19 Alamowitch S, Graus F, Uchuya M, Rene R, Bescansa E, Delattre JY: Limbic encephalitis and small cell lung cancer: clinical and immunological features. *Brain* 1997;120:923-928.
20 Inuzuka T: Limbic encephalitis: etiology, pathogenesis, diagnosis and therapy [in Japanese]. *Rinsho Shinkeigaku* 2004;44:799-801.
21 Kusuhara T, Shoji H, Kaji M, Ayabe M, Hino H: Non-herpetic acute limbic encephalitis [in Japanese]. *Rinsho Shinkeigaku* 1994;34:1083-1088.
22 Bien CG, Schulze-Bonhage A, Deckert M, Urbach H, Helmstaedter C, Grunwald T, Schaller C, Elger CE: Limbic encephalitis not associated with neoplasm as a cause of temporal lobe epilepsy. *Neurology* 2000;55:1823-1828.
23 Asaoka K, Shoji H, Nishizaka S, Ayabe M, Abe T, Ohori N, Ichiyama T, Eizuru Y: Non-herpetic acute limbic encephalitis: cerebrospinal fluid cytokines and magnetic resonance imaging findings. *Intern Med* 2004;43:42-48.
24 Watanabe Y, Shimizu Y, Ooi S, Tanaka K, Inuzuka T, Nakashima K: Steroid-responsive limbic encephalitis. *Intern Med* 2003;42:428-432.
25 Ances BM, Vitaliani R, Taylor RA, Liebeskind DS, Voloschin A, Houghton DJ, Galetta SL, Dichter M, Alavi A, Rosenfeld MR, Dalmau J: Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005;128:1764-1777.
26 Mori M, Kuwabara S, Yoshiyama M, Kanesaka T, Ogata T, Hattori T: Successful immune treatment for non-paraneoplastic limbic encephalitis. *J Neurol Sci* 2002;201:85-88.
27 Buckley C, Oger J, Clover L, Tuzun E, Carpenter K, Jackson M, Vincent A: Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol* 2001;50:73-78.
28 Thieben MJ, Lennon VA, Boeve BF, Aksamit AJ, Keegan M, Vernino S: Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. *Neurology* 2004;62:1177-1182.
29 Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, Clover L, Parkinson A, Bien CG, Omer S, Lang B, Rossor MN, Palace J: Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004;127:701-712.
30 Fauser S, Talazko J, Wagner K, Ziyeh S, Jarius S, Vincent A, Schulze-Bonhage A: FDG-PET and MRI in potassium channel antibody-associated non-paraneoplastic limbic encephalitis: correlation with clinical course and neuropsychology. *Acta Neurol Scand* 2005;111:338-343.
31 Pozo-Rosich P, Clover L, Saiz A, Vincent A, Graus F: Voltage-gated potassium channel antibodies in limbic encephalitis. *Ann Neurol* 2003;54:530-533.
32 Vincent A, Bien CG: Temporal lobe seizures, amnesia and autoantibodies - identifying a potentially reversible form of non-paraneoplastic limbic encephalitis. *Epileptic Disord* 2005;7:177-179.

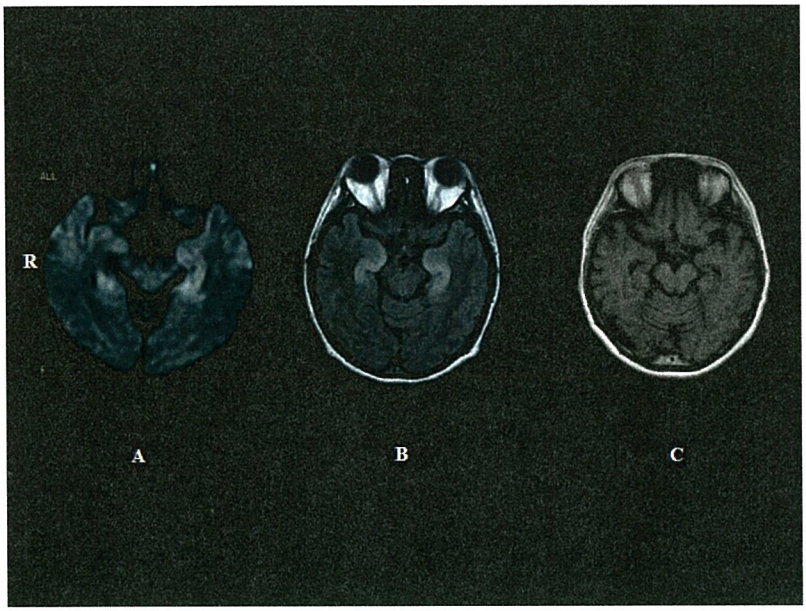

Figure 1. MR images
Patient 1 [A, B, C]: (A) An axial diffusion-weighted image (DWI) and (B) a fluid-attenuated inversion recovery (FLAIR) image show hyperintensity in the bilateral mesial temporal lobes in the acute phase (two days after admission). (C) A follow-up T1-weighted MR image shows the disappearance of signal abnormalities and the appearance of bilateral hippocampal and mild cortical atrophies (one year after the disease onset).

