erably varies among groups classified by age at onset. This information may help prioritize specific SCA gene testing.

In conclusion, we provided detailed clinical and genetic characteristics of patients with 16q-SCA, which is not a rare AD-SCA subtype in the Japanese population. The range of the ages at onset of 16q-SCA patients is considerably broad, which might be explained by the presence of a modifying gene. Our finding of an exceptional patient who lacked the C-to-T substitution in the *puratrophin-1* gene emphasizes the importance of further genetic analysis of the candidate region of 16q-SCA.

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Case Report

Venous congestive myelopathy of the cervical spinal cord: An autopsy case showing a rapidly progressive clinical course

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We report a rapidly progressive myelopathy in a 74-year-old Japanese man who was admitted to our hospital with a 4-month history of progressive gait disturbance and died of pneumonia followed by respiratory failure on the 22nd day of admission. During the course of his illness, magnetic resonance imaging (MRI) revealed intramedullary lesions with edematous swelling from the medulla oblongata to the spinal cord at the level of the fourth vertebra. After administration of contrast medium, the ventral portion of the lesion was mildly and irregularly enhanced and a dilated vessel was recognized along the ventral surface of the upper cervical cord. At autopsy, ischemic changes were observed in the upper-to-middle cervical cord segments, with so-called arterialized veins in the subarachnoid space. No neoplastic lesions were found within or outside the brain and spinal cord. These pathological findings were essentially those of venous congestive myelopathy (VCM) associated with dural arteriovenous fistulae (AVF), formerly known as Foix–Alajouanine syndrome. VCM associated with dural AVF, which is now considered to be treatable in the early stages, is rare found in the cervical spinal cord. The present autopsy case, with MRI findings, provides further information that might be useful for recognition and diagnosis.

Key words: cervical cord, dural arteriovenous fistula, Foix–Alajouanine syndrome, magnetic resonance imaging, venous congestive myelopathy.

INTRODUCTION

Venous congestive myelopathy (VCM), which results from spinal venous hypertension,[1–3] is a progressive disorder frequently associated with spinal dural arteriovenous fistulae (AVF), the most common spinal vascular disease.[4–9] Clinically, VCM presents as progressive paraparesis, sensory impairment of the lower extremities and bowel, bladder and sexual dysfunction.[5–9] Foix–Alajouanine syndrome (angiodysgenetic necrotizing myelopathy),[10] which usually affects the lower part of the thoracic and/or lumbosacral cord, is an old term previously used to describe this type of progressive myelopathy associated with spinal dural AVF. Since the first description by Foix and Alajouanine,[10] many similar cases have been reported in which clinical and post-mortem pathological studies have been undertaken.[11] However, VCM associated with dural AVF affecting the cervical cord is rare[5–9] and, to our knowledge, the number of autopsy reports is still very small.[12–14] Here we describe an elderly patient with a rapidly progressive myelopathy, in whom the diagnosis of cervical spinal cord VCM was made at autopsy.

CLINICAL SUMMARY

The patient, a 74-year-old man, was admitted to our hospital with a complaint of gait disturbance. Four months before, he had begun to wake frequently at night due to pain in the shoulder and neck. Subsequently, he felt difficulty in walking even on flat ground and was unable to climb stairs without assistance. On admission, a neurological examination showed mild muscle weakness in his four extremities. The patient's ability to perceive sensations except for vibrations was diminished below the neck. He showed a shuffling gait and a left-sided limp. He also

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exhibited dysuria and orthostatic hypotension: his blood pressure was 132/87 supine and 84/62 standing. Magnetic resonance imaging (MRI) showed an intramedullary lesion with low intensity on T1-weighted images and high intensity on T2-weighted images from the medulla oblongata to the spinal cord at the fourth vertebral level, with an edematous swelling (Fig. 1A). Flow voids were not observed on the T1- or T2-weighted images. After administration of contrast medium, the ventral portion of the intra-parenchymal lesion was mildly and irregularly enhanced (Fig. 1B), and in addition, a dilated vessel was recognized along the ventral surface of the upper cervical cord (Fig. 1C). A tentative diagnosis of cervical cord intramedullary neoplastic lesion was made. On the sixth day of admission, he suddenly developed flaccid paraparesis and urinary retention. His clinical symptoms were gradually progressive thereafter. On the ninth day, he showed complete paraplegia. Subsequently, severe muscle weakness ascended to his upper extremities and his respiratory function also became gradually impaired. On the 22nd day of hospitalization, he died of pneumonia followed by respiratory failure. As a result of a retrospective discussion about the patient's clinical course and MRI findings, especially those shown in Figure 1C, a cervical cord intramedullary lesion due to a certain vascular abnormality was considered to be a more probable clinical diagnosis. A general autopsy was performed 8 h after death, at which time the brain was somewhat edematous and weighed 1350 g.

PATHOLOGICAL FINDINGS

The fixed brain and spinal cord showed no apparent abnormalities in external appearance. The superficial arteries and veins of the brain and spinal cord appeared unremarkable (no angiodysgenetic or angiomatous lesions were evident).

A neuropathological examination was performed on 4-μm-thick sections using several stains: HE, Klüver–Barrera and Elastica–Goldner. Selected sections were also immunostained using the avidin–biotin–peroxidase complex method (Vector, Burlingame, CA, USA) with diaminobenzidine as the chromogen. The primary antibodies used were mouse monoclonal antibodies against phosphorylated neurofilament protein (SMI31; Sternberger Monoclonals, Baltimore, NJ, USA; 1:1000) and α-smooth-muscle actin (SMA; Dako, Glostrup, Denmark; 1:500).

Histologically, significant changes were evident in sections of the lower medulla oblongata and the upper-to-middle cervical spinal cord segments. In the cervical cord, patchy lesions manifested at decreased staining intensity were scattered in the white and gray matter (Fig. 2A). In the white matter, degeneration (vacuolation) and loss of myelin, as well as degeneration (swelling) and loss of axons were observed (Fig. 2B). In the gray matter, severe neuronal loss and gliosis with rarefaction of the neuropil (Fig. 2C), as well as increased numbers of small, thick hyalinized vessels were evident (Fig. 2D). The thoracic and lumbar spinal cord segments were unremarkable.

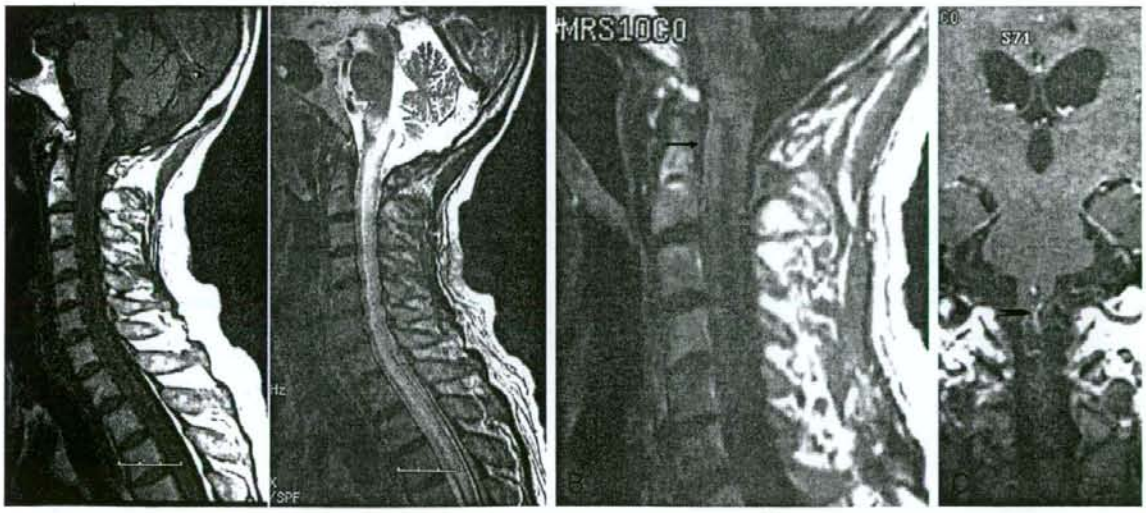

Fig. 1 Magnetic resonance imaging, (A) intramedullary lesion (mainly in the center of the cord) with low intensity on the T1-weighted image (left panel) and high intensity on the T2-weighted image from the medulla oblongata to the spinal cord at the level of fourth vertebra (right panel). The lesion is accompanied by marked edema, (B) The ventral parenchyma presents mild and irregular enhancement (→), (C) a dilated vessel along the ventral surface of the upper cervical cord (➡).

