reduced expression of T-bet by SNPs could inhibit the onset of autoimmune inflammatory diseases. T-bet deficiency has been shown to be protective against myasthenia gravis, inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis and type 1 diabetes mellitus (Ji et al., 2011). We speculate that intact T-bet activity without SNPs reducing Th1 differentiation do not disturb the adequate production of pro-inflammatory cytokines and CTLs, and the subsequent onset of RS.

We identified three SNPs (rs231775 and rs231779 in *CTLA4*; rs2227982 in *PDCD1*) as some of the SNPs associated with onset of Japanese RS. We need further studies in other populations to confirm these genetic associations. At the early stage of RS, patients usually manifest infrequent seizures and mild unilateral hemispheric dysfunction, so that a diagnosis of RS is difficult to establish. These genomic markers may contribute to early diagnosis of RS before the appearance of typical clinical characteristics, and early initiation of immunomodulatory treatments may result in better outcome. Furthermore, we want to conduct multivariate analysis including genetic predisposition (SNPs), age, sex, medication, etc. in larger numbers of patients and Japanese controls with clear background.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2013.09.004.

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INTERNAL MEDICINE

CASE REPORT

Ophthalmoplegia and Flaccid Paraplegia in a Patient with Anti-NMDA Receptor Encephalitis: A Case Report and Literature Review

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Abstract

We herein report the case of a 26-year-old woman with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis presenting with ophthalmoplegia and flaccid paraplegia. She developed disorientation and hallucination after fever and vomiting. Hypothermia, hypoventilation, hypertension, paralytic ileus and hyponatremia were present. Neurological examination showed mild consciousness disturbance and bilateral ophthalmoplegia on admission, flaccid paraplegia with leg areflexia on Day 4. Anti-NMDAR antibodies were detected in the serum and cerebrospinal fluid samples. Motor nerve conduction velocity was decreased in the tibial and peroneal nerves. F-wave amplitudes were reduced in the tibial nerve. MRI disclosed lesions in the callosal splenium, hippocampus and cerebral subarachnoid regions. In addition to various encephalitic symptoms, physicians should pay more attention to peripheral nerve damage in patients with anti-NMDAR encephalitis.

Key words: anti-NMDA receptor encephalitis, Guillain-Barré syndrome, Miller Fisher syndrome, transient splenial lesion, hyponatremia, SIADH

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis typically occurs in young women with neuropsychiatric symptoms followed by seizures, consciousness disturbance, language dysfunction and involuntary movements. Patients frequently develop central hypoventilation and dysautonomia (1-6). Ovarian teratoma is also an underlying pathogenesis in young women with this encephalitis (1-6).

Recently, anti-NMDAR encephalitis has been reported in several patients with other autoimmune disorders in the central nervous system, including multiple sclerosis, neuromyelitis optica and similar conditions (7-10). The full clinical spectrum associated with anti-NMDAR antibodies is likely to widen with increasing recognition. However, little is known about the peripheral nerve involvement, including Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS) (11, 12). We herein report a patient with ophthalmoplegia and flaccid paraplegia with leg areflexia during the course of anti-NMDAR encephalitis.

Case Report

A 26-year-old woman experienced a fever, anorexia and vomiting, and was diagnosed with acute gastroenteritis at a neighboring clinic. Three days later, disorientation and abnormal speech were observed, and the patient was admitted to our department. Physical examination showed hypothermia (34.3℃), a high blood pressure of 144/94 mm Hg and the loss of bowel sounds. Her consciousness state was slightly drowsy with visual hallucination. Ocular movements

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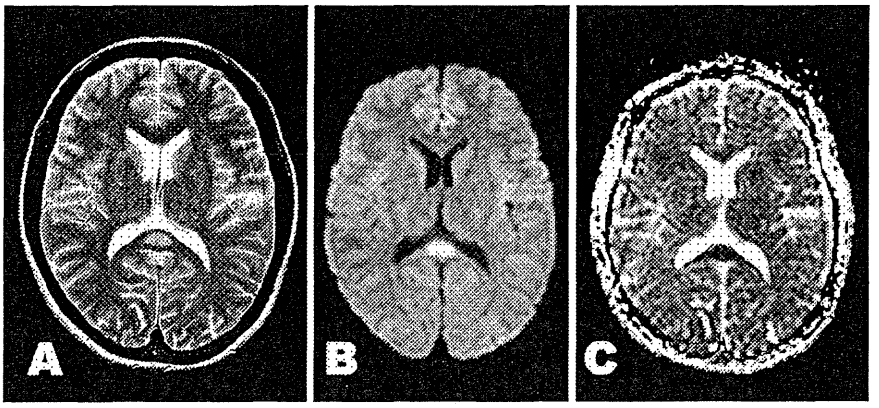

Figure 1. A transient splenial lesion on MRI. A) T2-weighted imaging. B) DWI. A hyperintense lesion was found in the callosal splenium. C) The ADC map showed a hypointense splenial lesion.

