patients, our survey covered as many large hospitals as possible in the area, to which patients with acute encephalitis are transferred in Tottori Prefecture. Moreover, at least one Japanese Neurological Society Board Certified neurologist was involved in the diagnosis and treatment in these hospitals. Although the population of Tottori Prefecture is the lowest in Japan, the number of Japanese Neurological Society Board Certified neurologists is the highest relative to the population. Tottori Prefecture is a suitable region for the epidemiological surveillance of neurological disorders.

Our current survey identified 49 adult patients (≥16 years of age) with acute encephalitis over the 5-year period in Tottori Prefecture, equating to an incidence rate of 19.0 per million person-years (95% CI = 14.4–25.1). In patients with acute encephalitis, 12 patients were diagnosed with NHALE. NHALE patients appeared every year in our area; there was no year when NHALE was epidemic. The incidence rate of NHALE was 4.7 per million person-year (95% CI = 2.6–7.6). Compared with HSE, the incidence of NHALE was almost the same as that of HSE, but the onset age of NHALE patients was lower than that of HSE patients.

There is some confusion concerning the term NHALE. First, the disorder has received various names, such as acute diffuse lymphocytic meningoencephalits [6], acute reversible limbic encephalitis [7] and acute juvenile female non-herpetic encephalitis [8]. Although there are some differences in clinico-pathological features amongst these disorders, the term of NHALE is broadly used in Japan. Second, as far as we know, the term NHALE is not used outside of Japan. In this survey, we used NHALE as a clinical entity of limbic encephalitis in which limbic systems are thought to be mainly affected without either evidence of viral infection or paraneoplastic disease process. The recent discovery of an association of antibodies to neuronal cell surface antigens facilitates the recognition of subtypes of limbic encephalitis [9]. These antibodies include anti *N*-methyl-D-aspartate receptor antibody, anti-glutamate receptor ε2 antibody and anti-voltage-gated potassium channels antibody [10–14]. Furthermore, some Hashimoto's encephalopathy patients, although it is rare, represent a clinical phenotype of limbic encephalitis [15,16]. Fujii *et al.* [17] reported an association of autoantibodies against the amino terminal of alpha-enolase with Hashimoto's encephalopathy. These studies indicated that assessment of the autoantibodies is useful for classification of subtypes of limbic encephalitis. However, this study is a retrospective study, the NHALE patients in this study were not fully assessed for these antibodies. Further prospective studies assessing these related antibodies may provide valuable findings on the epidemiological study of encephalitis.

Conclusion

Based on this result, as many as 550 new NHALE patients would appear every year in Japan, indicating that NHALE is not a rare disease at all. There are some subtypes in NHALE which depend on associated antibodies. Further prospective epidemiological study targeting limbic encephalitis is needed to investigate a precise epidemiology concerning NHALE.

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Patient Report

Longitudinal analysis of Epstein–Barr virus-associated illness

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Key words chronic active Epstein–Barr virus infection, cytokine, Epstein–Barr virus-associated hemophagocytic syndrome, real-time polymerase chain reaction.

Host immune status, such as cytokine production by activated cells, and immunodeficient status with respect to other pathogens, complicates the pathogenesis of Epstein–Barr virus (EBV)-associated illnesses, such as EBV-associated hemophagocytic syndrome (EBV-AHS) and chronic active EBV infection (CAEBV).[1–3] But no report has assessed the relationship between EBV load and cytokine profiles. Here we report two cases of EBV-associated illness that presented as EBV-AHS, with longitudinal analyses of both the EBV load and cytokine profile.

Case Reports

Case 1

A 16-month-old girl with a high-grade fever lasting for 4 days, and hepatomegaly was referred to Okayama University Hospital in July 2004. Laboratory tests indicated moderate pancytopenia, and a substantial increase in ferritin (144 480 ng/mL) and lactate dehydrogenase (LDH; 16 640 IU/L). EBV serology indicated viral capsid antigen (VCA)-IgG 1:40 fluorescent antibody test (FA), VCA-IgM <1:10 (FA), VCA-IgA <1:10 (FA), EBV nuclear antigen (EBNA) <1:10 (FA), and EA-IgG 2.2 (+) (enzyme-linked immunosorbent assay). The EBV load was 5.3×10^3 copies/μg DNA in the peripheral blood (PB) and 3.7×10^4 copies/μg DNA in the bone marrow (BM; Fig. 1). The BM was hypocellular with a few hemophagocytic histiocytes. Southern blot indicated EBV monoclonality. Based on these findings the patient was diagnosed as having EBV-AHS. No perforin mutation was identified using a previously described method.[4] After diagnosis she was treated with etoposide (VP-16), dexamethasone (DEXA), and cyclosporine A (CsA), and her clinical condition improved immediately. A low-grade fever appeared, however, on day 22 after admission and the EBV load in the PB increased to almost the same level as it was on admission. Although neither ferritin nor LDH was elevated on day 25 (88 ng/mL and 360 IU/L, respectively), they were elevated at 613 ng/mL and 1330 IU/L, 2 days later (on day 27). C-reactive protein was not elevated on either day 23 or 27. VP-16 was administered again based on the HLH-94 protocol[5] after EBV-AHS relapse.

Case 2

In June 2004 another 16-month-old girl developed a high-grade fever and erythema multiforme. A diagnosis of EBV-AHS was made in a different hospital based on pancytopenia, elevated LDH and ferritin levels, and a high EBV load in the PB. She was treated with prednisolone (PSL; 2 mg/kg per day) for 14 days, and her clinical condition improved initially. The patient relapsed, however, 2 days after discontinuing the PSL, and she did not respond to the re-administration of PSL. She was referred to Okayama University Hospital in July 2004, after receiving methyl-PSL pulse therapy (Fig. 2). Laboratory tests on admission indicated EBV VCA-IgG 1:160, VCA-IgM <1:10, EBNA 1:40, EA-IgG 1.6 (+), EBV load 2.1×10^4 copies/μg DNA in the PB and the patient was positive for EBV monoclonality. The perforin gene mutation was negative. Treatment with DEXA and CsA was continued because her condition and blood examination were relatively stable, except for the high EBV load, but the patient developed a fever >38°C, a dry cough, and tachypnea on day 30 after admission. Serological tests for fungi, *Mycoplasma pneumoniae*, cytomegalovirus, and adenovirus were negative. The chest computed tomography (CT) images were non-specific on day 43 (Fig. 3a). The possibility of EBV-related intestinal pneumonia (IP) was considered because of the high EBV load in the PB. After weekly administration of VP-16 the EBV load in the PB fell below 1×10^2 copies/μg DNA, but her respiratory symptoms worsened. Chest CT showed peribronchovascular interstitial thickening (Fig. 3b). KL-6 was elevated at 870 U/mL on day 70. A lung biopsy and bronchoalveolar lavage (BAL) were not performed because the patient had a severe bleeding tendency. Chest CT obtained before placing the patient on mechanical ventilation showed central predominant consolidation and ground-glass opacities (Fig. 3c). Despite additional immunochemotherapy the patient died of respiratory failure and sepsis on day 93.

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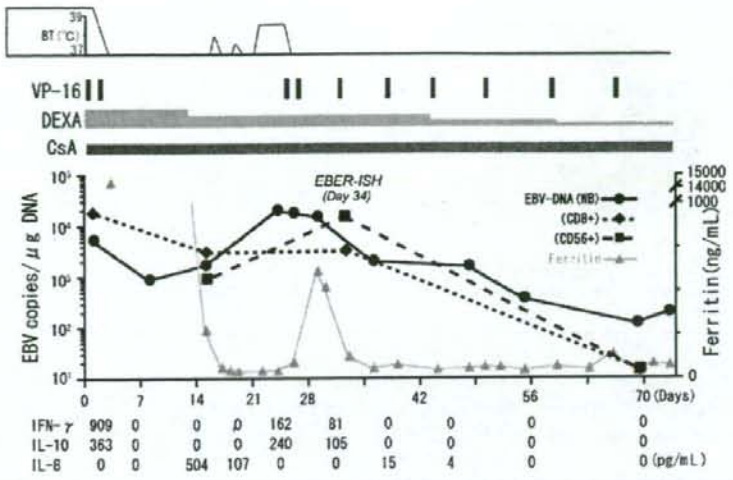

Fig. 1 Clinical course of patient during hospitalization. The quantification of the EBV load was more sensitive than ferritin to the relapse of EBV-AHS. IFN-γ and IL-10 were elevated during the progression of EBV-AHS. In contrast, IL-8 was elevated before the relapse occurred. BT, body temperature; CsA, cyclosporine A; DEXA, dexamethasone; EBER, Epstein-Barr virus-encoded small RNA; EBV, Epstein–Barr virus; EBV-AHS, EBV-associated hemophagocytic syndrome; IFN, interferon; IL, interleukin; ISH, *in situ* hybridization; VP-16, etoposide.