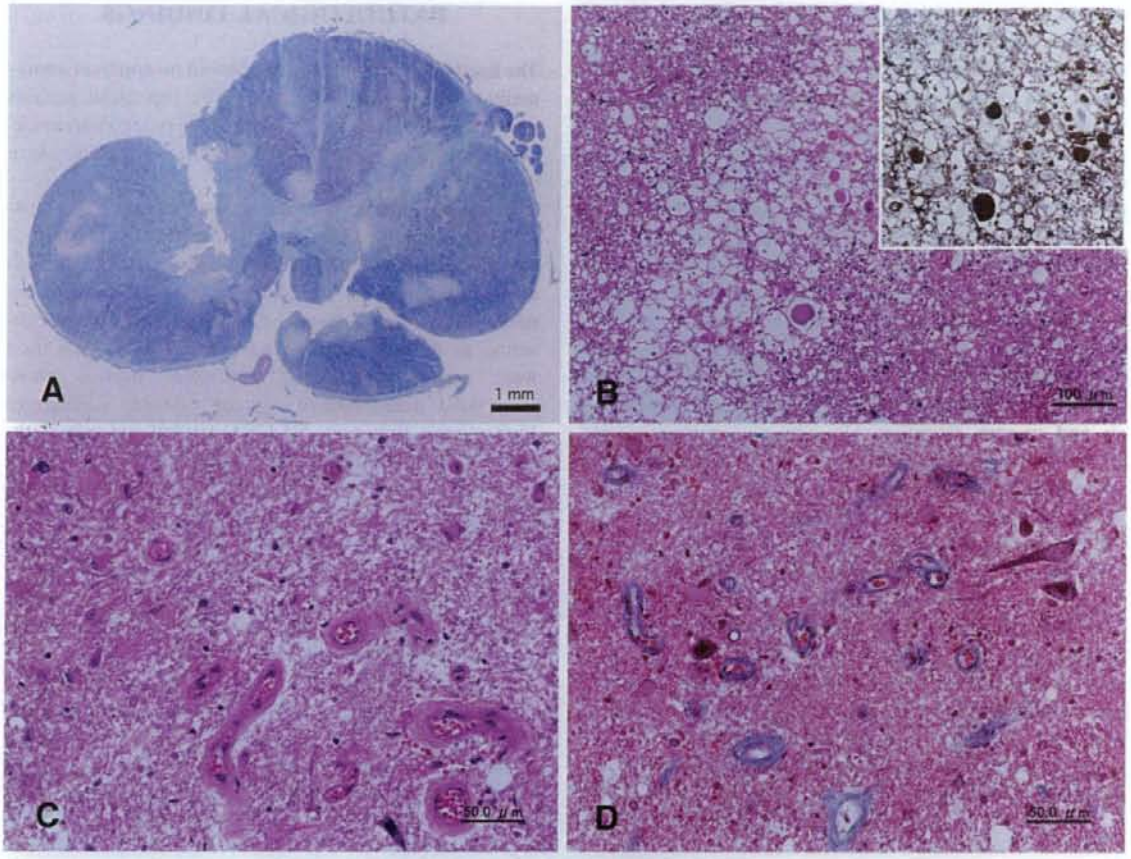

Fig. 2 Intra-parenchymal lesions in the upper-to-middle cervical cord segments, (A) multifocal, patchy irregular lesions in the gray and white matter (tissue lacerations are artifacts made at autopsy) by Klüver–Barrera stain, (B) vacuolar degeneration of myelin in the white matter. Note that some of the vacuolated myelin contains round, eosinophilic swollen axons (HE stain), inset, which are clearly recognized by immunostaining with an anti-phosphorylated neurofilament protein antibody (by SMI31 immunostaining), (C) neuronal loss and gliosis and rarefaction of the neuropil in the anterior horn (by HE stain), (D) increased small hyalinized vessels in the anterior horn (by Elastica–Goldner stain).

A feature of considerable significance was the presence of enlarged blood vessels with marked fibrous intimal thickening and lacking an internal elastic lamina (so-called arterialized veins) in the subarachnoid space at the cervical cord level. These blood vessels were easily identified anatomically as the anterior and posterior spinal veins (Fig. 3A–E), as well as the coronal veins. Similar alterations were also found in a section of the anterior spinal vein cut at the level of the lower medulla oblongata; the medulla oblongata itself was unremarkable, although some intramedullary veins were found to be somewhat dilated and congestive.

In conclusion, these pathological findings were essentially those of VCM associated with dural AVF; the multifocal lesions affecting myelin and axons, as well as neurons were apparently ischemic in nature.[8,11–13,15] Unfortunately, the presence or absence of associated dural AVF (spinal or intracranial) could not be identified histopathologically. Importantly, no neoplastic lesions were found within or outside the brain and spinal cord.

DISCUSSION

We have described an elderly patient who developed progressive muscle weakness in all four extremities and showed abnormalities in the cervical spinal cord and medulla oblongata on MRI. An autopsy examination confirmed that he had suffered from VCM affecting the cervical spinal cord, based on its characteristic pathological features. The present case, with MRI findings, was an

