Delirium associated with Joseph disease

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Abstract

Three Japanese patients with Joseph disease from different families developed sleep disturbance, followed by delirium at the middle to end stage. Brain CT scans of the three patients showed brainstem tegmental atrophy. EEG revealed slowing of background activity. Two necropsy cases showed degeneration of the reticular formation, raphe nuclei and locus ceruleus in the brainstem tegmentum in addition to the common pathological findings of Joseph disease. The clinicopathological correlation between the delirium and the brainstem tegmental atrophy in Joseph disease is discussed.

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Joseph disease¹⁻⁶ is an autosomal dominant inherited neurological disease. It is characterised clinically by cerebellar ataxia, pyramidal signs, progressive external ophthalmoplegia, and associated in variable degrees with dystonia, muscle rigidity, bradykinesia, and peripheral amyotrophy. The neuropathology of Joseph disease²⁻¹⁰ consists of degeneration in the substantia nigra, pontine nucleus, brainstem motor nuclei including oculomotor nuclei, spinal anterior horn, Clarke's column, spinocerebellar tract, pallidolusian system, dentate nucleus and its efferent system, and less severe involvement of the cerebellar cortex, with sparing of the inferior olivary nucleus.

Joseph disease was initially described in several Portuguese emigrant families in the USA by Nakano *et al*¹ and Wood *et al*² in 1972, followed by a report of Rosenberg *et al*.³ This disease has also been found in black-American,^{11 12} French,¹³ Italian-American,^{14 15} Indian,^{16 17} and Japanese^{6,8-10,18-25} families as well as Portuguese ones. In Japan, the initial necropsy report was by Sakai *et al*⁸ in 1983, of a patient reported to have "Marie's hereditary ataxia" by Ishino *et al*.²⁶ Yamaguchi *et al*,²⁷ describing two families with ataxia in 1959, had preceded these authors, and a necropsy was carried out by Endo *et al*²⁸ on one of these families in 1964. Subsequently, follow up studies have been conducted by Kurachi *et al*,²⁹ Matsubara,³⁰ and Fukutani *et al*,³¹ the authors of the Kanazawa School. The authors diagnosed the disease as "Marie's hereditary ataxia" until recently. Fukutani *et al*⁶ identified the

Marie's hereditary ataxia as Joseph disease from the clinicopathological standpoint.

Many reports of clinical and necropsy cases with Joseph disease have detailed neurological and neuropathological findings, but they lack any detailed description of the psychiatric features.²⁵ We present three Japanese Joseph disease patients from different families associated with delirium, which is presumed to be rare, and discuss the relationship between delirium and its pathological basis.

Case reports

Case 1 was a 46-year-old man. His mother, elder brother, uncle and cousins showed cerebellar ataxia. Hand tremor and double vision appeared at age 37, followed by unsteady gait and dysarthria. At age 40, he was admitted to our hospital. Neurological examination disclosed cerebellar ataxia, nystagmus, muscle hypotonia and bradykinesia. Vibration sense in his legs was impaired. After the age of 43, he was unable to walk. Dystonia in his face and upper limbs, and faciolingual fasciculation were clearly visible. After the age of 44, bulging eyes with limitation of upper gaze, muscle atrophy of his legs, and positive Babinski sign were found.

Mentally, he was alert and intelligent on admission. After a while, he often became depressed. At age 42, sleep disturbance occurred, and he suffered from delirious episodes. He sometimes took off his bedclothes and got out of bed at night. He said "I saw outside trees approaching me, I was frightened, terrible!". At age 45, his behaviour became disoriented. He took off his bedclothes and fingered his genitalia in the presence of others. He said "my spine commands me to go to the toilet" and "my foot contains drugs" etc. He was lethargic and could not perform simple calculations. He recovered from the delirium two months after receiving a remedy for disturbance of consciousness (citicoline) and neuroleptics. He was amnesic about the previous delirious episodes. Recently, mild memory disturbance without disorientation, and slowing of thought processes were noted.

Routine laboratory studies were normal. During the episode of delirium, EEGs showed a generalised slowing of the background activity with predominant 7-8 Hz waves, and two months after showed an 8-9 Hz regular pattern. Brain CT and MRI showed severe atrophy of the brainstem, especially of the tegmentum with dilatation of

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Figure 1 MRI of case 1 demonstrating severe pontine atrophy including its tegmentum and fourth ventricular dilatation with mild atrophy of the cerebellum.

the 4th ventricle, and mild atrophy of the cerebellum (fig 1). There was no cerebral atrophy. Hasegawa's dementia rating scale³² (HDS; a simple test for mental status commonly used in Japan to screen for dementia) at the age of 44 gave a perfect score. A year later WAIS gave a score of 87 on full IQ, 97 on verbal IQ and 74 on performance IQ.