Real-time polymerase chain reaction of EBV-DNA

The polymerase chain reaction (PCR) protocol used for the EBV-DNA assay has been described previously.[6] Briefly, genomic DNA was extracted from 200 μL of whole blood, using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The real-time PCR assay was performed using TaqMan probe for BALF5 gene and Prism Model 7700 Sequencing Detection System (PE Applied Biosystems, Foster City, CA, USA). PB lymphocytes were separated into the CD4+, CD8+, CD19+, and CD56+ cell fractions using positive selection with MACS Beads (Miltenyi Biotec, Suntec City, Singapore) according to the manufacturer's instructions. The manufacturer's protocol stated that the purified CD8+ cell fraction contains CD8+CD56+ cells after positive magnetic bead selection, and the median purity of the CD8+CD56- cells in the present patients was approximately 80%. It also states that the purified CD56+ cell fraction contains CD3+CD56+ cells, and the median purity of CD3-CD56+ cells in the present patients was approximately 70%. The purity was assessed using flow cytometry after staining with anti-CD8-FITC (PharMingen, Franklin Lakes, NJ, USA), anti-CD56-PE (PharMingen), and anti-CD3 PerCP (Becton Dickinson, Franklin Lakes, NJ, USA).

We quantified the EBV load longitudinally in each cell population by sorting using real-time PCR, as described here. In patient 1 the CD8+ cell fraction was found to contain a high EBV load on admission, and on days 14 and 30. The CD56+ cell fraction also contained a high EBV load, but less than the viral loads in the CD8+ cell fraction on day 14. On day 30, after the first relapse into EBV-AHS, it had a higher EBV load than did the CD8+ cell fraction. Based on *in situ* hybridization (ISH) of

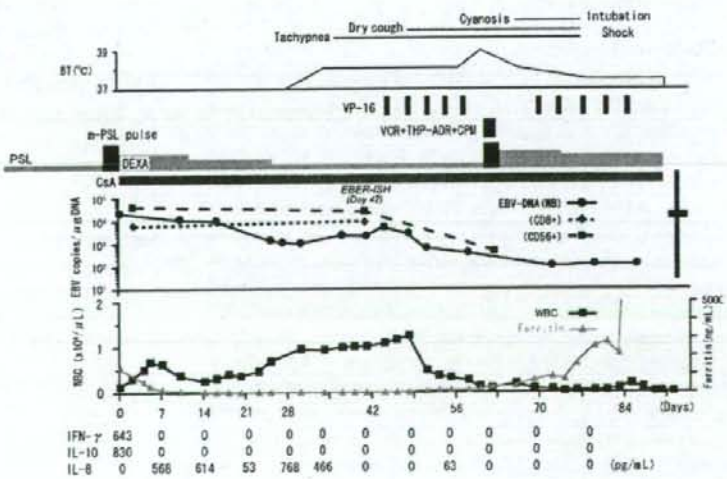

Fig. 2 Clinical course of patient 2 after admission to Okayama University Hospital. The quantification of the EBV load did not reflect the disease activity of the EBV-related interstitial pneumonia. IL-8 was elevated before the VP-16 was administered. BT, body temperature; CPM, cyclophosphamide; CsA, cyclosporine A; DEXA, dexamethasone; EBER, Epstein-Barr virus-encoded small RNA; EBV, Epstein–Barr virus; EBV-AHS, EBV-associated hemophagocytic syndrome; IFN, interferon; IL, interleukin; ISH, *in situ* hybridization; m-PSL pulse, methylprednisolone pulse therapy; PSL, prednisolone; THP-ADR, tetrahydropyranyl-adriamycin; VP-16, etoposide; WBC, white blood cells.

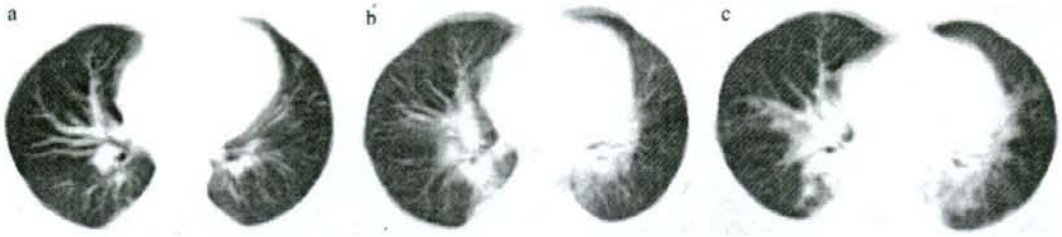

Fig. 3 Chest computed tomography of patient 2 was (a) non-specific on day 43, and (b) indicative of peribronchovascular interstitial thickening at 2 weeks. This subsequently developed into (c) marked central consolidation and ground-glass opacities when the patient was placed on mechanical ventilation.

Epstein-Barr virus-encoded small RNA (EBER)-1 and immunostaining of latent membrane protein (LMP)-1, only the CD56+ cell fraction was positive for EBV. The CD8+ cell fraction was negative according to these examinations. In patient 2 real-time PCR showed that both the CD8+ and CD56+ cell fractions were EBV positive on day 30, while the EBV load of the CD56+ cell fraction exceeded that of the CD8+ cell fraction. Using EBER-ISH and immunostaining of LMP-1, the CD56+ cell fraction was also positive in patient 2. During the course of the disease, the CD4+ and CD19+ cell fractions were EBV negative in both patients based on real-time PCR.

Analyses of cytokine profiles

Cytokines, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 (p70), granulocyte–macrophage colony-stimulating factor, interferon-γ (IFN-γ), and tumor necrosis factor-α in collected sera were sequentially examined using a LiquiChip human 10-cytokine kit (Qiagen) and analyzed with a LiquiChip workstation (Qiagen). In both cases the levels of IFN-γ and IL-10 were elevated on admission and relapse of EBV-AHS. The elevation of IL-8 was observed during the early phase after EBV-AHS. In this period the patients were clinically asymptomatic, but had high EBV loads in the PB. The remaining cytokines were negative throughout the illness.

Discussion

The quantification of EBV loads is very useful for evaluating complicated EBV infections, but there is only one case report in which the EBV load was analyzed longitudinally.[7] Therefore, in order to provide further details of the disease course, we examined the EBV load frequently, in addition to the cytokine profile.

First, following the relapse of EBV-AHS in patient 1, we found early elevation of the EBV load that coincided with a low-grade fever. The EBV load was higher than the level on admission, despite the slight elevation in ferritin and LDH. The quantification of virus loads is considered to be most sensitive in the systemic relapse of EBV infection.

Nevertheless, the EBV load in the PB was negative despite the worsening IP in patient 2. The EBV load did not reflect the disease activity if the patient's IP was derived from an EBV infection. The appearance of respiratory symptoms coincided with high EBV loads in the PB, but the effects of an unknown pathogen and therapy cannot be ruled out. A previous study of EBV-associated IP reported that the EBV load in the PB was positive in immunocompetent patients.[8] It is possible that the present negative results were due to immunochemotherapy, which reduced the number of EBV-infected cells in the PB.