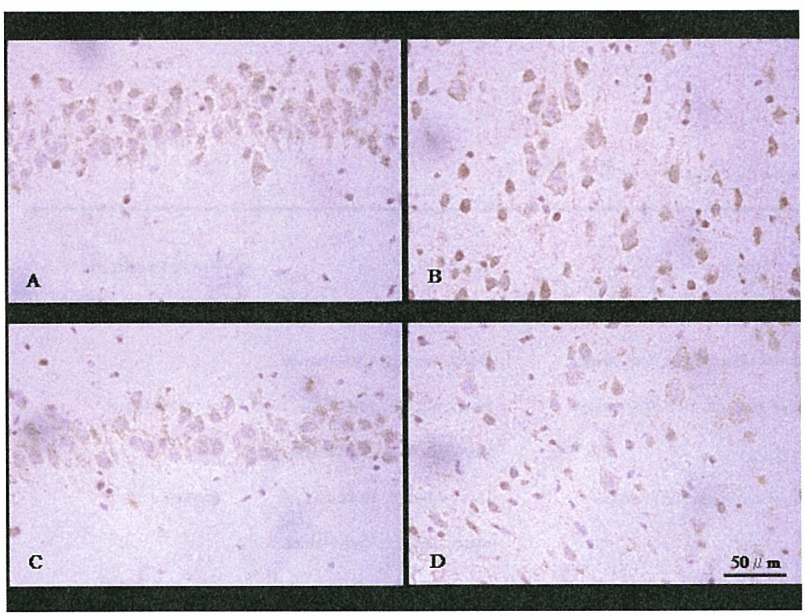

Figure 2. Immunohistochemistry
Upper row (A, B), coronal sections of rat brain immunoreacted with serum samples from Patient 1. Lower row (C, D), coronal sections immunoreacted with serum samples from Patient 4. The diluted sera (1:2000) of these patients reacted with the cytoplasm of rat hippocampal (A, C) and cortical (B, D) neurons. The same pattern of reactivity was observed for the serum samples from Patient 3 and the anti-NMDAε2 antibody. The sections are mildly counterstained with hematoxylin (magnification ×400).

Table 1 Autoantibodies against GluRε2

Patient No. age/sex	Clinical diagnosis	Anti-GluRε2 antibody (CSF, IgM/IgG)	Anti-GluRε2 antibody (serum, IgM/IgG)
1. 45/F	LE	+/+	+/+
2. 62/M	LE	+/+	-/-
3. 53/F	LE	+/+	+/+
4. 30/M	LE	+/-	+/+
5. 22/F	LE	-/-	-/-
6. 68/M	bacterial meningoencephalitis	-/-	-/-
7. 57/F	cryptococcal meningoencephalitis	-/-	-/-
8. 18/F	MELAS	-/-	-/-
9. 59/F	Neuro-Sweet disease	-/-	-/-
10. 65/M	PLE (anti-Hu antibody-positive)	-/-	-/+
11. 26/M	etiology-unknown meningoencephalitis	-/-	+/-
12. 56/M	brainstem encephalitis	-/-	-/-

LE, idiopathic limbic encephalitis; MELAS, mitochondrial encephalopathy with lactic acidosis and strokelike episodes; PLE, paraneoplastic limbic encephalitis

Table 2 Clinical features of patients with IgM autoantibody against GluRε2 in CSF

Patient No. age/sex	Clinical diagnosis	Initial symptoms	Sequelae	Steroid treatment
1. 45/F	LE	convulsion, visual and olfactory hallucinations	disorientation, amnesia, recent memory disturbance	responsive
2. 62/M	LE	convulsion, auditory hallucination	disorientation, amnesia, recent memory disturbance	not performed
3. 53/F	LE	convulsion, behavioral changes	disorientation, amnesia recent memory disturbance, psychiatric symptoms	responsive
4. 30/M	LE	convulsion, behavioral changes	amnesia, recent memory disturbance	responsive

LE, idiopathic limbic encephalitis

Table 3 Laboratory and neuroimaging findings of patients with IgM autoantibody against GluRε2 in CSF

Patient No.	WBC, CRP (/mm^3, mg/dl)	CSF cell (/mm^3)	CSF protein (mg/dl)	IgG index	Other autoantibodies	Initial brain MRI (DWI, T2, FLAIR)
1	13800, 1.30	81 (M81)	30	0.53	TPO Ab	hyperintensity in bilateral mesial temporal lobes
2	3500, 0.42	10 (M9, P1)	67	0.80	-	hyperintensity in left mesial temporal lobe
3	18240, <0.05	7 (M1, P6)	38	NE	ANA	hyperintensity in bilateral mesial temporal lobes, insulae and cingulate gyri
4	17090, 1.89	34 (M34)	36	0.73	-	normal

ANA, antinuclear antibody; TPO Ab, thyroid peroxidase antibody; M, mononuclear cell; P, polynuclear cell; NE, not examined

Neuropathology - Decision on Manuscript ID NEU-06-0031.R1

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Dear Dr. Kimura:

It is a pleasure to accept your manuscript entitled "Venous congestive myelopathy of the cervical spinal cord: an autopsy case showing a rapidly progressive clinical course" in its current form for publication in Neuropathology.

Thank you for your fine contribution. On behalf of the Editors of Neuropathology , we look forward to your continued contributions to the Journal.

Sincerely,
Dr. HITOSHI TAKAHASHI
Editor-in-Chief, Neuropathology
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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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Running title: Venous congestive myelopathy

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 Th4 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 fistula (AVF), formerly known as Foix-Alajouanine syndrome. VCM associated with dural AVF, which is now considered to be treatable in the early stage, is rare 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 fistula (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 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 postmortem 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, neurological examination showed mild muscle weakness in the four extremities. The patient's ability to perceive sensations, except for vibration, was diminished below the neck. He showed a shuffling gait and a left-sided limp. He also exhibited dysuria and orthostatic hypotension: his blood pressure was 132/87 supine and 84/62 standing. 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 Th4 vertebral level, with edematous swelling (Fig. 1A). Flow voids were not observed on T1- or T2-weighted images. After administration of contrast medium, the ventral portion of the intraparenchymal 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 6th day of admission, he suddenly developed flaccid paraparesis and urinary retention. His clinical symptoms were gradually progressive thereafter. On the 9th day, he showed complete paraplegia. Subsequently, severe muscle weakness ascended to the upper extremities, and his respiratory function also became gradually impaired. On the 22nd day of hospitalization, he died of pneumonia followed by respiratory failure. Having a retrospective discussion about the patient's clinical course and MRI findings, especially those shown in Fig. 1C, 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 1,350 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).

Neuropathological examination was performed on 4-μm-thick sections using several stains: hematoxylin-eosin, Klüver-Barrera, and elastica-Goldner. Selected sections were also immunostained using the avidin-biotin-peroxidase complex (ABC) method (Vector, Burlingame, CA) with diaminobenzidine as the chromogen. The primary antibodies used were mouse monoclonal antibodies against phosphorylated neurofilament protein (SMI31; Sternberger Monoclonals Inc., Baltimore, USA; 1:1000) and □-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 as 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.