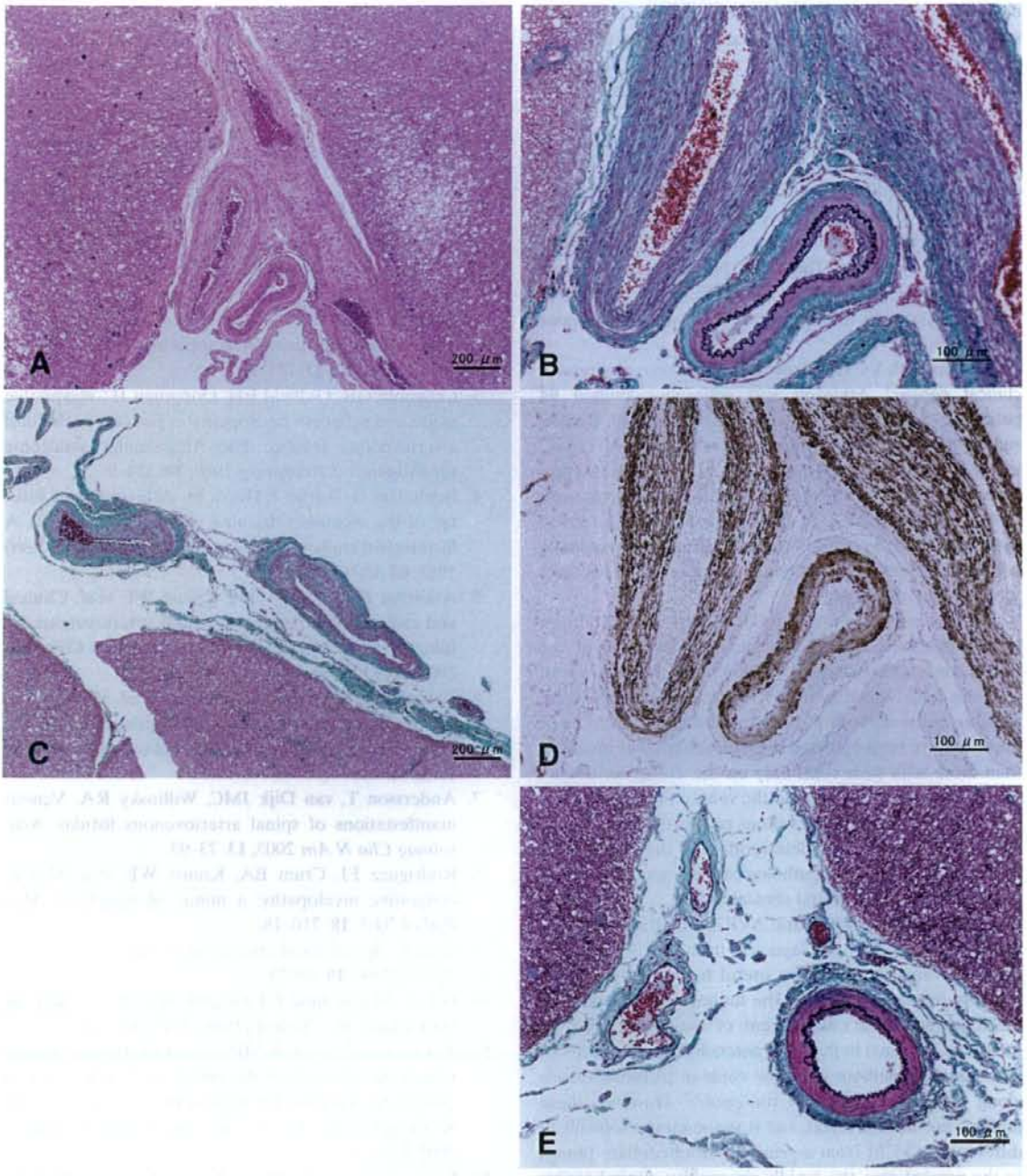

Fig. 3 Venous lesions in the subarachnoid space at the cervical cord level, (A) enlarged blood vessel sections showing marked fibrous intimal thickening(HE stain), (B) in these sections, no internal elastic lamina is evident (arterialized anterior spinal vein). Note the internal elastic lamina in an arterial section (anterior spinal artery) (by Elastica–Goldner stain), (C) arterialization is evident in the blood vessel sections seen here (posterior spinal vein) (by Elastica–Goldner stain), (D) In the thickened intima, many SMA-positive cells and fibers are present (fibromuscular intimal thickening) (by SMA immunostaining), (E) for comparison, sections of the anterior spinal artery and vein cut at the upper cervical cord level from a control subject are shown (by Elastica–Goldner stain).

unusual example of VCM in a rare anatomical location with a rapidly progressive clinical course. Although we failed to identify the associated dural AVF in the post-mortem examination, its presence as the causative abnormality could not be completely excluded.

VCM associated with dural AVF occurs only rarely in the brainstem and the cervical portion of the spinal cord.[16-18] In the present case, muscle weakness began in the lower extremities and then ascended to the upper extremities. Eventually, severe muscle weakness also extended to the respiratory muscles. There have been a few case reports of VCM in the cervical region, in which progressive neurological symptoms ascended from the lower to the upper extremities.[17-19]

Patients with VCM usually show a chronic progressive clinical course.[9] Atkinson and colleagues studied 94 patients (75 men and 15 women) with dural AVF treated surgically at their institution, and reported that with regard to the myelopathy, the mean time from the onset of symptoms to diagnosis was 23 months, the initial symptoms were most commonly fatigue or muscle weakness in the lower extremities and the symptoms usually progressed gradually with time.[5] However, some patients experienced acute or subacute deterioration.[5]

In most cases of spinal dural AVF, the venous drainage is predominantly localized at the dorsal surface of the spinal cord, with enlarged, tortuous vessels pursuing an irregular longitudinal course.[5,9,11,20] Patients with enlarged, tortuous veins on both the ventral and dorsal surfaces of the cord have been reported to be more seriously impaired than those with such veins only on the dorsal surface.[21,22] Extension of arterialization to the veins on the ventral surface may lead to increased venous pressure within the spinal cord and more rapid deterioration of the myelopathy. In the present case, the pathological findings appeared to be in accord with the rapid clinical course.

VCM associated with dural AVF is a treatable disorder without sequelae if it is diagnosed in the early stages.[5,8,15] MRI is a non-invasive, very useful tool for establishing an early diagnosis of VCM. The findings characteristic of VCM include mild enlargement of the spinal cord, an increased T2 signal in the cord, parenchymal enhancement with contrast medium and flow voids in tortuous vessels along the dorsal surface of the cord.[8,20] However, these findings are not universal, and it is sometimes difficult to differentiate VCM from a primary intramedullary tumor. In the present case, the rapidly progressive clinical course was an additional stumbling block to the early establishment of an accurate clinical diagnosis. On the other hand, an angiography, which was not done in the present case, remains the gold standard for accurately diagnosing VCM. However, even this examination sometimes fails to demonstrate the abnormal angio-architecture responsible for the disease.[8,9,15,21] In some cases, a biopsy is needed to obtain the diagnosis or rule out the possibility of neoplastic lesions.[8,15] The present case illustrates that when examining patients with progressive myelopathy, VCM associated with dural AVF should always be considered in the differential diagnosis.

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ORIGINAL ARTICLE

Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (Phase II study)

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Abstract
Amyotrophic lateral sclerosis (ALS) is a rare disease involving selective and progressive degeneration and disappearance of motor neurons. Oxidative stress is believed to contribute to its pathogenesis. We have investigated the efficacy and safety of edaravone, a free radical scavenger previously approved for treatment of acute cerebral infarction, in ALS patients. Within an open trial design, 20 subjects with ALS received either 30 mg (5 subjects) or 60 mg (15 subjects) of edaravone via intravenous drip once per day. Two weeks of administration was followed by a two-week observation period. This four-week cycle was repeated six times. The primary endpoint was the change in the revised ALS functional rating scale (ALSFRS-R) score, while the secondary endpoint was 3-nitrotyrosine (3NT) level in cerebrospinal fluid (CSF). Efficacy was evaluated in the 60 mg group. During the six-month treatment period, the decline in the ALSFRS-R score (2.3 ± 3.6 points) was significantly less than that in the six months prior to edaravone administration (4.7 ± 2.1 points); the difference between the two was 2.4 ± 3.5 points (Wilcoxon signed rank test, $p=0.039$). In almost all patients, CSF 3NT, a marker for oxidative stress, was markedly reduced to almost undetectable levels at the end of the six-month treatment period. Data from the present study suggest that edaravone is safe and may delay the progression of functional motor disturbances by reducing oxidative stress in ALS patients.

Key words: *Edaravone, ALS, clinical trial, ALSFRS-R, 3NT, oxidative stress*

Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by two major symptoms, i.e. muscular atrophy and reduced muscle strength. The disease rapidly progresses and, in the absence of artificial ventilation, respiratory disturbance results in death within two to four years (1,2).

At present, the only approved therapeutic treatment for ALS is the drug riluzole, an anti-glutamatergic agent. Within Europe and the United States, riluzole has been reported to prolong life expectancy by three months in ALS patients without tracheostomy (3–5). Currently, ALS is primarily treated symptomatically, for example by gastrostomy for dysphasia and artificial ventilation for dyspnea. More effective treatments for ALS are urgently needed.

