our hospital. Her mental state was still normal. Ocular movement was limited to lateral, in addition to upward directions. She was experiencing dysphagia and bradykinesia.

During November 1991, the patient cried at nighttime and had nightmares. In April 1993, she was noted on occasion to reject useful advice from the nurses. In July 1994, she was noted to speak loudly and become excited in the hallway at nighttime. At that time, her score on the revised version of the Hasegawa dementia scale (HDS-R, mental examination method commonly used in Japan with a scale up to 30) was 29 of 30. In February 1995, she was again observed speaking loudly, and rejecting advice from the nurses at nighttime, but the next day, she did not remember anything. From June to August, her psychotic state was labile. She would sometimes become excited, then cry or speak loudly and aggressively. She also repeatedly experienced delusional episodes. Doses of 100 mg of chlorpromazine had a mild effect on these symptoms. By 1999, her mental state had deteriorated, and she could not be examined using the WAIS. Her HDS-R score was 12 of 30. Background activity on EEG was 7 Hz. In 2000, her mental activity decreased, and it was difficult to evaluate her using the HDS-R scale. In the daytime, she was sleepy, exhibiting a slowing of the thought processes, and she sometimes cried. She died in October 2001 of sepsis following pyelonephritis. A year before her death, a brain MRI showed no cerebrocortical atrophy.

Her elder sister, younger brother, mother, grandfather, and great-grandfather had the same disease. Molecular analysis of her MJD1 gene revealed that she had an expanded allele (79 and 14 repeat units; normal, 14-38).

CASE 2

A 46-year-old man, the younger brother of the patient in case 1, reported experiencing gait and speech disturbance at age 27 years in 1979. In 1987, he was admitted to Niigata University Hospital. His mental activity was normal (WAIS score: verbal IQ, 97; performance IQ, 72; and total IQ, 86). He visited our institution with eyelid retraction, upward gaze palsy, horizontal gaze nystagmus, dysarthria, facial weakness, limb atrophy, dystonia in both big toes, limb and truncal ataxia, ataxic gait, hyperreflexia, and Babinski sign. A brain MRI revealed pontine atrophy and enlargement of the fourth ventricle.

In August 1990, he was admitted to our hospital. He was again experiencing dysphagia, bradykinesia, fasciculation in his face, hypotonia in the upper limbs, spasticity in the lower limbs, and pollakusia.

In October 1996, he reported having persecution delusions. In May 1997, he took off his undershirt and played with his stool. He sometimes experienced visual hallucinations and exhibited abnormal behavior (eg, stripping himself of his clothes, getting into another patient’s bed). He sometimes became excited and cried loudly. Administration of 50 mg of chlorpromazine had a mild effect. In March 1998, he died of a respiratory infection.

Neuropathological examination revealed neuronal degeneration in the globus pallidus that was more severe in the medial segment, subthalamic nucleus, substantia nigra, pontine nucleus, reticular formation, locus ceruleus, and dentate nucleus—all of which are comparable with the neuropathological findings in those with MJD. On immunohistochemical examination using a monoclonal antibody (1C2), which recognizes specifically expanded polyglutamine stretches, labeling in the neuronal nuclei appeared as small inclusions with occasional staining of the nucleoplasm in a diffuse or finely granular pattern. Some neuronal nuclei showed only diffuse staining without obvious inclusion formation. Nuclear labeling was observed in the thalamus and in cerebrocortical layers V and VI (Figure, A), as well as in the affected central nervous system regions mentioned above. In the frontal lobe, nuclear pathological abnormalities appeared in approximately 0.6% of neurons, predominantly involving pyramidal cells. The CAG repeats of the patient’s MJD1 gene were expanded to 77 and 19.

CASE 3

A 46-year-old woman reported difficulty in standing up at age 16 years in 1970, and her gait subsequently became unstable. In May 1993, she was admitted to our hospital. Her mental state was normal (HDS-R score, 28/30). She had a limitation of ocular movement in all directions; horizontal gaze nystagmus; dysphagia; dysarthria; muscle atrophy and limb weakness; dystonia in the forehead, fingers, and big toes; ataxia in the limbs and trunk; hyperreflexia; Babinski sign; and urinary disturbance. A brain MRI showed atrophy of the pons and cerebellum. In 1994, her verbal IQ on WAIS was mildly decreased to 67.

In August 1996, she frequently requested unnecessary support from the nurses. In October, she sometimes became excited and cried out loudly. In August 1998, she frequently cried, and showed slowing of the thought process. Chlorpromazine (as much as 375 mg) had a mild effect. She died in February 2000 of a respiratory infection.

Neuropathological findings showed typical neuronal degeneration compatible with that seen in patients with MJD. Neuronal intranuclear inclusions in the cerebral cortex, thalamus, and microscopically affected central nervous system regions, were stained with antipolyglutamine antibody. Although the distribution pattern of polyglutamine accumulation in the neuronal nuclei was similar to that of the patient in case 2, the accumulation appeared (in addition to aggregate form) as a diffuse pattern in the neuronal nuclei (Figure, B), and extended to more neurons (about 4.2% of neurons in the frontal lobe), including small neurons in the cerebrocortical layers V and VI.