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. 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 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 postmortem 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 stage.[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, angiography, which was not done in the present case, remains the gold standard for accurate diagnosis of VCM. However, even this examination sometimes fails to demonstrate the abnormal angioarchitecture responsible for the disease.[8,9,15] In some cases, 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.

REFERENCES

1, Aminoff MJ, Barnard RO, Logue V. The pathophysiology of spinal vascular malformations. *J Neurol Sci* 1974; 23: 255-263.
2, Kendall BE, Logue V. Spinal epidural angiomatous malformations draining into intrathecal veins. *Neuroradiology* 1977;13:181-190.
3, Criscuolo GR, Oldfield EH, Doppman JL. Reversible acute and subacute myelopathy in patients with dural arteriovenous fistulas: Foix-Alajouanine syndrome reconsidered. *J Neurosurg* 1989; 70: 354-359.
4. Benhaiem N, Poirier J, Hurth M. Arteriovenous fistulae of the meninges draining into the spinal veins. A histological study of 28 cases. *Acta Neuropathol* (Berl) 1983; 62: 103-111.
5. Atkinson JLD, Miller GM, Krauss WE et al. Clinical and radiographic features of dural arteriovenous fistula, a treatable cause of myelopathy. *Mayo Clin Proc* 2001; 76: 1120-1130.
6. Kataoka H, Miyamoto S, Nagata I. et al. Venous congestion is a major cause of neurological deterioration in spinal arteriovenous malformations. *Neurosurgery* 2001; 48: 1224-1229.
7. Andersson T, van Dijk JMC, Willinsky RA. Venous manifestations of spinal arteriovenous fistulas. *Neuroimag Clin N Am* 2003; 13: 73-93.
8. Rodriguez FJ, Crum BA, Krauss WE et al. Venous congestive myelopathy: a mimic of neoplasia. *Mod Pathol* 2005; 18: 710-718.
9. Koch C. Spinal dural arteriovenous fistula. *Curr Opin Neurol.* 2006; 19: 69-75.
10. Foix C, Alajouanine T. La myélite nécrotique subaigue (in French). *Rev Neurol (Paris)* 1926; 33: 1-42.
11. de Girolami U, Frosch MP, Tator CH. Reginal neuropathology: diseases of the spinal cord and vertebral column. In: Graham DI, Lantos PL (eds) *Greenfield's Neuropathology*, Vol 1, 7th edn. London: Arnold, 2002; 1071-1073.
12. Case record of the Massachusetts General Hospital. Case 44191. *N Engl J Med* 1958; 258: 949-954.
13. Flament J, Vicente AN, Coërs C, Guazzi G. La myélopathie angiodysgénétique (Foix-Alajouanine) et sa diférenciation des nécroses spinales sur angiomatose intra-médullaire (in French). *Rev Neurol (Paris)* 1960; 103: 12-29.
14. Matsko DE, Panuntsev VS, Ivanova NE et al. Arteriovenous malformation of the cervical spinal cord with unusual drainage into the cranial cavity. *Pathol Res Pract* 1996; 192: 942-947.
15. Hurst RW, Kenyon LC, Lavi E et al. Spinal dural arteriovenous fistula: The pathology of venous hypertensive myelopathy. *Neurology* 1995; 45: 1309-1313.
16. Satoh M, Kuriyama M, Fujiwara T et al. Brain stem ischemia from intracranial dural arteriovenous fistula: Case report. *Surg Neurol* 2005; 64:341-345.
17. Asakawa H, Yanaka K, Fujita K et al. Intracranial dural arteriovenous fistula showing diffuse MR enhancement of the spinal cord: Case report and review of the literature. *Surg Neurol* 2002; 58: 251-257.
18. Kobessho H, Uesaka Y, Nishimiya M et al. A 68-year-old man of dural arteriovenous fistula at the cranio-cervical junction with dysesthesia ascending from his both toes (in Japanese with English abstract). *Rinsho Shinkeigaku* 2004; 44: 171-175.
19. Miyoshi Y, Taniwaki T, Arakawa K et al. A case of cervical myelopathy due to dural arteriovenous fistula at the craniocervical junction (in Japanese with English abstract). *Rinsho Shinkeigaku* 1999; 39: 836-841.
20. Gilbertson JR, Miller GM, Goldman MS et al. Spinal dural arteriovenous fistulas: MR and Myelographic findings. *AJNR Am J Neuroradiol* 1995; 16: 2049-2057.
21. Berenstein A, Lasjaunis P. Spine and spinal cord vascular lesions. In: *Surgical Neuroangiography*: Endovascular Treatment of Spine and Spinal Cord Lesions. Berlin: Springer-Verlag, 1992: 1-109.
22. Yoshino M, Kohno M, Kanayama S et al. A case of spinal dural arteriovenous fistula draining to the ventral coronal venous plexus (in Japanese with English abstract). *No To Shinkei* 2005; 57: 617-621.