These cases were diagnosed as EBV-related diseases based on the results of EBER-ISH, immunostaining of LMP-1, and virus load quantification using real-time PCR. The results suggest that EBV infects CD56+ cells in these cases of EBV-AHS. They were atypical cases because EBV is mainly infected with CD8+T cells in EBV-AHS.[9,10] In EBV-related diseases, such as EBV-AHS and CAEBV, it remains to be determined whether EBV can infect two or more different types of cell, and whether the main type of cell infected with EBV changes with the disease status.

Regarding the cytokine profiles, it was proposed that IL-8 is an EBV-related chemokine. A previous study demonstrated the induction of IL-8 by LMP-1 via nuclear factor-κ B in EBV-related nasopharyngeal carcinoma.[11] In CAEBV patients the activation of innate immunity increased as a result of insufficient CTL[12] and it may lead to the production of IL-8. Vasculitis, which often occurs in CAEBV patients, might affect the IL-8 production by vascular endothelial cells. The present results suggest that a similar mechanism exists in EBV-AHS, but the role of IL-8 in EBV-AHS remains largely unknown. Further studies are necessary before the clinical implications of these findings become clear.

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TDP-43 Mutation in Familial Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder. Accumulating evidence has shown that 43kDa TAR-DNA–binding protein (TDP-43) is the disease protein in ALS and frontotemporal lobar degeneration. We previously reported a familial ALS with Bumina bodies and TDP-43-positive skein-like inclusions in the lower motor neurons; these findings are indistinguishable from those of sporadic ALS. In three affected individuals in two generations of one family, we found a single base-pair change from A to G at position 1028 in TDP-43, which resulted in a Gln-to-Arg substitution at position 343. Our findings provide a new insight into the molecular pathogenesis of ALS.

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Amyotrophic lateral sclerosis (ALS) is a fatal and incurable neurodegenerative disorder. One of the neuropathological hallmarks of ALS is the presence of ubiquitinated neuronal cytoplasmic inclusions (NCIs) in lower motor neurons.[1,2] Recently, the 43kDa TAR-DNA–binding protein (TDP-43) has been identified as the major component of NCIs in sporadic ALS (SALS) and superoxide dismutase 1 (SOD1)–negative familial ALS (FALS), as well as sporadic and familial frontotemporal lobar dementia (FTLD).[3–7] Furthermore, the abnormal-molecular-weight fragments of TDP-43 were

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detected in affected nervous tissues.[3–5,8] These results suggest that TDP-43 is a causative protein in these disorders. However, the significance of TDP-43 in the pathogenesis of these neurodegenerative disorders remains to be elucidated.

We have reported the case of a SOD1-negative FALS family, in which one autopsied case showed degeneration limited to the lower and upper motor neuron systems, with Bunina bodies and ubiquitinated skeinlike inclusions in the remaining lower motor neurons; the clinical and pathological findings are indistinguishable from those in SALS.[9] Subsequently, we demonstrated that the ubiquitinated inclusions were immunoreactive for TDP-43.[6] Here, we report a missense mutation in *TDP-43* in the case's family. Furthermore, we found a widespread distribution of TDP-43–immunoreactive neuronal and glial cytoplasmic inclusions, as well as abnormal-molecular-weight fragments of TDP-43 in the spinal cord of an affected individual with this mutation.

Subjects and Methods

Mutational Analysis of TDP-43

Sixteen ALS families in which mutation of the *SOD1* gene had been excluded were enrolled. High-molecular-weight genomic DNA was extracted after obtaining patients' informed consent. RNA was extracted from the spinal cord of an affected individual (Fig 1A; Subject II-2) and a control subject.[9] We also analyzed genomic DNA from 92 clinically diagnosed SALS patients, 20 autopsy-confirmed SALS cases, and 4 autopsy-confirmed cases with related disorders: frontotemporal lobar degeneration with ubiquitin-positive inclusion (FTLD-U) in 1 case; FTLD with motor neuron disease in 2 cases; and primary lateral sclerosis in 1 case. We amplified all the exons of *TDP-43* (NM_007375) with the use of a series of primers, followed by sequence reaction. This study was approved by the Institutional Review Board of Niigata University.

TDP-43 Immunohistochemistry

In an autopsied case (see Fig 1A; Subject II-2), the distribution of TDP-43–immunoreactive NCIs and glial cytoplasmic inclusions (GCIs) was studied.[9] We prepared 4μm-thick, paraffin-embedded sections. These sections were immunostained by the avidin-biotin-peroxidase complex method with the use of a Vectastain ABC kit (Vector Laboratories, Burlingame, CA) and a rabbit polyclonal antibody against TDP-43 (10782-1-AP; 1:4,000; ProteinTech Group, Chicago, IL).

Plasmid Constructs

Full-length, wild-type, human TDP-43 complementary DNA (cDNA) was isolated from the human whole-brain

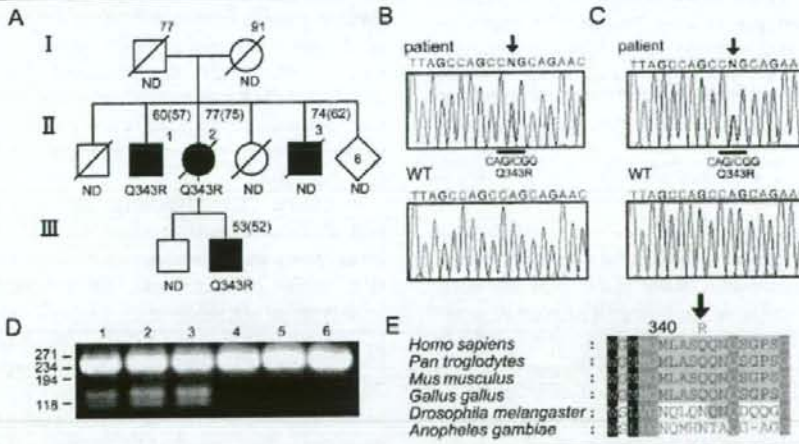

Fig 1. Detection of TDP43 *mutation in familial amyotrophic lateral sclerosis (FALS). (A) Partial family pedigree. Q343R, A1028G change in genomic DNA in heterozygous state. Age at death or current age and age at disease onset (n [m]) are indicated. (B) DNA sequence of genomic polymerase chain reaction (PCR) product.* Arrow *indicates A1028G in the patient. The resulting Q343R is shown at the bottom of the chromatogram of the patient. (C) DNA sequence of reverse transcribed polymerase chain reaction (RT-PCR) product from spinal cord of the autopsied case.* Arrow *indicates A1028G in the case. (D) Analysis of A1028G in genomic PCR products.* MspI *digestion of PCR products is shown; fragment sizes in base pairs are indicated on the left. Lanes 1 to 3 indicate patients; lanes 5 to 7 indicate normal control subject. (E) Sequence alignments of TDP-43 in different species. An amino-acid sequence of* Homo sapiens *NP_031401.1,* Pan troglodytes *XP_001135199.1,* Mus musculus *NP_663531.1,* Gallus gallus *XP_417612.1,* Drosophila melanogaster *NP_477400.1, and* Anopheles gambiae *XP_309663.2 were multiply aligned with the use of the ClustalW program, version 1.81.*[11] *The numbering on top of the alignments correlates with the human amino acid sequence. Amino acid 343, which is the site of Q343R, is indicated. ND = not determined.*

cDNA library (Clontech, Palo Alto, CA) and subcloned into the pcDNA DEST-40 (Invitrogen, Carlsbad, CA) or pEGFP-C3 vector (Clontech). TDP-43 mutant (Q343R) cDNA was generated with the use of a GeneTailor site-directed mutagenesis system (Invitrogen) and subcloned into the pcDNA DEST-40 or pEGFP-C3 vector to express green fluorescent protein-tagged TDP-43 in mammalian cells.