Case 2, a 57-year-old man, started to have unsteady gait at age 30. After age 42, he was unable to walk. His mother, daughter, and elder and younger brothers had a similar illness. At age 54, he was admitted to our hospital. Neurological examination disclosed cerebellar ataxia. He showed bilateral ptosis and nystagmus with limitation of upward gaze. Lingual movements with fasciculation were limited on voluntary effort. Bradykinesia, bilateral muscle hypotonia and peripheral amyotrophy were observed. Babinski sign was positive. Vibration sense of his legs was impaired.

Sleep disturbance and emotional lability appeared at the age of 52. Subsequently, he often suffered from delirious episodes and wandered in the ward at night. He was disorganised and sometimes became agitated and violent. He took off his bedclothes and exposed his genitalia in the presence of nurses. He was amnesic about the previous delirious episode the next morning. After a few weeks of treatment with tiapride, he recovered from the delirium for a while, but showed frequent recurrences. Except for the delirious episodes, he was alert and well oriented. Thereafter he gradually became

Figure 2 Cervical segment of spinal cord of case 2 showing severe atrophy with loss of myelin of the anterior spinocerebellar tract. Woelcke stain (bar = 5 mm).

Figure 3 A) Horizontal section through the upper level of the pons of a normal control. B) Horizontal section through the pons of case 2 at the same level as fig 3A. Note severe atrophy of not only the pontine basis but also the pontine tegmentum. Myelin pallor is seen in the pontine tegmentum including the reticular formation and raphe nuclei. Compare with fig 3A. A, B; Klüver-Barrera (K-B) stain (bar = 10 mm).

euphoric, and showed a slowing of thought processes and a decline in understanding.

Brain CT showed severe atrophy of the brainstem including its tegmentum and mild atrophy of the cerebellum. EEGs showed a gradual slowing of the background activity from 10 Hz α to 7 Hz θ waves, mixed with slower θ waves. He died of cardiac failure at the age of 57.

The weight of the brain was 1050 g. On gross inspection, the brainstem and spinal cord were considerably atrophic (fig 2). In the spinal cord, shrinkage of anterior spinocerebellar tract and anterior horn was remarkable. In addition to severe atrophy of the pontine basis, severe atrophy of the pontine tegmentum was found (fig 3B). For comparison, fig 3A shows a normal control pons horizontally sectioned through the upper level. Microscopically, the cerebral cortex and nucleus basalis of Meynert were well preserved. A severe neuronal loss was found in the internal segment of the globus pallidus and subthalamic nucleus. The thalamus showed fibrillary gliosis without neuronal cell loss in the centromedian and parafascicular nuclei, in which the efferent fibres arising from the reticular formation terminate (fig 4). In the midbrain, the substantia nigra showed a moderate neuronal loss. There was a mild

Figure 4 Holzer stain of case 2 shows fibrillary gliosis of centromedian and parafascicular nuclei in the thalamus, the terminal site of the efferent fibres from the reticular formation (bar = 10 mm).

loss of neurons in the red nucleus. A moderate loss of neurons was found in the oculomotor nucleus. The central tegmental tract showed moderate atrophy with fibrillary gliosis. In the cerebellum, Purkinje cells were mildly decreased in number, and the dentate nucleus showed a severe neuronal loss and grumose degeneration of the remaining neurons. The superior cerebellar peduncle showed severe atrophy (fig 3B). In the pons, a severe neuronal loss of the pontine nucleus was observed. There was a moderate neuronal loss in the locus ceruleus. The reticular formation and raphe nuclei showed a moderate neuronal loss with fibrillary gliosis, and their remaining neurons were degenerated (figs 5, 6). In the medulla oblongata, the anterior and posterior spinocerebellar tracts showed severe degeneration. A moderate neuronal loss of the hypoglossal nucleus,

Figure 6 Superior central nucleus in raphe nuclei of case 2 shows a moderate neuronal loss with astroglial proliferation. The remaining neurons are also degenerated. K-B stain (bar = 100 μ m).

dorsal motor nucleus of the vagal nerve was found. There was a slight neuronal loss of the inferior olivary nucleus. The accessory cuneate nucleus showed a severe neuronal loss. In the spinal cord, the anterior spinocerebellar tract showed severe degeneration (fig 2). The posterior column was mildly degenerated. A severe neuronal loss was found in Clarke's column and the anterior horn.