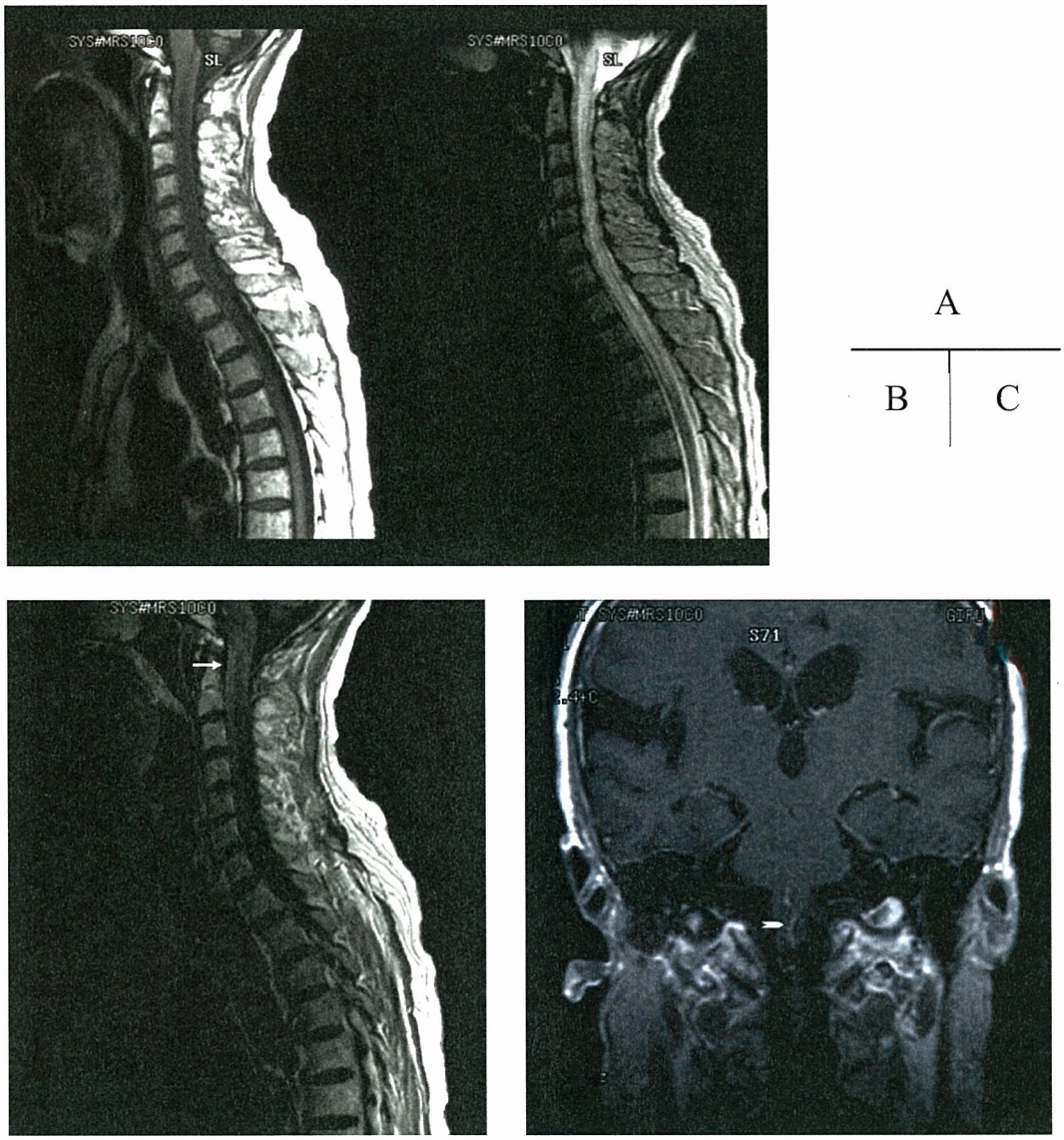

Fig. 1 Magnetic resonance imaging
(A) Intramedullary lesion (mainly in the center of the cord) with low intensity on the T1-weighted image (left) and high intensity on the T2-weighted image from the medulla oblongata to the spinal cord at the level of Th4 vertebra (right). Note that the lesion is accompanied by marked edema. (B) The ventral parenchyma presents mild and irregular enhancement (arrow). (C) A dilated vessel is recognized along the ventral surface of the upper cervical cord (arrowhead).

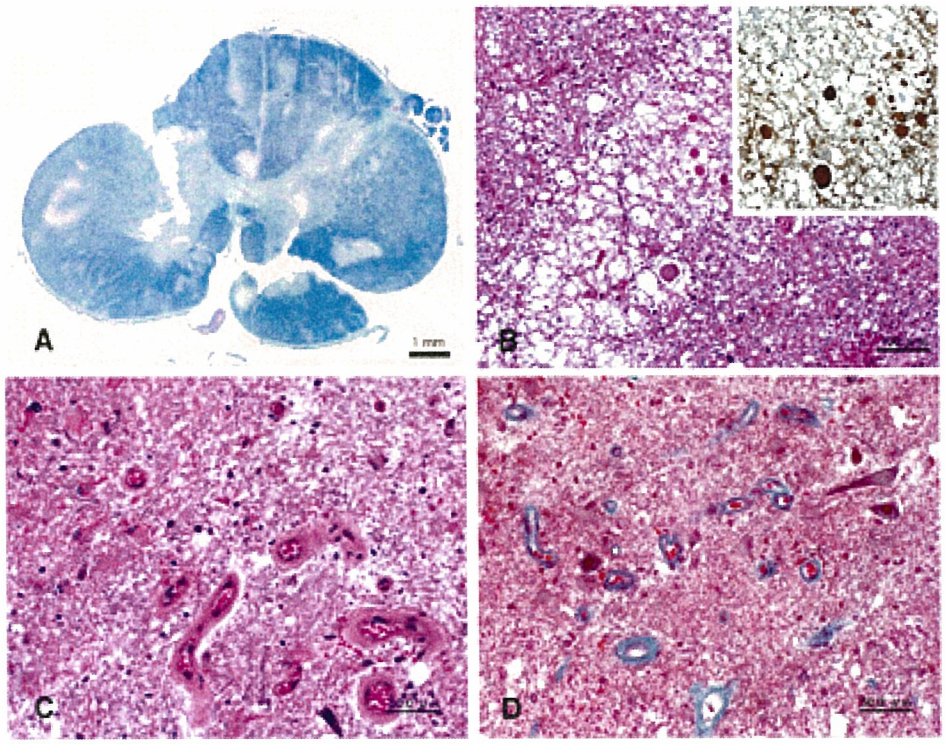

Fig. 2 Intraparenchymal lesions in the upper-to-middle cervical cord segments.
(A) Multifocal, patchy irregular lesions are evident in the gray and white matter (tissue lacerations are artifacts made at autopsy). K-B. (B) Vacuolar degeneration of myelin is evident in the white matter. Note that some of the vacuolated myelin contains round, eosinophilic swollen axons. H-E. Inset: Such swollen axons are clearly recognized by immunostaining with an anti-phosphorylated neurofilament protein antibody, SMI31. SMI31 immunostaining. (C) Neuronal loss and gliosis, and rarefaction of the neuropil are evident in the anterior horn. H-E. (D) Increased small, hyalinized vessels are evident in the anterior horn. Elastica-Goldner.