Fractionation of Frozen Spinal Cord Tissues and Immunoblotting

Proteins from the spinal cord of the autopsied case (see Fig1A; Subject II-2), five SALS patients, and three control subjects was extracted as described previously.[10] In brief, frozen tissues were homogenized in buffer A (10mmol/L Tris-HCl [pH 7.5], 1mmol/L EGTA, 1mmol/L dithiothreitol, 10% sucrose) and centrifuged. The resulting pellets were then extracted in buffer A containing 1% Triton X-100 (Sigma, St. Louis, MO) and centrifuged. These pellets were subsequently homogenized in buffer A containing 1% sarkosyl, incubated for 1 hour, and centrifuged. The sarkosyl-insoluble pellets were solubilized in 8mol/L urea buffer. After centrifugation, the supernatants were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and analyzed by immunoblotting with the anti–TDP-43 rabbit polyclonal antibody (10782-1-AP; 1:1,000; ProteinTech Group) and anti-neurofilament L rabbit polyclonal antibody (NA 1214; 1:1,000; BIOMOL International L.P, Exeter United Kingdom).

Cell Culture and Confocal Microscopy

COS-7, human embryonic kidney 293, and C6 cells were grown and transfected with the use of lipofectamine 2000 (Invitrogen). All images were acquired with an inverted microscope (TE-300NT; Nikon, Tokyo, Japan) and a confocal microscope (CSU-10; Yokogawa, Tokyo, Japan) equipped with a 40× objective.

Results

Mutation Detection

We analyzed the sequence of *TDP-43* in the 16 ALS families in which mutation of the *SOD1* gene had been excluded. We found a single base-pair change at position 1028 from A to G (A1028G) in exon 6, which resulted in a Gln-to-Arg substitution at position 343 (Q343R) in *TDP-43* in three affected individuals in two generations in one FALS family (see Figs 1A, B).[9] The sequence analysis of the reversed transcribed polymerase chain reaction products of messenger RNA, which was extracted from the spinal cord of the autopsied case (see Fig 1A; II-2), showed that both normal and mutant alleles were transcribed (see Fig 1C). This substitution results in the generation of a novel *Msp*I restriction site (see Fig 1D). By polymerase chain reaction restriction fragment length polymorphism analysis, we found that the A1028G substitution did not exist in any of 267 unrelated healthy individuals, 92 patients clinically diagnosed with SALS, 20 cases with autopsy-confirmed SALS, or 4 cases with autopsy-confirmed sporadic neurodegenerative disorders (FTLD-U [n = 1], FTLD with motor neuron disease [n = 2], primary lateral sclerosis [n = 1]). Furthermore, glutamine at position 343 is well conserved in several species (see Fig 1E).[11]

Clinical Features and Pathology

The age at onset of FALS is from 52 to 75 years (see Fig 1A).[9] All affected individuals predominantly experience development of dysarthria and dysphagia, which are features similar to those of bulbar-type SALS.[9] Furthermore, the neuropathological findings that include the presence of Bunina bodies and ubiquitin-positive NCIs in lower motor neurons are quite similar to those of SALS.[6] TDP-43–immunoreactive NCIs and GCIs were also observed in various regions of the subjects' central nervous systems (Table).

TDP-43 Expression Analysis

To characterize TDP-43 protein biochemically, we sequentially extracted proteins from the spinal cord of the autopsied case using buffers with increasing abilities to solubilize proteins and then analyzed the proteins by immunoblotting with an anti–C-terminal TDP-43 antibody. In addition to the band corresponding to full-length TDP-43, an approximately 25kDa band and an approximately 45kDa band were detected for all soluble and insoluble fractions (Fig 2A). Analysis of 1% sarkosyl-soluble fractions extracted from the spinal cord of the control subjects, SALS patients, and FALS patients with Q343R demonstrated that an approximately 25kDa band and an approximately 45kDa band were more distinctly observed in the FALS patient with Q343R than in the control subjects and SALS patients (see Fig 2B).

Because a TDP-43–positive inclusion is cytoplasmic and abolishes normal nuclear TDP-43 staining,[4,6] we investigated the consequences of the Q343R substitution at the cellular level. We transiently transfected wild-type or Q343R-myc– or GFP-tagged TDP-43 cDNA constructs into COS-7, human embryonic kidney 293, and C6 cells. Both the wild-type and Q343R TDP-43 proteins localized to the nucleus with a punctuated pattern, which partially colocalized with coilin, suggesting that the Q343R mutation has no adverse effect on subcellular localization of TDP-43 (see Fig 2C).[12]

Discussion

In this study, we show Q343R substitution in *TDP-43* in a family with ALS. Although we did not obtain DNA from unaffected individuals and we failed to show abnormal localization of TDP-43 with Q343R, we consider this Q343R substitution to be associated with the ALS phenotype in the family for the following reasons. First, Q343R was not present in 534 chromo-

Table. **Distribution of TDP-43–Immunoreactive Neuronal and Glial Cytoplasmic Inclusions**

Regions	NCIs	GCIs
Cerebral cortex		
Frontal	−	−
Motor	+	+
Parietal	+	−
Temporal	+	−
Insular cortex	+	+
Entorhinal	−	−
Subcortical areas		
Hippocampus	−	−
Amygdala	+	−
Basal nucleus of Meynert	NE	NE
Caudate and putamen	+	+
Globus pallidus	−	−
Internal capsule		−
Thalamus	+	+
Subthalamic nucleus	NE	NE
Brainstem		
Midbrain tectum	+	+
Reticular formation	+	+
Red nucleus	+	+
Substantia nigra	+	−
Cerebral peduncle		+
Locus ceruleus	NE	NE
Facial nucleus (motor)	+	+
Pontine nuclei	−	−
Superior olivary nucleus	−	−
Hypoglossal nucleus	+	+
Dorsal vagal nucleus	+	−
Nucleus ambiguus	+	−
Inferior olivary nuclei	+	−
Pyramis		+
Spinal cord		
Anterior horn	+	+
Intermediate lateral nucleus	−	−
Clarke nucleus	−	−
Posterior horn	+	−
White matter		−

NCI = neuronal cytoplasmic inclusions; GCI = glial cytoplasmic inclusions; + = present; − = absent; NE = not examined.

somes in Japanese control subjects. Second, the glutamine at position 343 is well conserved in several species. Third, Q343R was present in three affected individuals, including one autopsy-confirmed case, in two generations.[9]

We observed widespread distribution of TDP-43–immunoreactive NCIs and GCIs in the autopsied case who had this substitution.[6] The autopsied case demonstrated neuronal loss and gliosis restricted to the lower and upper motor neuron systems; however, the case demonstrated the TDP-43–immunoreactive NCIs and GCIs in various regions of the central nervous system (see the Table), suggesting that the case had a multisystem neuroglial proteinopathy of TDP-43.[6,9] Similar findings in SALS have also been described.[6] Interestingly, none of the affected individuals in the family showed dementia.[9] Although a few TDP-43–immunoreactive NCIs were found in the parietal, temporal, and insular cortices (no such inclusions were observed in the hippocampal dentate granule cells), no neurodegenerative features were evident in the autopsied case, indicating that Q343R substitution is not sufficient to cause FTLD.[6,9]

In this study, we failed to show abnormal functional consequence of Q343R substitution in *TDP-43*. However, we found abnormal-molecular-weight fragments of TDP-43 in the spinal cord of the autopsied case; these fragments are observed in SALS and in SOD1-negative FALS.[3–5,7] This result suggests that the Q343R substitution accelerates the production of abnormal-molecular-weight fragments of TDP-43. Furthermore, the Q343R substitution is located in the C-terminal region of TDP-43; this region is essential for binding to heterogeneous nuclear ribonucleoproteins and exhibits RNA-splicing inhibitory activity.[13] The result suggests that the substitution alters the ability of TDP-43 to bind to heterogeneous nuclear ribonucleoproteins and disturb RNA splicing.

Although the frequency of the mutation of the coding sequence of TDP-43 is rare,[14] further study for the functional consequences of Q343R substitution in neurons and glia should clarify the molecular basis for the association between Q343R substitution and the ALS phenotype, and may provide new insights into the pathomechanism of ALS.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Applied Genomics" from the Ministry of Education, Culture, Sports, Science and Technology of Japan (17019006, O.O.) and the Research Committee on Neurodegenerative Diseases, Ministry of Health, Labor and Welfare, Japan (200731015, HT).