Case 3, a 57-year-old man,²⁵ had a family history. The initial complaint was leg fatigue when aged 25, followed by unsteady gait and dysarthria. Neurological examination at age 50 years disclosed cerebellar ataxia, ophthalmoplegia with bulging eyes, pyramidal tract signs, peripheral amyotrophy with muscle weakness and sensory disturbance.

He developed mild mental deterioration characteristic of subcortical dementia. Insomnia appeared at 45. After 54, he sometimes had nocturnal delirium. He was disoriented and often wandered around the ward in a wheel chair covered with a blanket. He pointed his finger at the ceiling and said "there is something on the ceiling". He was amnesic about these episode the next morning.

Brain CT at age 52 showed moderate atrophy of the brainstem including its tegmentum, and mild atrophy of both the cerebral and cerebellar hemispheres. EEGs showed slower α (8–9 Hz) activity mixed with irregular θ waves. Polysomnographic study at age of 52 revealed an increase of Stage W and Stage 1 (slow wave sleep) and a decrease of Stage REM. He died of cardiac failure at age 57.

Figure 5 Reticular formation of case 2 shows a moderate neuronal loss with astroglial proliferation. The remaining neurons are also degenerated. K-B stain (bar = 100 μ m).

At post mortem, the brain weighed 1120g. There was a marked degeneration in the dentate nucleus, superior cerebellar peduncle, Clarke's column and spinocerebellar tract, a moderate degeneration in the substantia nigra, pontine nuclei and pallidolusian system, and a mild degeneration in the cerebellar cortex. The cerebral cortex and nucleus basalis of Meynert were well preserved. The tegmentum of the pons was severely atrophic and the reticular formation, raphe nuclei and locus ceruleus showed moderate loss of neurons with fibrillary gliosis. The parafascicular nuclei in the thalamus showed fibrillary gliosis without neuronal loss.

Discussion

The neurological features of these three cases and the neuropathological findings of the two necropsy cases are consistent with those generally seen in Joseph disease. The CT findings of the three cases are also compatible with those of Joseph disease.⁶

The nosology of Joseph disease is somewhat controversial. One author may regard it as Joseph disease and others as Marie's ataxia or spinopontine atrophy. We use the term 'Joseph disease' as proposed by Rosenberg,³³ because the term is common and familiar to us. Harding³⁴ examined the previous reports of the hereditary ataxias and regarded Joseph disease, Marie's ataxia and spinopontine atrophy as a subtype of autosomal dominant late onset cerebellar ataxia. We agree that Joseph disease, Marie's ataxia and spinopontine atrophy are the same disease entity from the clinicopathological standpoint.

The differential diagnosis for Joseph disease is distinguishable from olivopontocerebellar atrophy (OPCA) by the presence of dystonia, bulging eyes³⁵ and less severe atrophy of the cerebellum on CT.⁶ Neuropathologically, Joseph disease can be clearly distinguished from OPCA by the absence of inferior olivary atrophy.^{28,33} Myoclonus epilepsy with ragged-red fibres (MERRF),³⁶ a type of mitochondrial myopathy, shows inherited cerebellar ataxia. However, this disease can be clinically distinguished from Joseph disease by the presence of myoclonus, convulsion and paroxysmal discharges in the EEGs. Dentatorubropallidolusian atrophy (DRPLA)³⁷ is also an inherited ataxia, but patients with this disease have myoclonus and epilepsy. Neuropathologically, this disease exclusively shows dentatorubral-pallidolusian system atrophy, while the spinal cord is intact. Gerstmann-Sträussler-Sheinker disease³⁸ is also a hereditary spinocerebellar ataxia, but the clinical course of this disease is shorter than that of Joseph disease, and the remarkable pathological feature is the occurrence of plaque-like deposits.