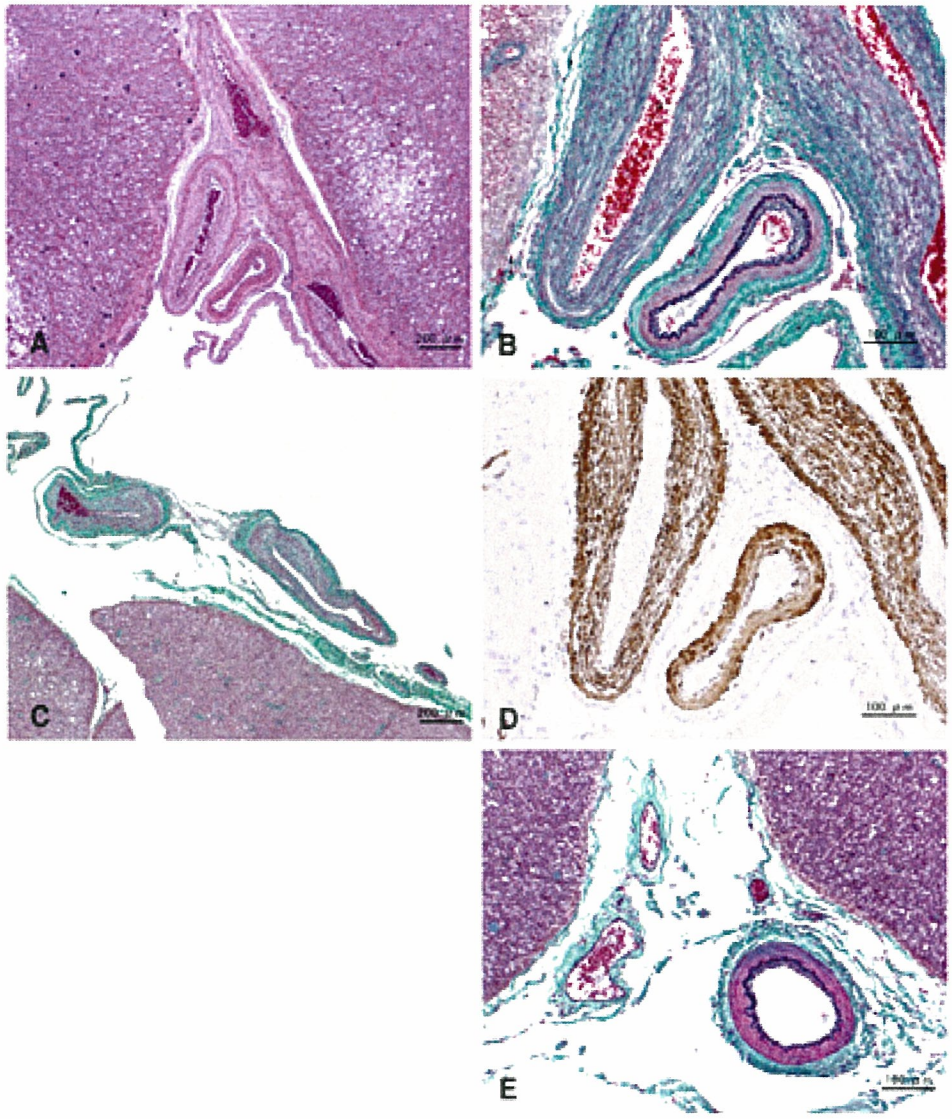

Fig. 3 Venous lesions in the subarachnoid space at the cervical cord level.
(A) Enlarged blood vessel sections, showing marked fibrous intimal thickening. H-E. (B) In these sections, no internal elastic lamina is evident (arterialized anterior spinal vein). Note the internal elastic lamina in an arterial section (anterior spinal artery). Elastica-Goldner. (C) Arterialization is also evident in blood vessel sections seen here (posterior spinal vein). Elastica-Goldner. (D) In the thickened intima, many SMA-positive cells and fibers are present (fibromuscular intimal thickening). 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. Elastica-Goldner.

Amyotrophic Lateral Sclerosis. 2006; 7: 241–245

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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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ISSN 1748-2968 print/ISSN 1471-180X online © 2006 Taylor & Francis
DOI: 10.1080/17482960600881870

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%)

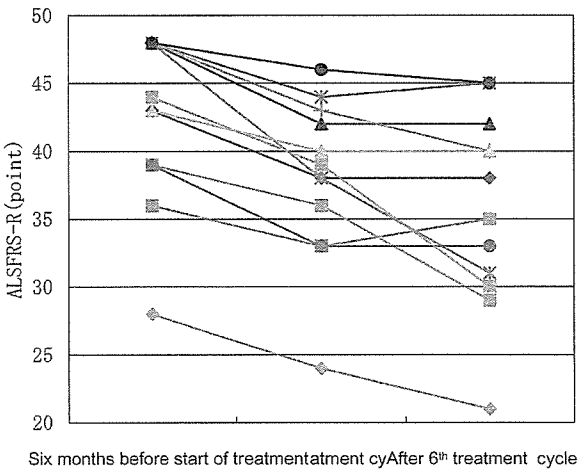

Figure 1. Time course of change in ALSFRS-R score in the 60 mg treatment group.

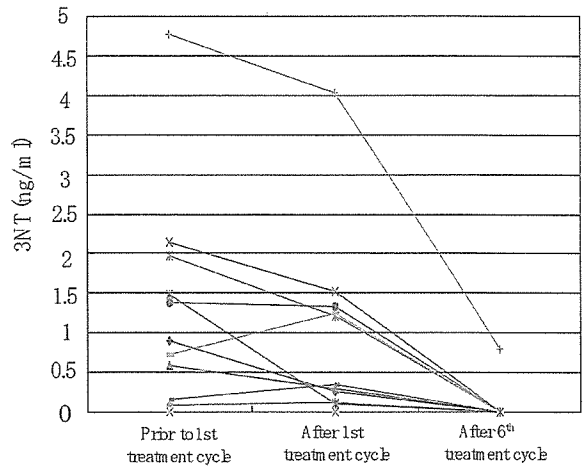

Figure 2. Time course of change in 3NT levels in cerebrospinal fluid in the 60 mg treatment group.