We thank the family for their participation.

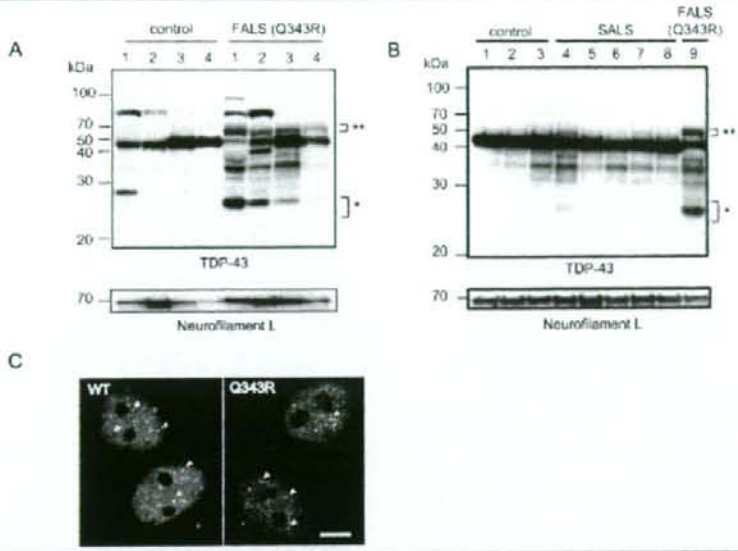

Fig 2. Biochemical analysis of 43kDa TAR-DNA–binding protein (TDP-43) in familial amyotrophic lateral sclerosis (FALS). (A) Immunoblots of extracts from spinal cords of control subjects and ALS patient with TDP-43 mutation probed with anti-TDP-43 (top) and anti-neurofilament L (bottom) antibodies. The 43kDa bands are observed for all the fractions. The approximately 25kDa (asterisks) *and approximately 45kDa bands* (double asterisks) *are detected for the patient fractions. Lane 1, low salt; lane 2, high salt with 1% Triton X-100; lane 3, 1% sarkosyl; lane 4, 8mmol/L urea. (B) One percent sarkosyl-soluble fractions from spinal cords were subjected to immunoblot analysis with anti-TDP-43 (top) and anti-neurofilament L (bottom) antibodies. Lanes 1 to 3, control subjects; lanes 4 to 8, sporadic ALS (SALS); lane 9, FALS with Q343R. (C) TDP-43 localization. COS-7 cells transfected with wild-type or Q343R GFP-tagged TDP-43 and TurboRed-tagged coilin are shown. The merged image shows TDP-43 (green) and coilin (red).* Arrowheads *indicate colocalization of TDP-43 and coilin. Scale bar = 10μm.*

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症例報告

大腸癌とその転移にともなう凝固線溶系の異常により脊髄円錐部出血をきたした1例

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木村 成志　荒川 竜樹　熊本 俊秀

要旨：症例は76歳女性である．4日間の経過で両下肢の脱力，感覚障害，排尿障害をきたし当科に入院した．74歳時に上行結腸癌，75歳時に転移性肺癌の手術を受けた．神経学的には下肢対麻痺，アキレス腱反射消失，L3以下の感覚消失，膀胱直腸障害をみとめた．腰部MRIにて脊髄円錐部にT_1強調像で等信号域，T_2強調像で低信号域を示し，周囲に造影効果をともなう病変をみとめ，脊髄内出血と診断した．血漿フィブリン分解産物，D-ダイマー，トロンビン・アンチトロンビンIII複合体の上昇をみとめ，凝固線溶系の活性化が示唆された．脊髄円錐部に出血をきたすことはまれであり，本症例では大腸癌とその転移にともなう凝固線溶系の亢進が誘因であると考えられた．

（臨床神経，48：263—266，2008）

Key words：脊髄円錐部，脊髄内出血，凝固異常，線溶系異常，大腸癌

はじめに

脊髄内出血は比較的まれな疾患であり，なかでも円錐部出血はこれまでに数例の報告をみとめるのみである[3)-13)]．今回，われわれは大腸癌とその転移にともなう凝固線溶系の異常に起因すると考えられた脊髄円錐部出血の1例を経験したので報告する．

症　例

患者：76歳，女性．

主訴：下肢の脱力・感覚障害，排尿障害．

既往歴：1980年頃より糖尿病にて内服加療中である．2002年に上行結腸癌，2003年に転移性肺癌の手術を受けた．

現病歴：2004年2月上旬に漬け物石を持ち上げようとしたときに腰部に疼痛が出現した．その12日後に右下肢，ついで左下肢の筋脱力を自覚した．その後脱力は徐々に増悪し，2日後には起立不能になった．さらに2日後には尿閉となったため，当科に入院した．

入院時現症：身長158cm，体重58kg，血圧149/72mmHg，脈拍60/分・整，体温36.5℃．心肺に異常はないが，腹部正中に手術痕があり，腹部正中から右鼠径にかけて弾性硬の圧痛をともなう腫瘤を触知した．四肢末梢の循環不全はみとめなかった．腹部膨満感があり食思不振であった．

神経学的所見：意識は清明で，脳神経系には異常をみとめなかった．運動系では，上肢の筋力は正常だが，下肢の不全対麻痺をみとめた．徒手筋力試験では，腸腰筋3/3(右/左)，大腿内転筋群3/3，大腿外転筋群3/3，大殿筋3/3，大腿四頭筋3/3，大腿屈筋3/3，前脛骨筋3/3，腓腹筋3/3，足趾伸筋1/1であった．筋トーヌスは正常で，筋萎縮はみとめなかった．感覚系では，自発痛はみとめないものの，両下肢ともL3以下に表在感覚(温痛覚，触覚)鈍麻をみとめ，振動覚，関節位置覚は両下肢で消失した．仙部回避はなかった．深部反射では両側のアキレス腱反射が消失していたが，その他は正常で，病的反射はみとめられなかった．踵膝試験は麻痺のため検査が十分できなかったが，起立・歩行は不能で体幹失調もあると判断した．自律神経系で尿閉をみとめた．

検査所見：血液検査では血算，血球分画に異常ないが，血沈は41mm/1時間と亢進した．血糖値139mg/dl，HbA1c 7.07%の他は血液生化学所見は正常であった．フィブリノーゲン413mg/dl，フィブリン分解産物（FDP）78.2ng/ml，プロテインC 64.1%，Dダイマー7.91μg/mlに加え，トロンビン・アンチトロンビン複合体（TAT）9.5ng/ml，α_2-プラスミンインヒビター79.6%，プラスミン・α_2プラスミンインヒビター複合体（PIC）2.6μg/mlが高値を示し，凝固・線溶系の亢進がみとめられた．腫瘍マーカーではCEA 232ng/ml，CA 19-9 774U/mlが高値を示した．髄液は，人工的出血をみとめたが，遠心後の髄液ではキサントクローミーはなかった．初圧は55mmH_2O（終圧50mmH_2O）と圧の低下と，軽度の蛋白上昇（53.5mg/dl）をみとめた．髄液中の腫瘍マーカーは未検だが，細胞診ではclass Iであった．

画像所見：胸部CTでは右肺に大小2つの結節像をみとめた（Fig. 1a）．腹部CTでは右鼠径リンパ節および腹腔内リン

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（受付日：2007年10月5日）

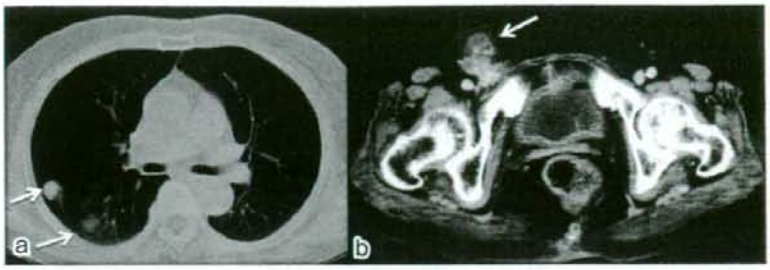

Fig. 1　(a) Computed tomography (CT) of the chest on admission shows two nodular shadows in the right lung field. (b) Abdominal CT on admission shows the enlargement of right inguinal and abdominal lymph nodes. The arrow shows the swelling of the former.

