Creutzfeldt-Jakob Disease with Paralysis of the Unilateral Vocal Cord and Soft Palate

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Creutzfeldt-Jakob disease (CJD) is a progressive disease that is characterized by the accumulation of abnormal prion-like proteins in the central nervous system. The cerebral cortex is primarily affected in CJD, leading to spongiform changes and dementia. To date, there have been no reported cases of CJD, with local neuroparalysis discovered at an early stage of the disease. Here, we describe a patient who presented unilateral vocal cord and soft palate paralysis before the progression of CJD. After developing forgetfulness 6 months ago, a 76-year-old woman was presented at department of Otorhinolaryngology in a general hospital for recently developed hoarseness and dysphagia. In the oral and laryngeal endoscopic findings, unilateral paralysis of the vocal cord and soft palate was noted. On videofluorography, the larynx failed to elevate straight on swallowing. The right tongue pharyngeal wall was lax, and some contrast agent was retained in the lower right piriform sinus. The paralysis was thought to be due to the glossopharyngeal nerve or vagal nerve damage, which was caused by peripheral nerve injury or infranuclear palsy. Diffusion-weighted magnetic resonance imaging (MRI) revealed high signals in the cerebral cortical area (a signature feature of CJD). The patient died 2.5 years after the onset of illness. The patient was diagnosed as probable sporadic CJD. Since we could not detect any peripheral organic findings that could cause the paralysis, we suspect that CJD is responsible for the paralysis. In treating CJD patients with neurological signs, exclusive investigation is required to obtain a more detailed picture of the disease.

Keywords: Creutzfeldt-Jakob disease; diffusion-weighted MRI; prion disease; soft palate paralysis; unilateral vocal cord paralysis

Clinical Findings

Patient: a 76-year-old woman

Complications and past history: Hypertension, diabetes mellitus, uterine fibroid surgically treated in her fifties, and no history of blood transfusion.

Dysmnesia first set in and the patient often forgot to take medication; this prompted her to visit a local clinic in October 2007. At this point, a mini-mental state examination (MMSE) was performed (Dick et al. 1984), and the patient scored 28 points with no evident dementia. All neurological signs were normal except for a slightly slow tendon reflex. MRI images of the brain with fluid-attenuated inversion recovery (FLAIR) revealed a high-signal zone in the cortices of the bilateral temporal and occipital lobes.
However, the contrast MRI images obtained using an Amersham brand of gadodiamide (Omniscan®; Daiichi SANKYO Co., Ltd., JAPAN) showed no obvious effect. As the examinations failed to reveal any obvious pathology, the patient was put under a wait-and-see approach. Subsequently, she consulted a local physician and was prescribed donepezil, and thereafter, she reliably followed the prescribed medication regimen.

The patient had no symptoms for 6 months after that, but she suddenly developed hoarseness and dysphagia in April 2008. Thus, she visited a clinic, and was referred to the department of otorhinolaryngology in a general hospital. Her vocal quality was breathy hoarseness, complicated by slight rhinolalia aperta.

At the initial visit, oral findings included the elevating incompetence of the right soft palate, the contractile dysfunction of the right pharynx, and its resultant curtain sign (Fig. 1A, B). Laryngeal endoscopic findings showed the contractile dysfunction of the right pharynx, right vocal cord paralysis, and retained saliva in the right piriform sinus (Fig. 2A, B).

On videofluorography of the larynx, the larynx was found not to elevate straight on swallowing in the frontal view of a swallowing contrast study. Rather, it elevated at an angle, tilting to the right (Fig. 3A). The right tongue pharyngeal wall was lax, and there was some contrast agent retained in the lower right piriform sinus. In the side view, the appearance of the peristaltic wave and transmitting velocity were not affected, but the amplitude of the peristaltic contraction wave was small. Nasopharyngeal reflux was
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noticed (Fig. 3B). Moreover, sensation in the laryngopharyngeal wall diminished because there was some contrast agent retained in the vallecula of epiglottis. The laxity of the cricopharyngeal muscle was maintained, and there was no aspiration. Esophageal peristalsis was diminished to the level of the lower esophagus, and the carrying speed from the esophagus to the stomach was decreased. Gastroesophageal reflux was also noticed. There were no mechanical problems such as esophagocele.

Physical examination revealed no visual field disturbance, multiple vision, or cerebellar manifestation. Muscle stress was normal, and there were no other apparent cranial nerve disorders. Neck and chest computed tomography (CT) scan, cervical echogram, or esophagastroduodenoscopy did not reveal any abnormal findings.