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

We thank the ALS patients who participated in the present study. We also thank the coordinators Ms Ozawa and Ms Nakamura, who were instrumental in obtaining informed consents and in the control of hospital visits. We also thank the medical technologist Ms Asano who measured 3NT, the chief nurse of the neurology ward for providing beds necessary for tests, and staff members of the neurology ward and of the outpatient clinic for faithfully following the protocols for drug administration and laboratory measurement.

References

1. Caroscio JT, Mulvihill MN, Sterling R, Abrams B. Amyotrophic lateral sclerosis: its natural history. Neurol Clin. 1987;5:1–8.
2. Braun SR. Respiratory system in amyotrophic lateral sclerosis. Neurol Clin. 1987;5:9–31.
3. Bensimon G, Lacomblez L, Meininger V, ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. N Engl J Med. 1994;330:585–91.
4. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V, ALS/Riluzole Study Group. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Lancet. 1996;347:1425–31.
5. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophoc lateral sclerosis (ALS)/motor neuron disease (MND). Amyotroph Lateral Scler Other Motor Neuron Disord. 2003;4:191–206.
6. Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993;362:59–62.
7. Beal MF, Ferrante RJ, Browne SE, Matthews RT, Kowall NW, Brown RH Jr. Increased 3-nitrotyrosine in both sporadic and familial amyotrophic lateral sclerosis. Ann Neurol. 1997;42:646–54.
8. Ferrante RJ, Browne SE, Shinobu LA, Bowling AC, Baik MJ, MacGarvey U, et al. Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis. J Neurochem. 1997;69:2064–74.
9. Shibata N. Transgenic mouse model for familial amyotrophic lateral sclerosis with superoxide dismutase-1 mutation. Neuropathology. 2001;21:82–92.
10. Edaravone Acute Brain Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Cerebrovascular Dis. 2003;15:222–9.
11. Watanabe T, Yuki S, Egawa M, Nishi H. Protective effects of MCI-186 on cerebral ischemia: possible involvement of free radical scavenging and antioxidant actions. J Pharmacol Exp Ther. 1994;268:1597–1604.

12. Mizuno A, Umemura K, Nakashima M. Inhibitory effect of MCI-186, a free radical scavenger, on cerebral ischemia following rat middle cerebral artery occlusion. Gen Pharmacol. 1998;30:575–8.
13. Yamamoto T, Yuki S, Watanabe T, Mituka M, Saito K, Kogure K. Delayed neuronal death prevented by inhibition of increased hydroxyl radical formation in a transient cerebral ischemia. Brain Research. 1997;762:240–2.
14. Ikeda K, Iwasaki Y, Kinoshita M. Treatment of wobbler mice with free radical scavenger. Molecular mechanism and therapeutics of amyotrophic lateral sclerosis. Elsevier Science B.V. 2001: 335–40.
15. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999;169:13–21.
16. Acworth IN, Bogdanov MB, Mccabe DR, Beal MF. Estimation of hydroxyl free radical levels in vivo based on liquid chromatography with electrochemical detection. Methods Enzymol. 1999;300:297–313.
17. Florence J, Brinkmann J, Szirony K, Sanjak M, Brooks B, Pestronk A, et al. Implementation of evaluation procedures in a multicenter study of treatment in ALS: ensuring reliability. Muscle Nerve. 1994;1(Suppl):S166.
18. ALS CNTF Treatment Study (ACTS) Phase I–II Study Group. The amyotrophic lateral sclerosis functional rating scale: assessment of activities of daily living in patients with amyotrophic lateral sclerosis. Arch Neurol. 1996;53:141–7.
19. BDNF Study Group (Phase III). A controlled trial of recombinant methionyl human BDNF in ALS. Neurology. 1999;52:1427–33.
20. ALS CNTF Treatment Study (ACTS) Group. A double-blind, placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. Neurology. 1996;46: 1244–9.
21. Oda E, Ohashi Y, Tashiro K, Mizuno Y, Kowa H, Yanagisawa N. Reliability and factorial structure of a rating scale for amyotrophic lateral sclerosis. Brain and Nerve. 1996;48:999–1007.
22. Ohasi Y, Tashiro K, Itoyama Y, Nakano I, Sobue G, Nakamura S, et al. Study of functional rating scale for amyotrophic lateral sclerosis: revised ALSFRS(ALSFRS-R)Japanese version. Brain and Nerve. 2001;53: 346–55.
23. Abe K, Pan LH, Watanabe M, Kato T, Itoyama Y. Induction of nitrotyrosine-like immunoreactivity in the lower motor neuron of amyotrophic lateral sclerosis. Neurosci Lett. 1995;199:152–4.
24. Sasaki S, Shibata N, Komori T, Iwata M. iNOS and nitrotyrosine immunoreactivity in amyotrophic lateral sclerosis. Neurosci Lett. 2000;291:44–8.
25. Tohgi H, Abe T, Yamazaki K, Murata T, Ishizaki E, Isobe C. Remarkable increase in cerebrospinal fluid 3-nitrotyrosine in patients with sporadic amyotrophic lateral sclerosis. Ann Neurol. 1999;46:129–31.
26. Bruijn LI, Beal MF, Becher MW, Schulz JB, Wong PC, Price DL, et al. Elevated free nitrotyrosine levels, but not protein-bound nitrotyrosine or hydroxyl radicals, throughout amyotrophic lateral sclerosis (ALS)-like disease implicate tyrosine nitration as an aberrant in vivo property of one familial ALS-linked superoxide dismutase 1 mutant. Proc Natl Acad. Sci. USA. 1997;94:7606–11.