The SOD1 gene was identified as a contributory factor in familial ALS (FALS) in 1993 (6). In addition, oxidative stress has been considered to contribute to the pathogenesis of ALS. Post-mortem examination of autopsy specimens from sporadic ALS (SALS) patients has revealed an increase in 3-nitrotyrosine (3NT) that is indicative of oxidative cellular damage (7). In addition, oxidative lesions have been found in nervous tissue of both SALS and FALS patients (8). Several subtypes of SALS exist, and various biochemical and pathological studies have indicated that oxidative stress contributes to the pathogenesis of this disease (9). Thus, oxidative stress appears to play a major role in motor neuron degeneration not only in FALS, but also in SALS, which accounts for the majority of ALS cases.

Edaravone is a free radical scavenger that has been approved as a therapeutic agent for treatment of acute cerebral infarction (10). This drug eliminates lipid peroxide and hydroxyl radicals by transferring an electron to the radical, being itself converted to 2-oxo-3-(phenylhydrazono) butanoic acid, and thereby exerts a protective effect on neurons within or adjacent to ischemic areas (11–13). Recently, beneficial effects of edaravone on wobbler mice with ALS-like symptoms have been reported (14). Thus, edaravone is a promising candidate for treatment of ALS. The goal of the present study was to

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investigate the safety and efficacy of edaravone treatment in ALS patients (Phase II study).

Methods

Participating institution and study period

The present study carried out within the Department of Neurology, Kohnodai Hospital, National Center of Neurology and Psychiatry, during the period from 1 November 2001 to 8 November 2002. Twenty subjects were enrolled after they had given informed consent to participate in the study. The study protocols were approved by the Institutional Review Board of the Kohnodai Hospital.

Patient selection and drug treatment protocol

The inclusion criterion was a diagnosis of SALS or FALS. In terms of respiratory function, exclusion criteria included tracheotomy, artificial respiration, or dyspnea. Additional exclusion criteria were complications such as advanced cancer, severe cardiac insufficiency, etc., stable ALSFRS-R score (15) and age of less than 20 years.

Edaravone injections were administered within an open trial setting. Either 30 or 60 mg of edaravone was dissolved in 100 ml of saline once per day immediately prior to injection and administered via an intravenous drip. Edaravone was administered every day for two weeks, then patients were observed for two weeks without edaravone treatment (first cycle). If no serious side-effects were seen during the observation period, edaravone was again administered for five days a week, for two weeks, followed by a two-week observation period using the same protocol as in the first cycle. This treatment-observation cycle was repeated five times (2nd–6th cycles). The total duration of the trial was thus six months.

Since edaravone had never previously been administered to ALS patients over a prolonged period, we first used a half (30 mg × 1/day) of the approved dose for cerebral infarction (30 mg × 2/day) in order to confirm safety. At the conclusion of the second cycle in the 30 mg group, the drug was determined to be safe, and administration of 60 mg was initiated in a second group of patients. A control group was not used because of the small number of patients in this initial study.

Patients did not receive any other investigational medications, and riluzole was maintained throughout the trial at the same dose and administration schedule that the patients had been receiving prior to enrollment. An enzyme immunoassay (EIA) method was used for measurement of 3NT in the cerebrospinal fluid (CSF), as described previously (16).

Evaluation of safety and efficacy

The primary endpoint in the current study was the change in ALSFRS-R in the six months following initiation of edaravone administration. Secondary endpoints also evaluated during the six months of edaravone administration included muscle function, respiratory function, blood gases, CSF protein (total protein, Alb, IgG) and 3NT, and lipid peroxide levels in the CSF and blood. The safety of edaravone was evaluated on the basis of physical findings, blood-urine tests, sensory testing and adverse event recording for the duration of the trial.

Data analysis

Data are presented here as the mean and S.D. The Wilcoxon signed rank test was used to determine the statistical significance of differences in rates of decline of ALSFRS-R score. The criterion of statistical significance was $p<0.05$.

Results

Composition of cases

Twenty subjects were initially enrolled in the present study (30 mg, 5 subjects; 60 mg, 15 subjects). In one subject in the 60 mg group, disease meeting the exclusion criteria of the present study was discovered, and edaravone administration was discontinued. In addition, one subject in the 30 mg group and two subjects in the 60 mg group were unable to complete the six treatment cycles of the study owing to deterioration of their disease (30 mg, 1 subject; 60 mg, 1 subject) or an adverse event (60 mg, 1 subject). To compare the changes of ALSFRS-R score in the six months prior to the start of treatment and the six months during treatment, efficacy was evaluated in the 12 subjects of the 60 mg group who completed the six treatment cycles, while safety was evaluated in all subjects.

The clinical background of the 19 subjects (30 mg, 5 subjects; 60 mg, 14 subjects) except one subject in the 60 mg group, in whom disease meeting the exclusion criteria was discovered, is summarized in Table I. The diagnosis of SALS was made for all patients except one, who was included in the 30 mg group. Riluzole was administered to four subjects in the 30 mg group, and nine subjects in the 60 mg group.

Efficacy

The changes in ALSFRS-R score during the natural course of ALS in the six months prior to administration were compared with the changes that occurred during edavarone treatment (Figure 1), and the difference in the rate of decline between the two periods was calculated. During the six-month

Table I. Patients' background.

Item	Category	30 mg Group	60 mg Group
	No. of cases	5	14
Gender	Male	3 (60.0%)	12 (85.7%)
	Female	2 (40.0%)	2 (14.3%)
Age (years)	Mean±S.D.	56.00±16.79	58.36±11.01
Body Weight (kg)	Mean±S.D.	53.74±10.05	55.01±7.61
Diagnosis	Sporadic	4 (80.0%)	14 (100.0%)
	Familial1	1 (20.0%)	0 (0.0%)
Period of Disease (years)	Mean±S.D.	2.06±1.70	2.88±2.86
Initial symptoms	Bulbar symptoms	1 (20.0%)	3 (21.4%)
	Extremity symptoms	4 (80.0%)	11 (78.6%)
Use of riluzole	No	1 (20.0%)	5 (35.7%)
	Yes	4 (80.0%)	9 (64.3%)

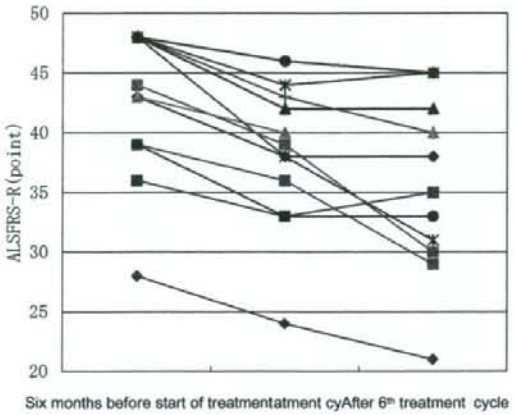

Figure 1. Time course of change in ALSFRS-R score in the 60 mg treatment group.

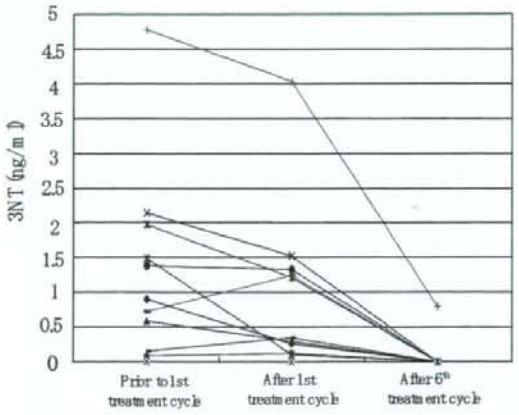

Figure 2. Time course of change in 3NT levels in cerebrospinal fluid in the 60 mg treatment group.

treatment period, the decline in the ALSFRS-R score (2.3±3.6 points) was significantly less than that in the six months prior to edaravone administration (4.7±2.1 points). Thus, treatment with edaravone (60 mg) appeared to reduce the rate of decline of ALSFRS-R score during the six-month treatment period by 2.4±3.5 points (Wilcoxon signed rank test, $p=0.039$; Table II).