From a head and neck MRI, the T1 and T2 images showed no abnormal findings. However, in the diffusion-weighted image, large areas of high signal were found from the bilateral cortical areas (Fig. 4A, B). The patient was transferred to a specialized treatment center for cranial nerve disease, where she underwent further examination. Single photon emission computed tomography (SPECT)
was carried out, and cerebral hypoperfusion was found bilaterally in the cortex. These findings were considered typical of CJD. On examination of the cerebrospinal fluid (CSF), the number of cells was within the normal range at 3, and there was a slight increase in total protein levels at 66 mg/dl, but neuron-specific enolase (NSE) was at 18.9 pg/ml (which is within the normal range), and the patient tested negative for prion-like protein gene. However, the clinical progression still suggested CJD as a potential diagnosis, and therefore, the patient was treated on an outpatient basis.

An EEG examination in May 2008 showed no abnormal findings (Fig. 5A). Six months later, the patient lost her ability to walk, and was, therefore, admitted to the hospital. An EEG examination in November revealed periodic synchronous discharge (PSD), with the simultaneous appearance of myoclonus (Fig. 5B). We detected progressive dementia, myoclonus, and akinetic mutism, a fairly typical EEG finding during an illness of this duration, and on the basis of these findings, we diagnosed this patient as suffering from probable sporadic CJD (see Table 1).

The patient's general health was deteriorating. By the end of September 2008, her mental status as well as her general physical status deteriorated, and she was subjected to tube feeding. At the beginning of 2009, the patient entered a state of akinetic mutism, and by October 2009, she developed repeated aspiration pneumonia and respiratory failure. On May 22, 2010, she succumbed to the worsening respiratory failure. Her family did not give their consent to perform an autopsy.

Discussion

In humans, the annual prevalence rate of prion disease is reported to be 1 case per 1,000,000 individuals (Dalsgaard 2002; Pedersen and Smith 2002). According to the cause, the disease is classified into 3 types: sporadic, familial, and infectious CJD. Sporadic CJD occurs with the highest frequency, accounting for 80%-85% of all human prion diseases.

Sporadic CJD is further sub-divided into 2 types: rapidly progressing and slowly progressing. The former is also known as classical CJD, where dementia, involuntary movement (myoclonus), pyramidal tract symptoms (such as weakness, hyperreflexia, and hypertonicity), and extrapyramidal tract symptoms (including tremor and rigidity) progress rapidly, causing akinetic mutism in 3-7 months. In contrast, slowly progressing CJD gradually develops into a chronic state, and is characterized by dementia and neurological manifestations. It usually takes more than a year for these patients to develop myoclonus or akinetic mutism. Thus, sporadic CJD of either the rapidly or slowly progressing type is a fatal disorder, without any reliable treatment.

In CJD patients, PSD of the brain wave is a characteristic finding, and is employed as one of the most important diagnostic criteria (Zeidler et al. 1998). However, in the early stages of CJD, PSD of the brain wave is not clear, and only a nonspecific slow wave is evident. Often, PSD can be seen after the second examination (Shiga et al. 2004). Steinhoff et al. (2004) report that in one-third of the cases re-investigated, PSD did not appear, thus suggesting that the occurrence of PSD is less common than conven-
tionally thought. Therefore, brain wave alone is considered insufficient as an auxiliary diagnosis, especially in the early stages of the disease.

It has been reported that specific proteins in the CSF, such as 14-3-3 protein, tau protein, S-100 protein, and NSE, are useful as diagnostic markers of CJD. 14-3-3 protein may be present in the CSF because of the sudden destruction of cerebral neurocytes (Lemstra et al. 2000; Shiga et al. 2006), and is used as a diagnostic criterion of CJD (Table 1; Zeidler et al. 1998). The positive ratio of 14-3-3 protein is generally high in CJD, but this protein does not seem to be a highly specific marker (Lemstra et al. 2000; Huang et al. 2003). There are other reports that the 14-3-3 protein ratio is also elevated in cases of cerebral vessel disorder, brain fever, meningitis, metabolic encephalopathy, low-oxygen encephalosis, Hashimoto's encephalopathy, nervous system paraneoplastic disorders, and Alzheimer disease (Saiz et al. 2006). Bersano et al. (2006) reported that a high level of 14-3-3 protein was also observed in Guilian-Barré syndrome, a peripheral nerve disease. Therefore, we must be careful when interpreting positive results for this protein. Currently in Japan, methods to measure 14-3-3 and tau proteins in cerebrospinal fluid are available only in one facility; in fact, they were not measured in the patient. We measured spinal fluid NSE, but the value was not abnormally elevated. The positive rate of NSE in the spinal fluid is thought to be slightly lower than those of other relevant proteins (Sanchez-Juan et al. 2006).