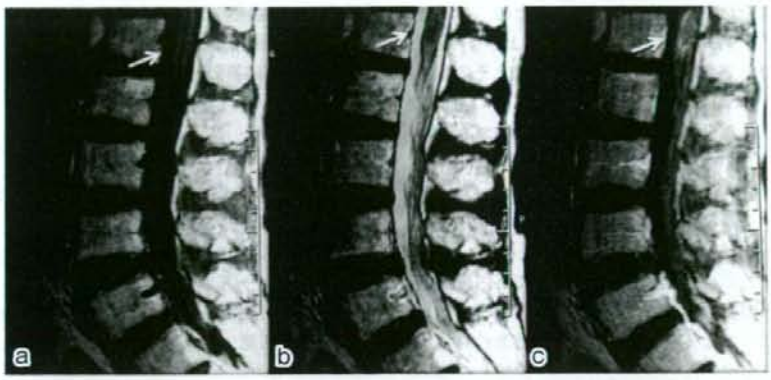

Fig. 2　Sagittal magnetic resonance imaging (MRI) scan of the lumbosacral regions on admission shows a 9×3-mm homogenous mass with isointensity on T1-weighted images (a) and low intensity on T2-weighted image (b) indicating intramedullary hemorrhage in conus medullaris. Gadolinium-enhanced T1-weighted images demonstrates contrast enhancement of the surrounding of mass (c).

パ節の腫大がみとめられ，肺とともに大腸癌の転移巣と考えられた（Fig. 1b）．

腰部MRIでは脊髄先端は第1腰椎レベルにあり，矢状断で第1腰椎レベルの脊髄円錐部にT_1強調像で等信号，T_2強調像で低信号を示す9mm×3mmの大きさの病変をみとめた（Fig. 2a, b）．同部はガドリニウム（Gd）造影T_1強調像にて周囲により強い造影効果をみとめ，亜急性期の血腫と考えられた（Fig. 2c）．

入院後経過：入院の時点ですでに対麻痺の発症より5日も経過しており，大腸癌による全身状態の不良もあることから手術適応は無いと考え，保存的に経過を観察した．入院13日目には運動障害の範囲が両側大腿部へも広がり，17日目には排便障害と膝蓋腱反射の消失をみとめた．入院1週間後の腰部MRIのT_2強調像では，入院時にくらべ出血巣の周辺に被膜と思われる高信号域がみられた（Fig. 3a, b）．1カ月後には出血巣周辺の高信号域はみられず，被膜が吸収されている像と思われた（Fig. 3b）．それに一致してGd造影T_1強調像では出血巣周辺の造影効果は経時的に減少した（Fig. 3c）．すべてのMRIで血腫内部は均一で異常血管を示す陰影はみとめられず，海綿状血管腫は否定的だった．また椎体には有意な変化をみとめなかった．右鼠径リンパ節転移部の疼痛が強くなり，疼痛緩和医療の目的で入院46日目にかかりつけの近医へ転院した．その後，同院にて多臓器不全および肺炎により6カ月後に死亡した．転院後の経過中，神経症候の進行・改善はみとめなかった．

考　察

脊髄内出血は“脊髄内を数節にわたり長軸方向に広がる出血”と定義され，原因により外傷性，特発性および二次性に分類される[1]．このうち90%以上が外傷によるものである[1]．特発性，すなわち原発性の非外傷性脊髄内出血は血管奇形などの異常血管の破裂によるものが多く，その他に梅毒，動脈硬化，高血圧，心不全，凝固異常にともなうこともある[1][2]．二次性脊髄内出血は脊髄腫瘍や脊髄空洞症などの脊髄内病変に続発しておこるものをいう[1]．

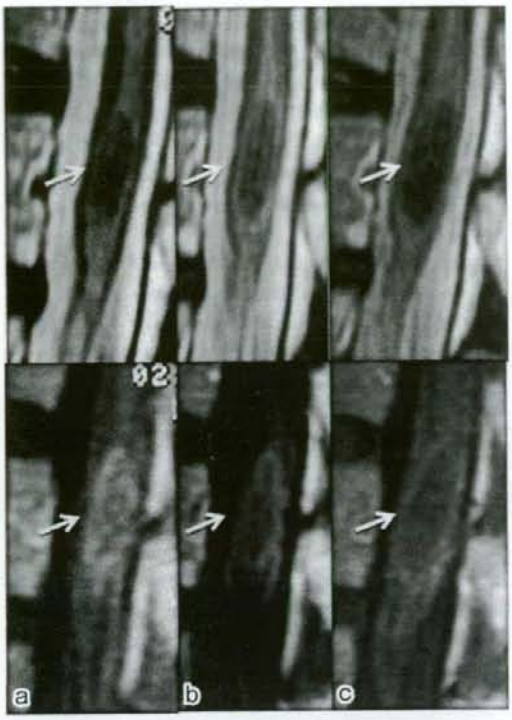

Fig. 3 Follow-up T2-weighted (upper) and gadolinium-enhanced T1-weighted (lower) MRI scan of the lumbosacral regions. Sagittal T2-weighted image taken 7 days after admission shows hyperintensity on surrounding of low intensity lesion (b) despite of no hyperintensity on admission (a). MRI without and with gadolinium taken 30 days after admission no longer shows any hyperintense lesions in T2-weighted image and any surrounding enhancement (c).

本症例では脊髄円錐部に出血巣をみとめたが，同部に出血をきたした報告例は意外と少なく，われわれの調べえたかぎりではこれまでに11例をみとめるのみであった[3]~[13]．このうち外傷性出血は1例[6]のみで，4例が髄内の腫瘍性病変によるもの[3][6][7][10]，1例が脊髄円錐部の形成異常による二次性脊髄内出血であった．残る5例がJellinger[1]のいう特発性脊髄出血に分類されるものであったが，うち4例は異常血管によるもので[5][11]~[13]，残る1例のみが原因不明の脊髄内出血であった[9]．凝固異常にともなうものは1例もなかった．

本例では基礎疾患として悪性腫瘍の存在が指摘されていた．だが，画像所見上腫瘍の直接浸潤や遠隔転移は否定され，髄液所見でもこれらを示唆する所見はみとめなかった．また，動静脈奇形（AVM）などの異常血管もみとめられなかった．しかし本症ではFDP，プロテインC，Dダイマー，TAT，α_2-プラスミンインヒビター，PICなどの凝固・線溶系の異常がみとめられた．

このうちFDP，Dダイマー，TATの高値とプロテインCの低値は凝固系の亢進を示唆するものである．大腸癌にともなって凝固系がしばしば亢進することがあるが，それにはフィブリノペプチドA，第X因子分解産物，血小板因子IV，ベータトロンボグロブリンといった凝固因子が関与し，大腸癌のフォローにこれらの値を利用することが有用であることが示唆されている[14]．

一方，α_2-プラスミンインヒビターの低値，PICの高値は線溶系の亢進を示唆するものである．血小板数，アンチトロンビンIIIは正常範囲であることから，線溶系の亢進は血管内凝固に続発するいわゆる二次線溶亢進ではなく，プラスミノーゲンアクチベーターの亢進による一次線溶亢進の状態であることが示唆された．転移をともなう大腸癌においてその間質細胞からウロキナーゼ型プラスミノーゲンアクチベーターが過剰に産生され線溶亢進をおこしうることは過去にも指摘されており[15][16]，本例の出血の原因は大腸癌とその転移にともなう凝固線溶系の異常，とくに一次線溶の亢進であると考えられた．

脊髄円錐部に画像上原因を指摘できない出血をきたした例は本例で2例目であり，貴重な症例と考えられたため報告した．

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Abstract

A case of hematomyelia caused by coagulation—fibrinolysis abnormality accompanied with colon cancer and its metastasis

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A 76-year-old woman developed weakness and sensory loss in the lower limbs and urinary disturbance in four days. She had a history of operation for the ascending colon cancer and lung metastasis one year ago. Neurological examination revealed flaccid paraplegia, absent Achilles tendon reflex, severe disturbance of superficial and deep sensation below the L3 level, and vesicorectal abnormality. Magnetic resonance imaging (MRI) studies showed an intramedullary T1-iso, T2-low lesion with Gd-DTPA contrast enhancement in conus medullaris at LI level. The laboratory examination revealed the elevated level of serum FDP, D-dimer and TAT. She was diagnosed as hematomyelia, which may be caused by the activation of coagulation and fibrinolysis system. We suggested that the ascending colon cancer and lung metastasis may contribute to the coagulation-fibrinolysis abnormality.