神経内科，64(6)：609-613，2006

原著

急性小脳失調で発症したHIV感染を伴う神経梅毒の1例*

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Key Words: neurosyphilis, HIV infection, cerebellar ataxia, SPECT

はじめに

成人において急性に小脳失調をきたす疾患はさまざまであるが，神経梅毒により小脳失調をきたした報告例は少ない．われわれは，急性小脳失調で発症したHIV感染を伴う神経梅毒の1例を経験したので報告する．

症　例

患者：48歳，男性．

主訴：両手のふるえ，歩行時のふらつき．

既往歴：下顎部の膿瘍(41歳時に手術)．

家族歴：父が食道癌．

現病歴：2005年1月9日から38℃台の発熱，咽頭痛が出現した．12日に熱が続くため近医を受診し，抗生剤の点滴を施行され解熱した．24日，再び38℃台の発熱が出現し，同時に手がふるえ書字が困難になった．28日，同院で歩行時のふらつきを指摘されて，当科を紹介され入院した．

入院時現症：身長169cm，体重76kg．体温37.4℃，血圧129/74mmHg，脈拍86/分．リンパ節腫大は認めず，扁桃腺部に軽度の発赤を認めた．心音，呼吸音に異常なく，腹部は平坦かつ軟であった．皮疹は認めなかった．

神経学的所見では，意識清明，知能正常であり，失行，失認などの高次機能障害は認めなかった．脳神経領域では，正面視および全方向注視時の振り子様眼振を認め，眼球運動は正常であり，瞳孔異常，視野障害は認めなかった．運動系では，四肢筋力に異常なく，筋トーヌスは正常であった．上肢腱反射は正常．膝蓋腱反射，アキレス腱反射は減弱しており，病的反射は認めなかった．協調運動では，両側反復拮抗運動が拙劣で，企図振戦があり，歩行はwide basedで，継ぎ足歩行が不能であり，四肢・体幹失調を認めた．失調症状に明らかな左右差は認めなかった．関節位置覚や振動覚などの深部感覚および表在感覚に異常はなかった．Romberg徴候，髄膜刺激徴候，膀胱直腸障害はいずれも認めなかった．

入院時検査所見：検血および一般生化学検査では，WBC11,650/m*l*(正常：3,400～9,200/m*l*)と軽度上昇，軽度肝機能障害〔AST 74IU/*l*(正常：7～35IU/*l*)，ALT 159IU/*l*(正常：7～40IU/*l*)〕を認めた．血清のガラス板法，TPPA抗体は陽性を示し，血清TPHA-IgM 2倍(正常：2倍未満)，TPHA-IgG 512倍(正常：2倍未満)，FTA-ABS

* Neurosyphilis with HIV infection developing acute cerebellar ataxia. A case report. (Accepted April 10, 2006).

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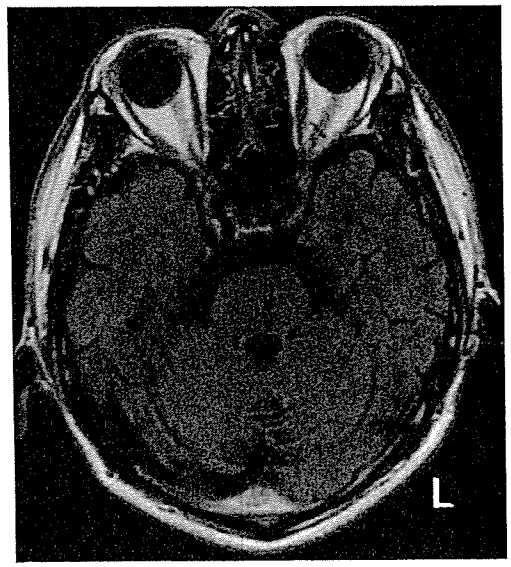

図1　頭部MRI・T1強調画像

1,280倍(正常：20倍未満)であった．入院後の血液検査でHIV抗体(ELISA法)が陽性を示し，ウェスタンブロット法でも陽性であった．CD_4リンパ球数は828/μl(28.3%)(正常：35～65%)であり，HIV-RNA量は7.6×10^4copy/mlであった．ビタミンB_1は30ng/ml(正常：20～50ng/ml)と正常値で，抗ガングリオシド抗体はGM_1, GM_{1b}, GD_{1a}, GalNAc-GD_{1a}, GQ_{1b}, GD_{1b}, GT_{1a}につき検索したが，抗GalNAc-GD_{1a}抗体IgGが(1＋)を示した以外は陰性であった．髄液検査では，細胞数は80/mm^3(単核球79/mm^3，多核球1/mm^3)と上昇し，蛋白も69mg/dlと軽度上昇を認めた．髄液中の糖，Clは正常であった．髄液ガラス板法は陰性であったが，髄液TPPA抗体1,280倍(正常：80倍未満)，FTA-ABS 20倍(正常：20倍未満)と陽性であった．入院時の頭部MRI画像では，小脳の萎縮や異常信号域は認めず，脳幹およびテント上レベルにおいても萎縮や異常信号域は認めなかった(図1)．^{123}I-IMP-SPECT画像では，両側小脳で明らかな血流低下が認められ，頭頂後頭葉では右側優位に軽度の血流低下を認めた(図2)．

入院後経過：入院後から神経梅毒の治療としてPCG 2,400万単位/日を3週間持続的に投与した．治療開始後から四肢・体幹失調は改善傾向を示し，血清ガラス板法，髄液細胞数は減少した．治療開始から3週間後では，眼振を除き症状はほぼ消失し，髄液所見も正常となった(図3)．HIV感染症に関しては，CD_4リンパ球数，HIV-RNA量は日和見感染症をきたすほどの低下は示しておらず，抗ウイルス療法の適応とはならず経過観察とした．