In our patient, diffusion-weighted MRI showed high signals along the brain cortex from the early stage of the disease. Shiga and colleagues (2004) reported that the sensitivity of the diffusion-weighted MRI image is 92.3%, while its specificity is 93.8%; thus, it is better suited to detect CJD-related lesions in comparison to T2-weighted MRI or FLAIR MRI. Our experience patient suggests that diffusion-weighted MRI imaging can detect abnormalities peculiar to CJD before PSD appears in the brain wave, or even in cases where PSD is not seen in the brain wave. Combined with the findings from clinical and CSF examinations, this can be extremely useful for an early diagnosis of the disease. From a viewpoint of functional brain imaging, SPECT is also suggested to be useful. Matsuda et al. (2001) reported that in 7 early-stage CJD cases, where brain atrophy was not evident on either CT or MRI scans, and where PSD was not observed in the brain wave, a decrease in regional cerebral blood flow was observed by 123I-IMP SPECT.

However, in this patient, although upon CSF examination NSE levels were within the normal range and the prion gene test was negative, rapidly progressive dementia, myoclonus, akinetic mutism, and the appearance of PSD in the brain wave were evident. Therefore, we diagnosed the patient probable sporadic CJD.

There have been some reports of bilateral vocal fold paralysis appearing at the end stages of CJD (Kudo et al. 1984; Li et al. 2009). Li et al. (2009) studied electromyograms (EMGs) recorded from the throat cavity and concluded that bilateral, recurrent nerve paralysis was attributable to dysfunction of the upper motor neurons. However, there have been no reports to date of unilateral vocal cord paralysis or soft palate paralysis, nor have there been any
reports of cases where local neuroparalysis was discovered at such an early stage of the disease. Since no abnormal pharyngeal peristaltic wave was noticed in the videofluorography of larynx, and the amplitude of the peristaltic contraction was low, the paralysis of the vocal cord and the soft palate were thought to be due to the glossopharyngeal nerve or vagal nerve damage, which was caused either by peripheral nerve injury, or by infranuclear palsy including ambiguous motor nuclei.

It is generally thought that in CJD, the cerebral cortex shows mainly spongiform changes (Parchi et al. 1999; Zerr et al. 2000; Shiga et al. 2004); however, in 16%-18% of chronic CJD cases, cranial nerve problems and brain-stem lesions occur (Roos et al. 1973; Brown et al. 1994; Frank et al. 2000). It is relatively rare that cranial nerve function is disrupted at an early stage, but there is a report of a patient developing facial nerve palsy (Heye and Cervós-Navarro 1992).

Additionally, we considered that prion infection was started at the vagal nerve termini in our patient, with the infection ascending as it spread. In this scenario, the infection would not directly invade the central nervous system from the brain-stem, but would remain for a while at the peripheral nerve level, and cause local neuroparalysis, or vagal nerve damage, which was caused either by peripheral nerve injury, or by infranuclear palsy including ambiguous motor nuclei.

There are approximately four CJD patients reported in the literature, in which dysphonia, dysarthria, and dysphagia occurred (Russell 1980; Frank et al. 2000). However, in most of them, only their symptoms were mentioned, and no otolaryngologic examinations were performed. It is therefore possible that in some of these patients, ambiguous nuclear disorders at the peripheral nerve level were involved.

**Conclusion**

We describe a patient who manifested unilateral paralysis of the vocal cords and soft palate in a comparatively early stage of CJD. The diffusion-weighted MRI showed high-signal zones along the brain cortex area from the time of presentation patient; this aided in making a differential diagnosis of CJD. Because autopsy was not performed due to the lack of familial consent, the relationship between CJD and paralysis of the vocal cord or soft palate could not be confirmed. However, since we could not detect any peripheral organic findings in neuro-imaging or other tests, we have concluded that CJD is responsible for the paralyses appeared in the present patient.

**Conflict of Interest**

The authors have no conflict of interest.

**References**


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