In almost all patients in the 60 mg group, the level of CSF 3NT, a marker of oxidative stress, was markedly reduced to almost undetectable levels at the end of the sixth cycle of administration (Figure 2).

Safety

With regard to side-effects, one subject in the 60 mg group developed soft stools and diarrhea, which appeared to be related to the drug administration, and which disappeared during the course of treatment. In several cases, laboratory tests showed abnormalities, but none was considered to be a consequence of edaravone administration. Some subjects demonstrated titubation, but this was largely due to the progression of ALS, and none of these events was considered attributable to the edaravone treatment.

Table II. Effect of edavarone on decline of ALSFRS-R score.

Group	No. of cases excluding dropouts	Total ALSFRS-R: Score at 6 months before start of treatment	Total ALSFRS-R: Score prior to 1st cycle of administration	Total ALSFRS-R: Score after 6th cycle of administration	Change in the 6 months before the start of treatment	Change in the 6 months after the start of treatment	Difference in rate of decline*	Wilcoxon signed rank test
30 mg	4	39.3±8.0	32.0±9.6	27.0±9.6	−7.3±2.8	−5.0±3.6	2.3±3.9	0.500
60 mg	12	42.7±6.3	38.0±6.0	35.8±7.3	−4.7±2.1	−2.3±3.6	2.4±3.5	0.039

* Difference in rate of decline=change of ALSFRS-R score in the six months before the start of treatment minus change of ALSFRS-R score in the six months after the start of treatment (i.e. during treatment with edavarone).

Discussion

ALS is caused by selective damage to motor neurons. The primary symptom associated with ALS is progressive atrophy of skeletal muscle. In the United States, the ALSFRS was developed for clinical evaluation of ALS patients, and its reliability has been tested (17,18). It has been used not only in clinical examinations, but also in evaluating the efficacy of clinical trials (19,20). In the present study, we used change of ALSFRS-R as a primary endpoint to evaluate the efficacy of edaravone treatment in ALS patients. The ALSFRS-R is a revision of the ALSFRS that incorporates items to evaluate respiratory function. In the clinical trial of the therapeutic agent riluzole, the modified Norris Scale (Japanese Edition) (21) was used. However, the ALSFRS-R has one additional category, and is also considered to afford better reliability than the modified Norris Scale (22).

ALS is a progressive disease, and the ALSFRS-R scores are known to decrease almost linearly throughout the course of the disease (15). We found that the decrease of the ALSFRS-R score during the six-month edaravone treatment period was significantly smaller than that in the six months prior to the start of treatment. This result suggests that edaravone may delay the progression of functional disturbances in ALS patients.

Because of the uncontrolled design of this initial, safety-focused study with a small number of patients, a placebo effect cannot be ruled out. To support the suggested efficacy of edaravone, we therefore looked for changes in oxidative stress in CSF of the treated patients, using 3NT as a marker. A decrease in 3NT levels in the patient's CSF would be consistent with the known action mechanism of the drug, and could plausibly be expected to benefit patients. In almost all subjects, 3NT levels measured at the end of the sixth cycle of administration were markedly reduced, and were close to or below the threshold of detection. A previous study found that 3NT was increased in the spinal cord of FALS patients who exhibited mutation in the SOD1 gene, and in the spinal cord of SALS patients (7). Immunostaining revealed precipitation within the soma of motor neurons (23,24). Furthermore, increased 3NT levels in the CSF of SALS patients have been reported (25). It was also shown that 3NT levels are elevated in the spinal cord of transgenic mice expressing G37R SOD1, beginning at the early preclinical phase and continuing throughout the progression of clinical signs (26). Accordingly, the marked reduction of 3NT seen in the present study suggests that the free radical scavenger edaravone almost completely eliminated oxidative stress in the spinal cord of ALS patients.

Safety was not an issue in the group that received 30 mg (half the dose used to treat cerebral infarction patients). Side-effects were noted twice in one subject within the 60 mg group; however, these effects were not serious. Thus, no serious side-effect was seen in the 60 mg group of ALS patients, who received the same dosage as that given to cerebral infarction patients.

The present study was conducted within an open-trial, Phase II setting and the number of patients evaluated was small. Although the data from the current study are promising, it will be necessary to confirm the efficacy and safety of edaravone administration within a randomized, placebo-controlled, double-blind design.

Acknowledgements

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症例報告

Creutzfeldt-Jakob病と類似の臨床経過を示した，Basedow病を伴った橋本脳症の1例

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木村暁夫[1)] 保住功[1)] 米田誠[2)] 犬塚貴[1)]

Case Report of a Patient with Hashimoto's Encephalopathy Associated with Basedow's Disease Mimicking Creutzfeldt-Jakob Disease

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Abstract

A 79-year-old female was admitted to our hospital because of unconsciousness and convulsion following mental deterioration. On admission, she exhibited myoclonic movement of the right side of the face and right fingers in addition to rigospasticity and tremors in the right arm and leg. Laboratory tests revealed hyperthyroidism with an increased anti-TSH-R antibody titer. In addition, an echogram indicated excessive blood flow at the thyroid; hence, the patient was diagnosed with Basedow's disease. Interestingly, the tests also revealed increased titer of anti-TPO antibody, anti-Tg antibody, and anti-NH_2 terminal of α-enolase (NAE) antibody; in addition, an EEG showed abnormal findings potentially indicating periodic synchronous discharge. Brain MRI showed cerebral atrophy, and brain ^{99m}Tc-ECD-SPECT images demonstrated an overall decrease in the accumulation of ^{99m}Tc in the cerebrum. The abovementioned findings are common to patients with Creutzfeldt-Jakob disease (CJD). We initiated treatment for hyperthyroidism with thiamazole and lugol, but this did not regain consciousness. Because she had anti-thyroid antibody was observed, we considered a differential diagnosis of Hashimoto's encephalopathy and, in fact, methylprednisolone pulse therapy alleviated her symptoms and normalized the EEG findings.

The condition in this case clinically mimicked CJD; therefore, the differentiated diagnosis is important because Hashimoto's encephalopathy is treatable disease.

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Key words : Hashimoto's encephalopathy, Basedow's disease, Creutzfeldt-Jakob disease, anti α-enolase antibodies

はじめに

橋本脳症は甲状腺自己抗体と臨床症状が相関する，自己免疫性の脳症と考えられている。意識障害，ミオクローヌスなど多彩な神経症状を示し，時に脳波でperiodic synchronous discharge (PSD) 様の突発異常波を伴うことからCreutzfeldt-Jakob病(CJD)と鑑別を要することがある。橋本脳症では，CJDと異なりステロイド治療などが有効であるため，その鑑別は非常に重要である。近年，橋本脳症では血清抗N末端 α-enolase (NAE) 抗体が高率に陽性であることから，その診断に有用と報告されている[1,2]。

また橋本脳症は基礎疾患として一般に橋本病を伴う

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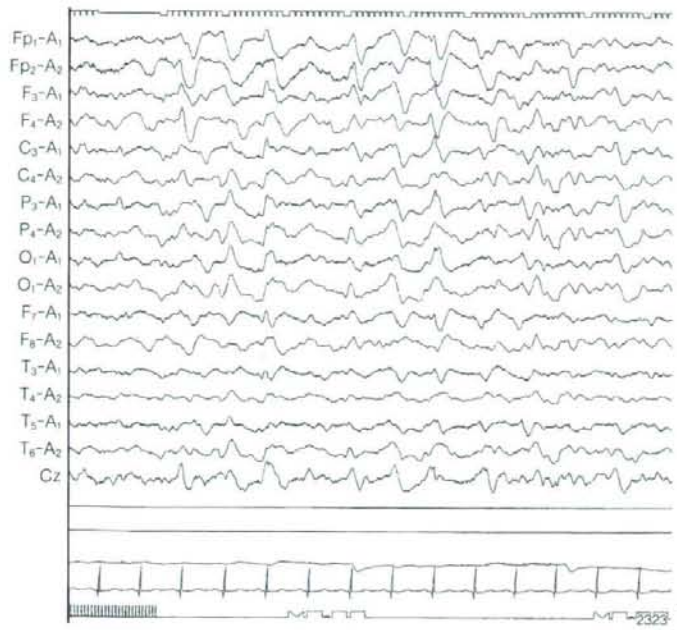

Fig. 1
The electroencephalogram (EEG) on admission at monopolar recording showed paroxysmal abnormal EEG like power spectral density (PSD) at monopolar recording.