(Clin Neurol, 48: 263—266, 2008)

Key words: conus medullaris, hematomyelia, coagulopathy, abnormal fibrinolysis, colon cancer

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原著

長期の人工呼吸管理後軽快した重症辺縁系脳炎の1例*

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Key Words : non-herpetic limbic encephalitis, viral encephalitis, epilepsy, artificial respiration, ovarian teratoma

緒　言

非ヘルペス性辺縁系脳炎は，若年女性に好発し比較的予後良好な疾患群とされているが，発症機序に関してはいまだ不明な点が多い．また，経過中一時的に人工呼吸管理を要することも稀ではない疾患であるが，多くは数カ月の経過で改善し，半年以上の人工呼吸管理を要する症例や，1年以上の長期経過で症状の改善がみられた例は稀である．われわれは，長期にわたる人工呼吸を必要としたが，1年の経過で意識レベルの改善がみられた重症非ヘルペス性辺縁系脳炎の1例を経験したので報告する．

症　例

患者：26歳，女性．

主訴：意識障害，痙攣．

既往歴，家族歴：特記すべきことはなかった．

職業歴：会社員(コンピューター関係)．

現病歴：2005年9月20日頃から38度台の発熱，頭痛があった．9月27日から頭痛が強度となり近医を受診，感冒と診断され処方を受けたが帰宅後全身の強直性痙攣をきたし，翌日近医に入院した．入院後痙攣に対する治療が開始されたが発熱が続き，記銘力障害(近時記憶障害)，幻覚，妄想，不隠症状，躁症状様の人格変化がみられた．9月28日の髄液検査では細胞数40/μl(単核球優位)であった．9月30日に施行した頭部MRIでは異常を認めなかったが，同日から意識レベルの低下がみられたため，精査加療目的で10月4日当科に転入院した．

入院時現症：体温37.4℃，脈拍100/分・整，血圧138/80mmHg．30秒程度の無呼吸を頻回に認めた．その他，内科学的所見に異常はみられなかった．神経学的所見は深昏睡，JCS300．項部硬直，Kernig徴候は認めなかった．四肢は弛緩．腱反射は正常で病的反射は認めなかった．入院時に痙攣は認めなかった．

入院時検査所見：10月4日の血液検査所見では，WBC 11,900/μl(好中球89.0%)，GOT 70IU/l，GPT 77IU/l，CPK 2,164IU/l，CRP 0.90mg/dlであり，甲状腺機能は正常であった．ウイルス抗体価はHSV，EBV，CMV，VZV，コクサッキーウイルス，エコーウイルスはいずれも有意な抗

* Limbic encephalitis—recovery after long-term respirator aid. A case report. (Accepted December 25, 2007).
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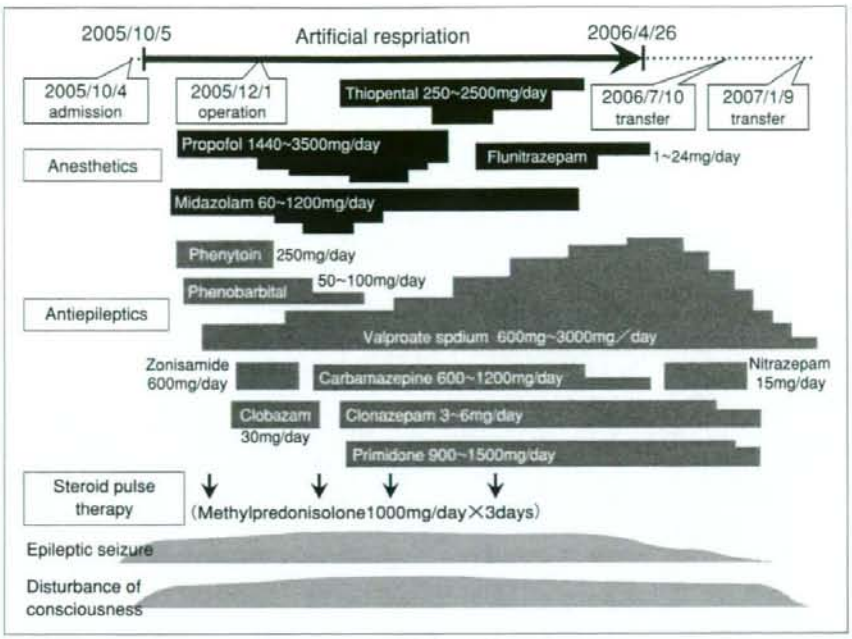

図1 臨床経過

体価の上昇は認めなかった．自己抗体はANAが40倍であったが，特異抗体は検出されなかった．髄液検査は，水様透明，初圧28cmH_2O，終圧15cmH_2O．蛋白22mg/dl，糖65mg/dl，細胞数31/μl（単核球99％），IgG index1.0であった．髄液中HSV，CMV，VZV抗体価は陰性であり，ウイルス分離同定も陰性であった．頭部CTには異常を認めず，腹部CTで両側卵巣腫瘍を認めた．

入院後経過（図1）：入院直後から無呼吸および誤嚥に伴う呼吸不全が進行したため，入院翌日から人工呼吸管理を要し，アシクロビル，グリセロールの投与，ミダゾラム持続投与を開始した．入院第3病日から顔面，四肢に部分発作が出現し，二次性全般化から重積へ移行したため，ミダゾラム増量，フェニトイン投与を開始したが症状の悪化傾向が続いた．そのためプロポフォールの持続投与を追加し，フェノバルビタール，バルプロ酸ナトリウム，カルバマゼピン投与を開始した．アシクロビル投与終了後ステロイドパルス療法を行ったが症状は改善せず，プロポフォールを減量すると痙攣発作が出現する状態が遷延した．発作間欠期には顔面や上肢にミオクローヌス，振戦，アテトーゼなどの不随意運動を認めた．入院第21病日の脳波検査（図2）ではδ波が中心であったが，ミダゾラム，プロポフォールの減量によってややシャープなθ～δ波の出現がみられた．血清，髄液中の抗グルタミン酸レセプター（GluR）抗体を測定した結果，血清中からIgG-GluRδ2抗体が検出された．髄液からは同抗体は検出されなかった．

意識障害の遷延が卵巣腫瘍と関連したparaneoplastic limbic encephalitisの可能性も考えられたため，当院産婦人科で入院59病日に両側卵巣腫瘍核出術を施行した．右卵巣腫瘍は良性卵巣奇形腫，左卵巣腫瘍はチョコレート嚢胞であった．しかし，術後も脳炎症状は軽減せず，その後ステロイドパルス療法を計4回施行したが効果はなく，手指のアテトーゼ様の不随意運動の出現と上下肢への進展，全身の強直間代痙攣への移行を頻回に認めた．入院83病日に施行した脳波検査では前頭部から側頭部で2.5～3 Hzのδ波が連続的に出現し，振幅の増大，鋭波化がみられた（図2）．大量γグロブリン療法も試みたが，初回投与時にγグロブリン投与に関連すると思われる気管支喘息症状が出現したため中止した．喘息症状は投与中止により速やかに改善した．