Her mother, grandmother, 2 uncles, 2 aunts, and 1 cousin had the same disease. The CAG repeats of her MJD1 gene were expanded to 75 and 14.

CASE 4

A 51-year-old man complained of gait disturbance at age 36 years in 1983. Thereafter, he noticed speech disturbance, and later, urinary disturbance. In April 1992, he was...
admitted to our hospital. His mental state was normal (HDS score; 32.5/32.5). He had upward gaze limitation, horizontal gaze nystagmus, dysphagia, and dysarthria. Fasciculation was found in his face. His muscle tone was hypotonic. Limb and truncal ataxia was found, and walking was possible only with assistance. Deep tendon reflexes were exaggerated, and examination for Babinski sign was positive bilaterally.

In August 1996, he was readmitted to our hospital. His mental activity was still normal (HDS-R score; 29/30). Ocular movement was limited in all directions. He developed bradykinesia, dystonia in his face and in both big toes, and urinary disturbance. He was unable to walk. A brain MRI revealed atrophic findings in the brainstem and cerebellum.

In November 1996, he began to feel disoriented in his room at night, and on another occasion at night, he left the hospital. The next day, he did not remember what had happened. The following month, he insisted that he had to visit a family member in another hospital at nighttime. In January 1997, he set off a foam extinguisher in a ward, also at nighttime. In February, he insisted “I must go on an airplane” and “I must go to work on the president’s instructions” at night. He also repeatedly turned lights on and off and stripped himself of his clothes at night. After being discharged from our hospital, he died in a nursing home in November 1998 of a respiratory infection.

His younger brother, father, and 1 uncle had the same disease. The CAG repeats of his MJD1 gene were expanded to 74 and 25.

In reports describing the clinical symptoms of MJD, the mental state has been considered normal, and dementia has not been mentioned.14-16 Recently, a few reports suggesting the presence of dementia in patients with MJD have been published. In a review of MJD in 1993, Sequeiros and Coutinho17 noted 2 patients with memory disturbance, and many patients with sleep disturbance, which was sometimes associated with nocturnal crying, agitation, and nightmares. In 1993, Fukutani et al17 reported 3 patients experiencing delirium. They noted nocturnal delirium and a slowing of background activity on EEG. They speculated that brainstem lesions (eg, reticular formation, raphe nuclei, and locus ceruleus) induced a delirious state from the neuropathological findings of 2 patients. In 1997, Maruyama et al18 reported cases of 10 patients with dementia among 108 patients with MJD. In 1998, Løkkegaard et al19 reported 3 patients with dementia among 23 patients with MJD. One had disturbance of memorizing, storing, and evoking verbal materials. As for examination of cognitive function, Maruff et al20 reported specific cognitive deficit in visual attentional function in the MJD patients. They insisted that this symptom occurred without the presence of dementia.

The molecular diagnosis of MJD was confirmed for all of our patients by analyzing CAG repeats of the MJD1 gene. The common features of our 4 patients were relatively young onset age (16-36 years), long latency to the occurrence of dementia and delirium (13-25 years), and much longer CAG repeat lengths (74-79) (Table 1). They all had normal mental activity in the early stages. Their dementia and delirium began after age 40 years. Initial abnormal episodes in daily living included crying in 2 patients, and delusion and disorientation in 1 patient. In all patients, abnormal episodes often occurred during short a time as a few hours or half of a day, especially at night. After these symptoms disappeared, their mental and consciousness levels returned to normal, suggesting a delirious state. In a short time, disturbance of mental activity developed, including slowness of thought, and mental test scores began to decrease. Interestingly, the symptoms of dementia and delirium in our 4 patients were

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very similar (e.g., abnormal behavior, excitation, uncooperative attitude, crying, disorientation, slow thought processes, hallucinations, and delusions) (Table 2). For the treatment of delirium in these MJD patients, low doses of chlorpromazine proved mildly effective.

Hitherto, neuroradiological examinations such as CT and MRI scans did not elucidate cerebrocortical atrophy in patients with MJD. None of our 4 patients showed cerebrocortical atrophy on CT or MRI scans even after the appearance of dementia and delirium symptoms. On the other hand, Kitamura et al22 noted frontal cortical atrophy, and Murata et al23 showed frontal and temporal cortical atrophy in the patients with MJD. Using single-photon emission CT, Etchebehere et al24 showed low perfusion in the frontal lobe, in the lateral portion of the temporal lobe, and in the parietal lobe. Recently, by means of a positron emission tomography study, Soong et al25 revealed hypometabolism in the occipital cortex, and Taniwaki et al26 showed diffuse hypometabolism of the cerebral cortices in patients with MJD. Slow background activity on EEG was reported in patients with MJD having dementia and delirium,17 and it was also observed in all 4 of our patients (Table 1). These reports suggest dysfunction of the cerebral cortices and the possibility of cerebrocortical atrophy in patients with advanced MJD.