が，時に Basedow 病を伴う報告もある[3-5]。われわれは臨床症候と脳波所見が CJD に類似し，Basedow 病を伴った橋本脳症の 1 例を経験したので，文献的考察を加え報告する。

I．症　　例

〈患　者〉 76 歳，女性

主　訴　意識障害，全身痙攣

既往歴　74 歳時に脳梗塞（左片麻痺），症候性てんかん，数年前より，高脂血症，高血圧症にて近医通院中

家族歴　特記すべきことなし

現病歴　74 歳時に脳梗塞を発症し，左不全麻痺は残存したが独歩可能な状態であった。その頃から，時計が読めない，日付がわからないなどの認知障害があったが，意思疎通は可能で日常生活は自立していた。

76 歳時の 4 月頃から徐々に発語が減少し，寝たきりの状態となった。「ありがとう」「ごちそうさま，ご飯おいしかった」など数語の発語程度になった。5 月上旬，30 秒間ほどの全身性の強直性間代性痙攣を認め，近医に入院した。その後も意識障害（GCS E1V2M4）は遷延し，数回の痙攣発作を認めたため，6 月上旬当科に転院した。

入院時現症　身長 147 cm，体重 34 kg，体温 37.2℃，血圧 112/76 mmHg，脈拍 103/min。頸部リンパ節腫大，扁桃腺部の発赤・腫張は認めなかった。眼球突出はなく，明らかな甲状腺腫大は認めなかった。心音，呼吸音に異常なく，腹部は平坦かつ軟であった。皮疹はなく，下腿浮腫も認めなかった。

神経学的所見では，意識レベルは GCS E1V2M4 で，呼びかけに対して時に「ハイ」と返事をするのみであった。脳神経領域では，瞳孔は左右同大で，対光反射は両側とも迅速であった。左共同偏視を認めた。運動系では，脳梗塞後遺症による左上下肢の筋力低下を認めた。頸部の rigidity，右上下肢の rigospasticity，右上下肢の振戦様不随意運動に加えて，顔面右側・右手指のミオクローヌス様不随意運動を認めた。四肢の腱反射は正常で，病的反射は認めなかった。感覚系，協調運動は不明で，髄膜刺激徴候は認めなかった。自律神経系では，明らかな異常を認めなかった。前頭葉徴候として，snout reflex，両側 palmomental reflex を認めた。

入院時検査所見　検血および一般生化学検査では，TSH 0.01 μIU/mL 以下（正常 0.35～4.94 μIU/mL）と低下し，freeT3　5.93 pg/mL（正常 1.71～3.71 pg/mL），freeT4　2.16 ng/dL（正常 0.70～1.48 ng/dL）と上昇し，甲状腺機能亢進を認めた。抗 TPO 抗体 155 U/mL（正常 0.3 U/mL 以下），抗 Tg 抗体 13.9 U/dL（正常 0.3 U/dL 以下），抗 TSH-R 抗体 23.4%（正常 15% 以下）と上昇を認めた。抗核抗体，他の各種自己抗体（リ

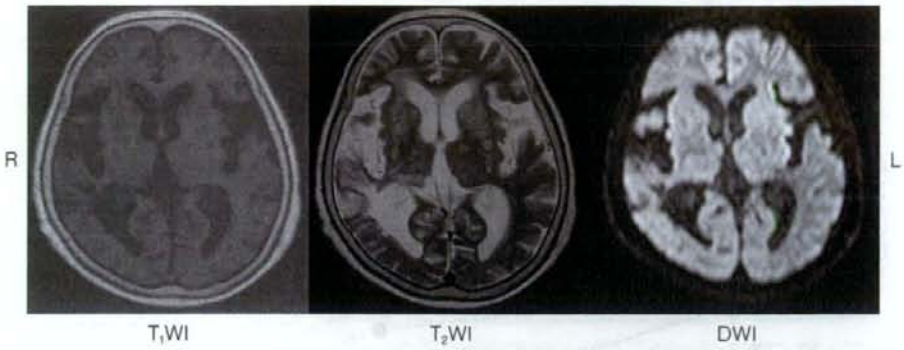

Fig. 2

T_1-weighted image (TR 522ms, TE 11ms) showed cerebral atrophy, and T_2-weighted image (TR 4,075 ms, TE 100 ms) showed high intensity at the periventricular lesion and basal ganglion. Diffusion-weighted image (TR 2,675 ms, TE 66 ms) demonstrated no high-intensity lesion.

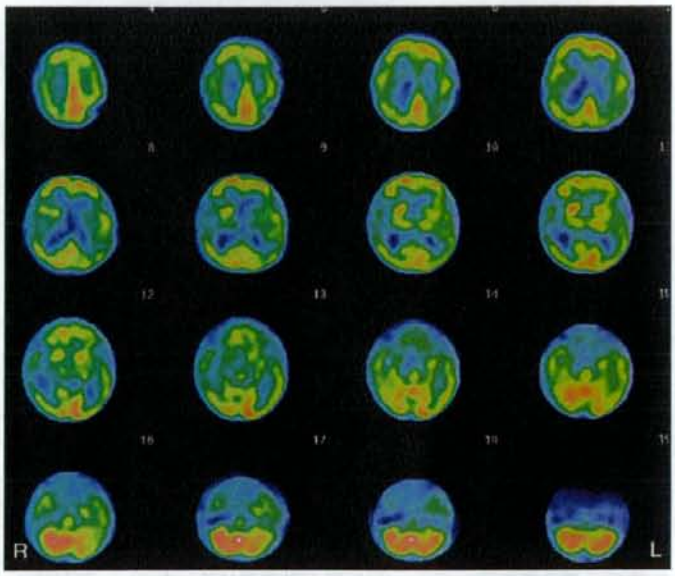

Fig. 3

Brain ^{99m}Tc-ECD-SPECT image on admission demonstrated an overall decrease in the accumulation of ^{99m}Tc in the cerebrum.