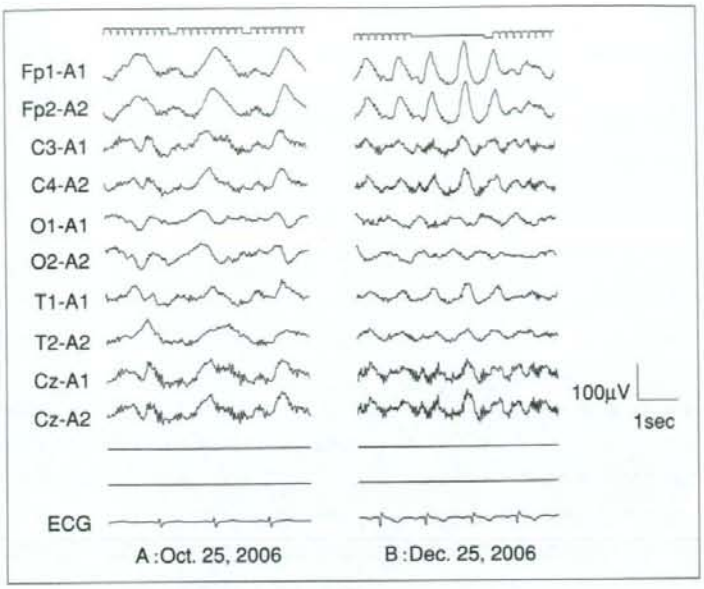

図2 脳波所見
2005年10月25日(A)および2005年12月26日の所見(B)を示す．Aでは2 Hz δ-wave, Bでは2.5Hz spike-waveを認める．

その後も痙攣は難治性であり，チアミラール，フルニトラゼパムによる鎮静を追加し，クロナゼパム，プリミドン，ニトラゼパム投与も行いコントロールされる状態であった．しかし，入院173病日に施行した頭部MRIでは異常を認めなかった．

抗痙攣薬の効果により入院後204病日となる4月26日，人工呼吸器より離脱し得たが，その後も痛み刺激には反応せず意識レベルの改善を認めない状態であった．手指の不随意運動は残存していたが，痙攣発作の出現頻度は徐々に減少傾向となった．2006年7月11日他医に転院し加療を継続したところ，2006年9月頃から不随意運動および痙攣発作は消失し，自発開眼がみられるようになった．同年10月初旬には追視，単語の発声も可能となり，簡単な意思疎通が行えるようになった．2007年1月には明確な意思伝達を行うことができるようになり，本を読んだりして日中過ごすようになった．明らかな麻痺の残存もなく，車椅子への移乗には介助を要するが，車椅子操作は問題なく行えるようになった．認知機能テストでは短期記憶障害が残存し，HDS-R21/30点，MMSE23/30点であった．2007年1月9日にリハビリ病院に転院し，現在リハビリ加療を継続している．

考　察

非ヘルペス性辺縁系脳炎は，HSV陰性で，両側海馬，扁桃体などを病変の主座とする疾患群であり，楠原ら[1]の報告以降，本邦を中心に症例の蓄積が進んでいる．庄司ら[2]は急性非ヘルペス性辺縁系脳炎の定義として，①急性脳炎であること，②両側海馬，扁桃体などにMRI異常を示すこと，③髄液で軽度の細胞増加，蛋白増加を示すこと，④髄液でHSVが検出されないこと，⑤悪性腫瘍の合併がなく傍腫瘍症候群が否定的であること，⑥比較的経過が良好であることをあげている．本症例は急性脳炎の発症様式を示し，記銘力障害(近時記憶障害)，幻覚，妄想，不隠症状，躁症状様の人格変化などの辺縁系症状を示し，髄液所見で軽度の細胞増加を認め，HSVを含めウイルスは検出されなかったため，辺縁系の急性脳炎と診断したが，MRI, CTともに異常がみられなかった．湯浅ら[3]は，感冒症状での発病から精神症状を主とする脳炎症状をきたしたMRI陰性の急性辺縁系脳炎を報告している．極

し，比較的若年女性を冒し画像所見に乏しい急性可逆性辺縁系脳炎—4症例の報告と考察．神経内科 2003；59：45-50.
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＜Abstract＞

Limbic encephalitis—recovery after long-term respirator aid. A case report.

by
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A 26-year-old woman developed a fever (38℃) and a headache on September 20, 2005. On September 28, she developed manic agitation followed by a decline of consciousness levels to a stupor. She was admitted to our hospital on October 4. After admission, she developed involuntary movements associated with asphyxia. On October 7, she was put on a respirator and anti-convulsive drugs were administered. A spinal tap showed mild elevation of mononuclear cells. Tests for antiviral antibodies and PCR for herpes simplex virus were all negative. Brain CTs and MRIs revealed no abnormalities. The patient's involuntary movements and consciousness levels did not change in response to steroid pulse therapy. Bilateral ovarian tumors found by abdominal CT were surgically removed, since paraneoplastic syndrome was also suspected. However, the patient's condition did not change for a long period of time. Based upon these findings and the course of the illness, we diagnosed her with non-herpes viral limbic encephalitis.

The patient's involuntary movements started to decrease in Feb. 2006. We were able to turn off her respirator on April 26, 2006. Her involuntary movements further subsided and her consciousness level gradually improved. She started to speak for the first time in over one year. At present (Feb. 2007), she only suffers from mild short-term memory impairment and is able to operate a wheelchair by herself.

We report a patient with non-herpes limbic encephalitis who recovered after more than 1 year of illness and needed respirator aid for more than 6 months.

筋肉サルコイドーシスの臨床と筋の崩壊機序

熊本俊秀

【要旨】

筋肉サルコイドーシス，特に腫瘤型における筋崩壊機序は，マクロファージ，類上皮細胞及びリンパ球などの炎症性細胞が非壊死性筋線維内に直接浸潤してそこに小肉芽腫を形成し，直接筋線維を崩壊することが主因であり，機械的圧迫や虚血によるものではない．さらに類上皮細胞やマクロファージ由来のカテプシンB，m-カルパイン，ユビキチン－プロテアゾームが筋の崩壊に重要な役割を果たす．文献を基に急性筋炎，慢性ミオパチーを呈する筋肉サルコイドーシスについて述べる．これまで腫瘤が四肢全体あるいは体幹の広範囲に進展した腫瘤型の報告例があるが，いずれも長期間にわたって筋力低下及び筋萎縮を認めていない．このことは，慢性ミオパチーにおける筋の崩壊機構は腫瘤型と異なっている可能性がある．急性筋炎，あるいは慢性ミオパチーの臨床所見，とくに進行性の筋力低下と筋萎縮を示す筋肉サルコイドーシスの中には皮膚筋炎，筋炎－オーバーラップ症候群，重症筋無力症などの自己免疫性ミオパチーと関連したものがある．

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キーワード：筋肉サルコイドーシス，慢性ミオパチー，プロテアーゼ，皮膚筋炎，オーバーラップ症候群

Clinical Feature and Pathomechanism of Muscle Fiber Destruction in Muscular Sarcoidosis

Toshihide Kumamoto

【ABSTRACT】

The pathomechanism of muscle fiber destruction in muscular sarcoidosis, especially nodular type, may be caused by direct invasion of inflammatory cells rather than by mechanical compression or ischemia. The invasive cells consist of macrophages, epithelioid cells and lymphocytes, enter into muscle fibers during the process of granuloma formation. Furthermore, protease cathepsin B, m-calpain and ubiquitin-proteasome, which are derived from epithelioid cells and macrophages in granulomas, apparently play an important role in muscle fiber destruction. Muscular sarcoidosis manifesting acute myositis or chronic myopathy is discussed along with a review of the literature. Some patients with nodular muscular sarcoidosis extending to all limb muscles or trunk were reported. These patients, however, did not develop any muscle weakness and wasting for a long time, suggesting that the pathomechanism of muscle fiber destruction may be different in chronic myopathic form from that in nodular muscular sarcoidosis. Some muscular sarcoidosis presenting clinical features, especially progressive muscular weakness and wasting, of acute myositis or chronic myopathy are associated with autoimmune myopathies such as dermatomyositis, myositis-overlap syndrome, or myasthenia gravis.

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Keywords: Muscular sarcoidosis, Chronic myopathy, Proteases, Dermatomyositis, Overlap syndrome

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