On the other hand, neuropathological examination did not suggest atrophy or neuronal loss in the cerebral cortex, even in patients with dementia.17,19 In 2 of our patients, the cortical structures also showed normal findings by macroscopic and microscopic examination.

Recently, similar to other polyglutamine diseases caused by elongated CAG repeats in abnormal genes,13-15 neuronal intranuclear inclusions in the affected regions of the MJD patients were reported.12 By immunohistochemical examination using an antipolyglutamine antibody in patients with MJD (including our patient 2), Yamada et al16 identified abnormal staining in many neurons of the cerebral cortex, thalamus, the nucleus basalis of Meynert, and autonomic ganglia that had been reported as usually spared by conventional microscopic examination. Conventional microscopic examination did not reveal cortical neuronal loss or gliosis in these patients. Abnormal staining by antipolyglutamine antibody showed intranuclear inclusions, and sometimes intranuclear fine granular or diffuse staining. Neuronal intranuclear inclusions stained by antipolyglutamine antibody were shown in pyramidal neurons in the frontal, temporal, parietal, and occipital cortices of cortical layers III, V, and VI. There were no significant differences in the distribution pattern and frequency of the staining between these cortices. Patients with longer CAG repeats tended to have higher numbers of labeled neurons.

In this study, patients with longer CAG repeats in the MJD1 gene manifested a tendency toward dementia and delirium, and immunohistochemical studies of patient brains with longer CAG repeats showed many more neurons

### Table 1. Summary of Clinical Background and Examination Results in 4 Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Age, y/sex</td>
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<td>46/M</td>
<td>46/F</td>
<td>51/M</td>
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<tr>
<td>Age at onset, y</td>
<td>26</td>
<td>27</td>
<td>16</td>
<td>36</td>
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<tr>
<td>Duration to occurrence of dementia and delirium, y</td>
<td>14</td>
<td>16</td>
<td>25</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age at occurrence of dementia and delirium, y</td>
<td>40</td>
<td>43</td>
<td>41</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>HDS-R score (year administered)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First administration</td>
<td>29/30 (1994)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second administration</td>
<td>12/30 (1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain CT/MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy of pons and cerebellum</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Atrophy of cortex</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>CAG repeat length in MJD1†</td>
<td>79/14</td>
<td>77/19</td>
<td>75/14</td>
<td>74/25</td>
<td></td>
</tr>
<tr>
<td>Neuropathologic examination</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Antipolyglutamine antibody in cerebral cortical neuronal nuclei</td>
<td>. . .</td>
<td>+</td>
<td>+</td>
<td>. . .</td>
<td></td>
</tr>
</tbody>
</table>

*HDS-R indicates Hasegawa Dementia Scale—Revised; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalography; pluses and minuses, the presence or absence, respectively, of a given characteristic; and ellipses, not applicable.
†Abnormal repeat length, 56-84.

### Table 2. Details of Delirium and Dementia in 4 Patients

<table>
<thead>
<tr>
<th>Characteristic/Behavior</th>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Abnormal behaviors</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Undressing oneself</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Leaving hospital</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Playing with stool</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Excitation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Uncooperative attitude</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Crying</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Disorientation</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Slowness of thought</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hallucination</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Delusion</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

*Pluses and minuses indicate the presence or absence, respectively, of a given characteristic or behavior.
ronal nuclei stained by antipolyglutamine antibody. Schilling et al showed that transgenic mice of a dentatorubral-pallidolysian atrophy model have neuronal intranuclear inclusions and stainings similar to those of the patients with MJD without neuronal degeneration developed the neurological phenotype of dentatorubral-pallidolysian atrophy, suggesting dysfunction of the cortical neurons in mice with dentatorubral-pallidolysian atrophy. Although the precise mechanism is unknown, the existence of cortical neuronal intranuclear inclusions and a fine granular or diffuse pattern stained by antipolyglutamine antibodies suggests dysfunction of these neurons, notwithstanding the absence of morphological change by conventional microscopic examination.

In our patients in cases 2 and 3 and in a previous study, neuronal intranuclear inclusions stained by antipolyglutamine antibody were identified in the cerebrocortical layers V and VI, and occasionally III (Figure). On the other hand, in patients with dementia with Lewy bodies (DLB), cortical Lewy bodies are also found in the cerebral cortical layers V and VI, and occasionally III, especially in the insular, anterior cingulate, and temporal cortices. In these cortices, we sometimes find neuronal degeneration and sponginess, and degeneration of the nucleus basalis of Meynert also usually occurs. The clinical findings of fluctuating cognition, visual hallucinations, and delusions are of interest to the focus of dementia in patients with DLB, symptoms of dementia and delirium may occur in the advanced stage, and these symptoms may be induced by cerebrocortical neuronal dysfunction.

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