ウマチ因子，抗 DNA 抗体，抗 Sm 抗体，抗 SS-A 抗体，抗 SS-B 抗体，P-ANCA，C-ANCA）は陰性であった。髄液検査では，細胞数 1 /mm^3（単核球），蛋白 24 mg/dL，糖 58 mg/dL と正常範囲であり，髄液抗 TPO 抗体は 0.3 U/mL 以下であった。甲状腺エコー検査では，甲状腺のび漫性の腫大と，内部血流の著明な増加を認めた。これらの所見は Basedow 病の診断ガイドラインで“確からしい Basedow 病”に該当するものであった。

脳波では，時に PSD 様の異常波を認めた（Fig. 1）。頭部 MRI では，T_1WI で大脳の全体的な萎縮を認め，T_2WI で両側側脳室周囲白質，基底核領域，右側頭葉に高信号域を認めた（Fig. 2）。DWI で有意な異常高信号域は認めなかった。Evans index は 0.3 以下であり，高位円蓋部の脳溝，くも膜下腔の狭小化は認めなかった。脳血流^{99m}Tc-ECD-SPECT（Fig. 3）では，大脳皮質，基底核領域を含む，全体的な血流の低下を認めた。

入院後経過（Fig. 4） 入院時，甲状腺機能亢進状態に対し，チアマゾール（15 mg/day），ルゴール（3 mL/day）を投与し，freeT3 は正常範囲内となったが，症状の改善は認めなかった。甲状腺に対する自己抗体が検出され橋本脳症と診断し，入院 19 日後よりステロイドパルス療法（methylprednisolone 1g/day×3days）と，後療法として

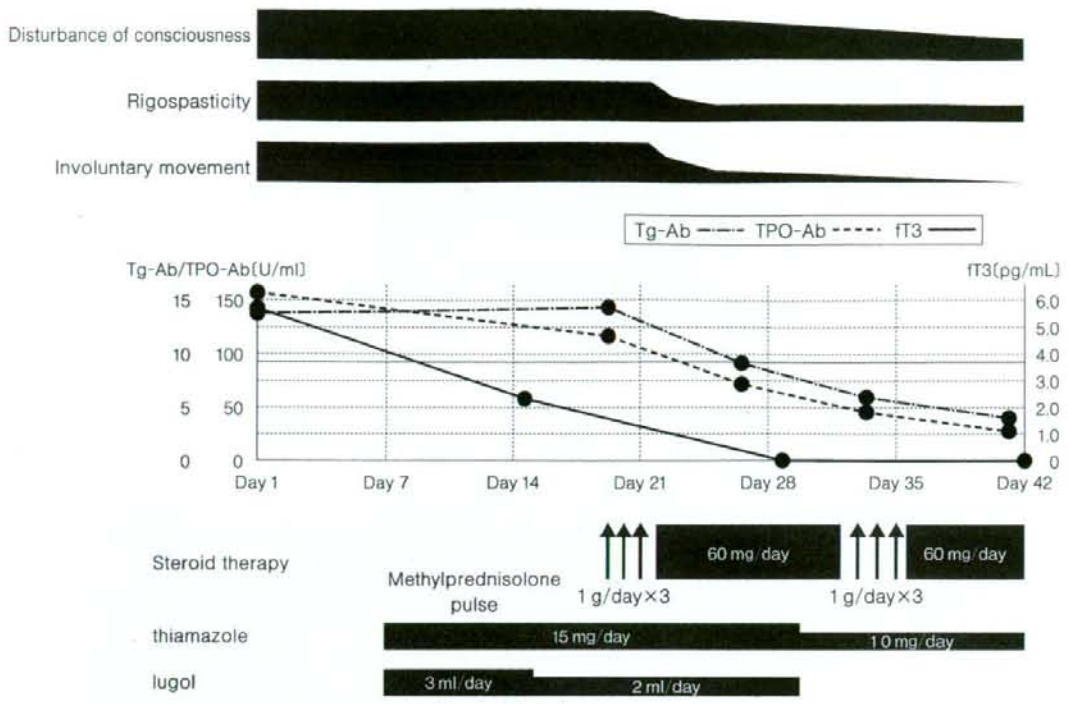

Fig. 4 Clinical course

Al though we treated the patient with thiamazole and lugol, she didn't recover. She recovered rapidly after the initiation of steroid therapy.

経口プレドニンを 60 mg/日から開始，漸減した。ステロイド治療開始 3 日目より意識レベルの改善を認め，名前，年齢を言うことができるようになり，自発語を認めるまでに改善した。また，右上下肢の rigospasticity は軽減し，顔面右側・右上下肢の不随意運動は消失した。ステロイドパルス療法後，抗甲状腺抗体の抗体価は低下傾向となった。ステロイド治療開始 12 日目の脳波では 9 Hz 前後の α 波を基礎波に認め，PSD 様の異常波はまったく消失した(**Fig. 5**)。後に，治療前の患者血清中に NAE に対する抗体が免疫ブロット法にて強陽性と確認された(**Fig. 6**)。なお，プリオン蛋白遺伝子では codon129 Met/Met，codon219 Glu/Glu の正常多型であり，髄液中 14-3-3 蛋白は陰性であった。

ステロイド療法による症状改善後，神経症候は不変であったため，2006 年 8 月上旬，長期療養目的で転院となった。

II. 考　　察

1966 年 Brain ら[6]が，橋本脳症について，甲状腺自己抗体に関連する脳症として報告し，何らかの自己免疫機序を想定した。その後同様の報告が散見され，副腎皮質ステロイド薬などの免疫抑制剤が著効することが明らかとなった[7]。

橋本脳症の臨床症状に関しては，急性ないし亜急性に進行する多彩な神経症状を呈する。意識障害(73.2%)，精神症状(50.4%)，知能低下(34.6%)，全身痙攣(66.1%)，不随意運動〔ミオクローヌス (33.9%)，振戦 (様) 不随意運動 (26.0%) など〕がよく認められる[7]。脳波では，76.3%で全般性徐波を認め，三相波，棘波，棘徐波，てんかん性脳波，突発性徐波を数%に認める[7]。三相波の陰性波が鋭くなると鋭波徐波複合に類似した波形となることがあり，周期性同期性放電様所見が認められることがある[8]。頭部 CT ないし MRI 画像では，34.7%で非特異的な所見を伴うとされる[7]。側頭葉，前頭葉優位の全般性脳萎縮が軽度に認められることがある[8]。SPECT 検査では，93.3%で脳全体の低灌流所見が認められる[7]。

一方，CJD の臨床症状に関して，急速に進行する認知症，ミオクローヌスを主に認め，数カ月で無動性無言になる。また，広範な中枢神経系の障害を示し，錐体路，

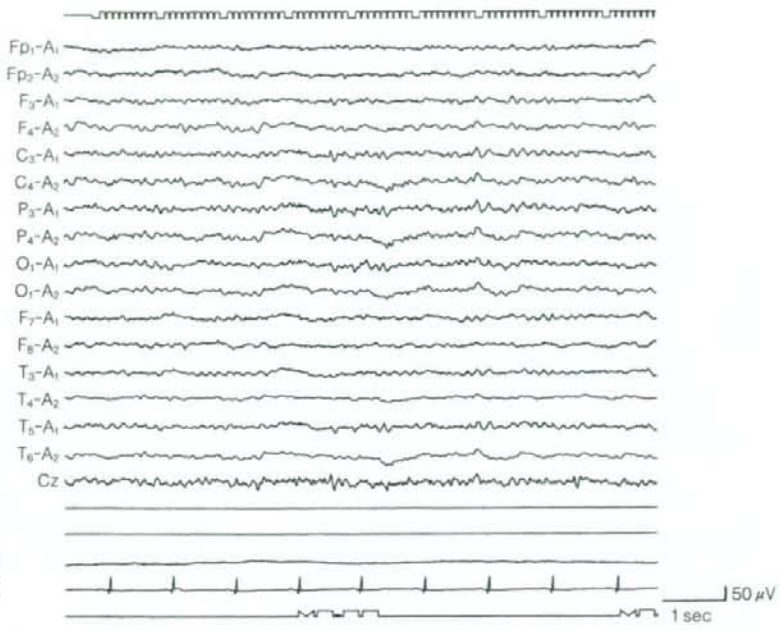

Fig. 5
EEG after treatment with corticosteroids demonstrated an α-rhythm without paroxysmal abnormal EEG like PSD at monopolar recording.