In addition to the common clinical features of Joseph disease, all our cases showed delirium corresponding to the criteria of DSM III-R.³⁹

Delirium is an organic mental disorder

characterised by a recognition disturbance based on impairment of consciousness, presenting perceptual disturbances, incoherence, increased psychomotor activity and disturbance of the sleep-wake cycle.^{39,40} EEGs show an increase of slow-wave activity and slowing and disruption of the normal α rhythm during the delirium episode.⁴⁰ After recovering from the delirium the patient sometimes does not recall his behaviour during the delirious episode.⁴⁰

It is widely accepted that the intelligence is totally intact in Joseph disease.⁴¹ However, there has been no systematic investigation of mental status in this condition.²⁵ Furthermore, psychiatric symptoms have received little attention.²⁵ Delirium associated with Joseph disease seems to be rare. Only a few authors^{20,24,26} have reported delirium associated with this condition. Ishino *et al*²⁶ reported a patient who developed nocturnal delirium in the middle stage. The patient became euphoric and demented. Ikeda²⁰ reported a patient showing sleep disturbance and delirium with visual and auditory hallucinations in the middle stage. The patient also developed a mild dementia with slowing of thought processes, inertia and indifference. Kogure *et al*²⁴ also reported a patient associated with delirium at the end stage. In our three cases, the delirium following sleep disturbances also appeared at the middle to end stage of the illness. All of them showed nocturnal delirium. In our three cases, brainstem tegmental atrophy was detected by radiological and neuropathological studies. The two necropsy cases revealed degeneration of the reticular formation, raphe nuclei and locus ceruleus, all of which are located in the brainstem tegmentum. The slowing of background activity on the EEGs of the patients supports a dysfunction of the reticular formation, by the absence of obvious cerebral pathology.²⁵ Atrophy of the brainstem tegmentum in Joseph disease has been noted in several papers,^{18-20,24,25,30} but has attracted little attention. A few reports also neuropathologically described brainstem tegmental atrophy associated with degeneration of the reticular formation,^{20,24} raphe nuclei^{20,24} and locus ceruleus,^{7,20,24} although they^{7,20,24} did not discuss its pathological significance. In several other necropsy reports, there is no description of brainstem tegmental atrophy despite the fact that it is macroscopically apparent in their photographs. In Joseph disease most authors pay attention to the brainstem basis rather than to the brainstem tegmentum, and thus the brainstem tegmental atrophy may be overlooked. This also frequently occurs in sporadic OPCA.⁴² Based on our experiences from the radiological and neuropathological findings,^{6,10,25,30,31} brainstem tegmental atrophy is thought to be a particular pathological change in Joseph disease.

It is well-known that the reticular formation of the brainstem plays an important role in the maintenance of arousal,⁴³ and the locus ceruleus and raphe nuclei in the regulation of the awake-sleep rhythm.⁴⁴ Serotonergic

neurons in the raphe nuclei and noradrenergic neurons in the locus ceruleus are considered to be related to non-REM sleep and REM sleep, respectively.⁴⁴ Kitamura *et al.*²³ reported five patients with Joseph disease who showed sleep disturbance and the central type of sleep apnoea, and pointed out the relationships between the sleep apnoea and abnormalities in monoamine metabolism of the locus ceruleus and raphe nucleus. Kazukawa⁴⁵ carried out a polysomnographic study on nocturnal sleep of patients with Marie's ataxia and found that these patients had sleep disorders characterised by disturbances of sleep process, fragmentation of sleep stage, lightening of sleep and a decrease of REM sleep. Shimizu⁴⁶ also polygraphically studied patients with OPCA, Shy-Drager syndrome and progressive supranuclear palsy, and found that these patients had sleep disturbance, with their abnormal sleep state, named Stage 1-REM, playing an important role in nocturnal delirium. He also suggested that this abnormal sleep state and concomitant delirious behaviour are due to degeneration of the locus ceruleus or its related structures in the brainstem. Accordingly, the involvement of the brainstem tegmentum in Joseph disease may contribute to the development of the sleep disturbance and delirium.

We recently reported four patients with Joseph disease²⁵ and a patient with OPCA⁴² associated with subcortical dementia, to which the brainstem tegmental atrophy may have contributed. Our three present cases also developed mild mental deterioration characterised by subcortical dementia. The brainstem tegmental atrophy may be responsible not only for consciousness disturbance such as delirium but also for mental deterioration. These psychiatric symptoms might depend on the stage and progress of the illness, as our cases showed delirium at the middle to end stage. A slow neuronal disappearance in the brainstem tegmentum, which commonly occurs in neurodegenerative diseases such as Joseph disease, may be closely related to the development of sleep disturbance and delirium as well as mental deterioration.

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