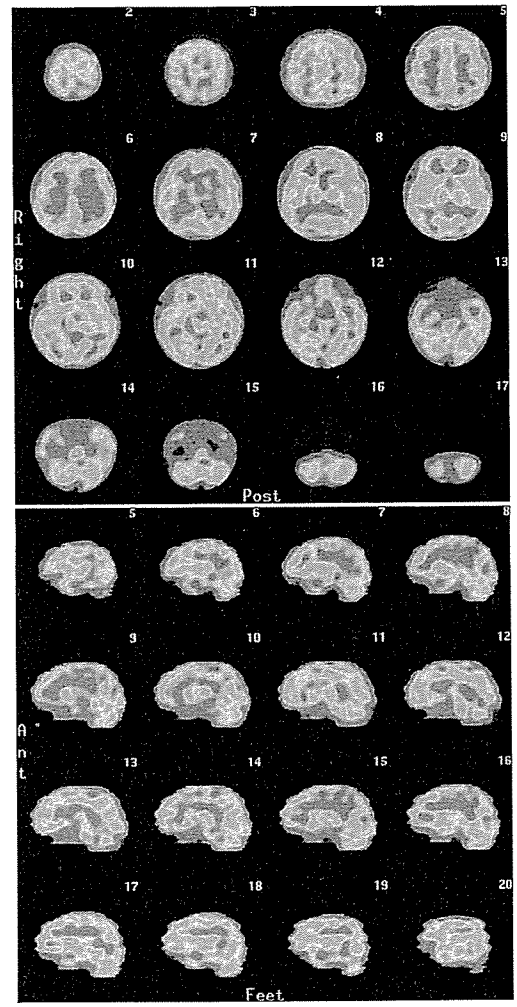

図2　^{123}I-IMP-SPECT
両側小脳で明らかな血流低下が認められ，頭頂後頭葉では右側優位に軽度の血流低下を認めた．

考　察

本症例は急性に小脳失調症状を呈し，脳血流シンチにより小脳の血流低下を認め，神経梅毒の治療により症状の改善が得られたため神経梅毒に伴う急性小脳炎と診断した．なお，入院時認めた眼振に関しては，今回の発症以前から認められるものであり，先天性眼振と考えられた．

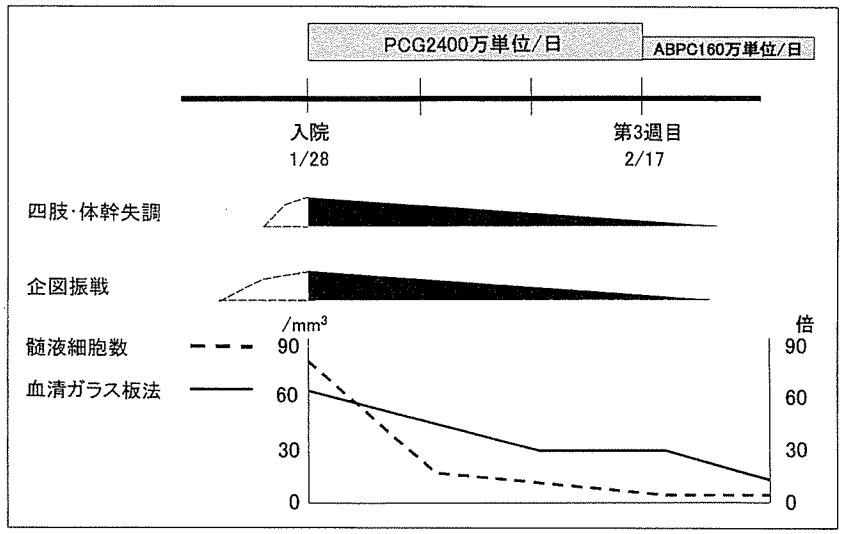

図3 臨床経過

表1 小脳症状を伴う神経梅毒の既報告例

報告者(報告年)	年齢・性	型	症状	SPECT
自験例(2005)	48歳・M	髄膜血管型	四肢・体幹失調，企図振戦，両下肢腱反射低下	小脳後頭頭頂葉の血流低下
Umashankarら(2004)[5]	43歳・M	髄膜血管型	小脳失調，頭痛，水平性眼振，左上下肢異常感覚，左上下肢筋力低下	
Morikawaら(2002)[4]	39歳・M	進行麻痺	手指振戦，平衡障害，無関心，自閉，物忘れ	小脳の血流低下
高橋ら(2002)[3]	39歳・M	進行麻痺	対光反射遅延，脳梁離断性失行，小脳失調，知能低下，性格変化	後頭葉優位の大脳半球全般の血流低下
藤井ら(1999)[2]	49歳・M	進行麻痺(ALD合併)	小脳失調，言語障害，左手運動障害，健忘症状	
大郷ら(1989)[1]	43歳・M	髄膜血管型	頭痛，小脳失調	

神経梅毒による小脳失調の報告例は少なく，1970年以降で文献を検索した範囲では5例のみであった[1)~5)]．その内訳としては，進行麻痺が3例，髄膜血管型が2例であった(表1)．SPECTが施行された症例は5例のうちの進行麻痺の2例であり，そのうちの1例に本例同様小脳の血流低下と治療による改善を認めている．一方Umashankarらは，髄膜血管型神経梅毒により両側の後下小脳動脈の閉塞をきたし，小脳梗塞に至った症例[5)]を報告している．閉塞の機序として，梅毒による直接的な侵襲もしくは免疫学的な機序の関与による動脈内膜炎としている[6)]．本症例の神経梅毒のタイプとしては，症状や治療による症状の可逆性から髄膜血管型が推定され，入院時認めた小脳失調およびSPECTにおける血流低下は動脈内膜炎あるいは動脈炎による小脳の血流低下の関与が考えられた．

また，本例ではHIV感染症を伴っていた．CD_4陽性リンパ球数やHIV-RNA量を測定したが，その数値から判断して日和見感染を起こす可能性は低いと考えられた．さらに髄液を含めた各種培養検査，血液検査では日和見感染症を示唆する所見は認めなかった．また，頭部MRI画像上小脳の萎縮や異常信号域は認めず，HIV感染に伴うADEM[7)]や小脳萎縮[8)~13)]といった疾患の可能性は低いと考えられた．HIV感染初期に伴う髄膜脳炎[14)~20)]の可能性も考えられたが，PCGを用いたのみで症状と検査所見が改善したことからは神経梅毒が症状に関与していると考えた．

梅毒患者がHIV感染を高率に合併していること