錐体外路徴候を認める[9]。脳波では，82.2%に PSD を認める[9]。頭部 MRI では急速に進行する脳萎縮を認め，脳血流シンチでは，早期から巣状あるいは広汎な集積低下を呈し，病期の進行に伴い，より広汎に集積低下が進行する[10]。

これらの臨床症状や検査所見から橋本脳症と CJD との鑑別が問題になることがあるが[11-16]，橋本脳症は治療可能な疾患であることからその鑑別は重要である。CJD との鑑別を問題にした報告例[11-16]は散見され，その中には，生検病理所見で CJD 類似の海綿状白質変化を示した症例[17]や，髄液で 14-3-3 蛋白が陽性に出現した症例[14]も報告されている。本例でも，入院当初，約2カ月間の進行性の自発性低下，ミオクローヌス様の不随意運動，脳全般の萎縮，PSD 様の脳波所見から CJD との鑑別が問題となった。

Peschen-Rosin らは橋本脳症の診断基準として，原因不明の繰り返すミオクローヌス，全身性痙攣，局所神経症状や精神症状を認める患者の中で，①脳波異常，②抗マイクロゾーム抗体の上昇，③髄液蛋白の上昇またはオリゴクローナルバンドの出現，④副腎皮質ステロイド薬に良好に反応すること，⑤頭部 MRI で異常所見がないこと，のうち3つ以上を満たすこと，を挙げている[18]。本例では入院後検査が進みこの診断基準を満たすことになり，橋本脳症と考えられた。近年，橋本脳症の患者血清

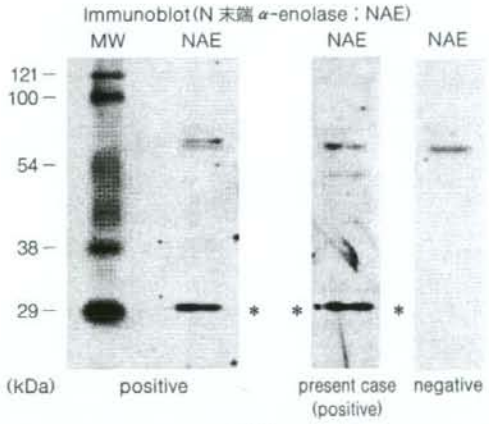

Fig. 6
Immunoblot analysis of the NH_2-terminal of α-enolase (NAE) with sera yielded strongly positive results for NAE. The asterisks indicate the position of NAE.

に抗 NAE 抗体を高率に認めることが報告されている[1,2]。この抗体は橋本脳症の 68%に陽性であり，脳炎，CJD，中毒性疾患，脳血管障害などの他疾患や自己免疫疾患（多発性硬化症，傍腫瘍性神経症候群など），膠原病（全身性エリテマトーデス，混合性結合織炎，Sjögren 症候群，Beçhet 病など），Basedow 病では検出されず，疾患特異性が極めて高いとされている[19]。また，脳症を呈しな

い橋本病では11%しか抗NAE抗体は検出されず，脳症に特異性が高い[19]。本例では入院時，臨床症候，脳波所見からCJDと鑑別を要したが，甲状腺自己抗体の陽性，ステロイド治療による効果，抗NAE抗体が陽性を示したことから橋本脳症と診断した。

橋本脳症の基礎疾患は一般的に橋本病であるが，稀にBasedow病を伴った橋本脳症の報告がある[3-5]。日本甲状腺学会でのBasedow病の診断ガイドラインでは，臨床所見として，①頻脈，体重減少，手指振戦，発汗増加などの甲状腺中毒症所見，②び漫性甲状腺腫大，③眼球突出または特有の眼症状，のうち1つ以上を認め，検査所見として，(i)遊離T 4，遊離T 3のいずれか一方または両方高値，(ii) TSH低値（0.1 μU/ml以下），(iii)抗TSH受容体抗体（TRAb，TB II）陽性，または刺激抗体（TSAb）陽性，(iv)放射性ヨード（またはテクネシウム）甲状腺摂取率高値でかつシンチグラフィでび漫性，のうち，4つを満たすときはBasedow病と診断し，(i)，(ii)，(iii)を満たす場合を確からしいBasedow病とする[20]。本例では，臨床所見として②を認め，検査所見で(i)～(iii)を認めることから，“確からしいBasedow病”に相当する。日本甲状腺学会による橋本病診断ガイドラインでは，臨床所見で，①び漫性甲状腺腫大（ただしBasedow病などの他の原因が認められないもの），検査所見で，(i)抗甲状腺マイクロゾーム（またはTPO）抗体陽性，(ii)抗サイログロブリン抗体陽性，(iii)細胞診でリンパ球浸潤を認める，とし，臨床所見，検査所見の1つ以上を有するものを橋本病と診断する[21]。本例では，Basedow病の除外規定以外は橋本病の診断基準を満たしている。

ただし，両疾患とも臓器特異性自己免疫疾患で抗甲状腺抗体陽性率は共に高く，両疾患が混在することや両疾患の移行例を時に認めることがあり，Hashitoxicosisという臨床概念が提唱されている[22]。森は，HashitoxicosisとはBasedow病と橋本病の合併であり，臨床的に活動性Basedow病の所見を有し，かつ組織学的に橋本病像を認めるものと定義している[23]。また，自己免疫性甲状腺疾患の病因・病態に関するレインボー説では，自己免疫性甲状腺疾患は連続的なスペクトラムを形成する種々の疾患群からなると考え，典型的な橋本病とBasedow病は対照的な両極に位置するとしている[24]。Hashitoxicosisは両者の中間にあり，時間経過を考慮すると三者はお互いに移行する場合があると考えられている。Basedow病発症頻度は橋本病患者の約1.5～5%であり[22,24]，本例では組織学的検査を行っていないが，橋本病の組織変化も伴っていた可能性を推測する。

ま と め

神経症候，脳波所見からCreutzfeldt-Jakob病と類似し，Basedow病を伴う橋本脳症の1例を経験した。各種の甲状腺自己抗体陽性，副腎皮質ステロイド薬の著効から橋本脳症と診断した。本例はBasedow病の診断基準を満たすが，橋本病の共存の確証のためには組織学的検索が必要である。

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症例報告

介護従事者にみられた水痘脊髄炎

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A Case of Varicella Myelitis for Nursing Care Worker

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Abstract

Varicella myelitis is very rarely observed in healthy adult. We report the case of 25-year-old nursing care worker who suffered from chickenpox for the first time. Approximately 2 weeks prior to the development of the symptoms, she cared for an old man who suffered from herpes zoster. She was admitted to our hospital, and she complained of weakness and paresthesia in the lower limbs. Subsequently, she experienced vesicorectal disorders: this was followed 5 days later by the appearance of a rash. Spinal T_2-weighted MR images showed a high-intensity lesion in the spinal cord at the level of Th9/10, and both IgM-type anti-VZV antibodies and VZV-DNA were present in her cerebrospinal fluid. Treatment comprising a combination of acyclovir at 1,500 mg/day for 14 days and γ-globulin with high titer of IgG-type anti-VZV antibodies at 5 g/day for 5 days result in remarkable improvement. She was able to walk again. The high-intensity lesion in the spinal T_2-weighted MR images disappeared. Urinary dysfunction disappeared completely after 5 months. Care persons without anti-IgG antibodies against VZV are at a high risk of contracting varicella infection. Guidelines for infection control in home care, as well as hospitals, are necessary for caregivers.

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Key words : varicella-zoster virus, varicella, myelitis, spinal MRI, nursing care worker

はじめに

近年，小児期に水痘・帯状疱疹ウイルス（varicella-zoster virus: VZV）に感染する機会が少なくなっているため，成人の水痘発症は増加の傾向にある。また一般的に成人発症の水痘は，肺炎を合併するなど，小児例に比べ重篤になりやすい[1,2)]。

われわれは，水痘発症5日後に高度な対麻痺，膀胱直腸障害を呈し，5カ月後に回復した水痘脊髄炎の1成人例を経験したので報告する。

Ⅰ．症　　例

〈患　者〉25歳，女性，介護福祉士

主　訴　両下肢筋力低下による歩行困難，排尿・排便

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