were impaired in all directions of both eyes. The pupillary size was equal (2.0 mm), and light reflexes were normal on both sides. Other cranial nerves were normal. Muscle stretch reflexes were normal and plantar responses were flexor. The remaining function was normal, including the motor, the sensory and the cerebellar system. Routine laboratory studies showed serum sodium levels of 124 mEq/L and plasma antidiuretic hormone (ADH) levels were 2.5 pg/mL (normal ranges of 0.3-3.5 at normal serum sodium levels). Plasma ADH levels were not suppressed by marked hyponatremia. Urine volumes were 0.9-1.2 L/day, and urine sodium levels were more than 20 mEq/L. Central venous pressures (CVP) was 10-13 cm H_2O. Serum and cerebrospinal fluid (CSF) samples were analyzed for anti-NMDAR antibodies using an enzyme-linked immunosorbent assay (13-15) and cell-based assay (2). Serum and CSF levels of antibodies to GluRε2-NT2, GluRε2-CT1, GluR ζ1-NT and GluRδ2-NT were increased respectively at 2-10 folds compared to controls. Both serum (1:40) and CSF (1:2) reacted with human embryonic kidney (HEK293) cells transfected complementary DNA encoding NR1 and NR2B subunits of NMDAR. Serum levels of antibodies to gangliosides GM1, GD1a, GD1b, GQ1b and GT1a were not detected. Serological tests of antinuclear and voltage-gated potassium channel antibodies were negative. Pathogen tests for *Campylobacter jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein-Barr virus, rubella virus, herpes simplex virus and other viruses were negative. Chest X-ray, electrocardiography and carotid ultrasonography were normal. Abdomen X-ray disclosed marked retention of gastrointestinal gas. At 4 days after neurological onset (Day 4), hypoventilation and flaccid paraplegia were present. Muscle stretch reflexes were reduced in the upper extremities and absent in the lower extremities. A CSF study exhibited protein of 139 mg/dL, 246 mononuclear cells/mm^3 and normal cytology. Myelin basic protein was increased to 787 μg/mL (normal ≤102). Oligoclonal immunoglobulin G band was not detected. Motor and sensory nerve conduction studies were performed on Day 6. Motor nerve conduction velocity (MNCV) was decreased in the peroneal (37.1 m/s) and the tibial nerve (38.9 m/s). That of the median and the ulnar nerve was 58.0 m/s and 48.1 m/s, respectively. Amplitudes of compound muscle action potentials were within the normal ranges in these nerves. Sensory nerve conduction velocity and amplitudes of sensory nerve action potentials were within the normal ranges in the median, the ulnar, the peroneal and the sural nerve. F-waves were elicited in the median (94%), the ulnar (100%) and the tibial nerve (94%). Amplitudes of F-wave were decreased in the tibial nerve. Electroencephalogram showed slow waves, predominantly in the frontal region. Auditory brainstem response and short-latency somatosensory evoked potentials using the stimulation in the median nerve were normal. Brain magnetic resonance imaging (MRI) was performed on Day 2. T2-weighted imaging and diffusion-weighted imaging (DWI) disclosed a hyperintense lesion in the central splenium of the corpus callosum. The apparent diffusion coefficient (ADC) map showed a hypointense lesion in the callosal splenium (Fig. 1). Fluid-attenuated inversion recovery (FLAIR) imaging displayed hyperintense lesions in the medial temporal lobes and the cerebral subarachnoid regions (Fig. 2). Second brain MRI revealed no splenial lesion on Day 9. Spinal cord MRI was unremarkable. Pelvic MRI exhibited a small massive lesion in the left ovary (Fig. 3). Gynecological examination and the radiological finding strongly suggested a diagnosis of ovarian teratoma.

Clinical course and treatment: mechanical ventilator was used from Day 4. The patient was treated with intravenous immunoglobulin (0.4 g/kg/day for five days) twice on Day 5 and Day 17. Her consciousness disturbance, hypothermia, respiratory failure, dysautonomia and hyponatremia were gradually ameliorated. When external ophthalmoplegia became severe on Day 14, the pupillary size was 3.5-4.0 mm and light reflexes were mildly sluggish on both sides. There were no brainstem lesions on conventional and gadolinium-enhanced follow-up MRI. Intravenous methylprednisolone (1,000 mg/day for three days) was administered on Day 35, followed by prednisolone (50 mg/day, per os). The patient was removed from mechanical ventilation on Day 40. Oph-

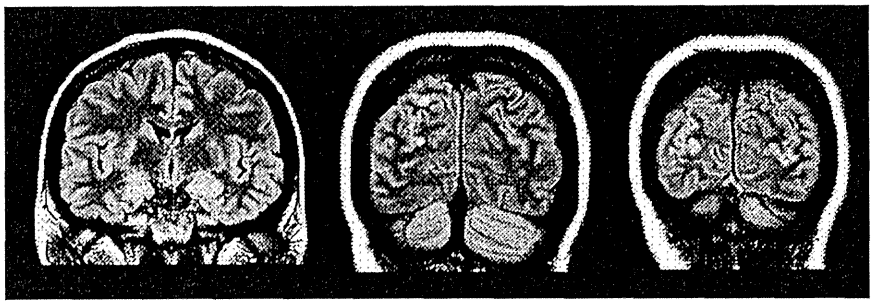

Figure 2. Hippocampal and cerebral subarachnoid lesions on MRI. FLAIR imaging showed hyperintense lesions in the medial temporal lobes and the cerebral subarachnoid region.

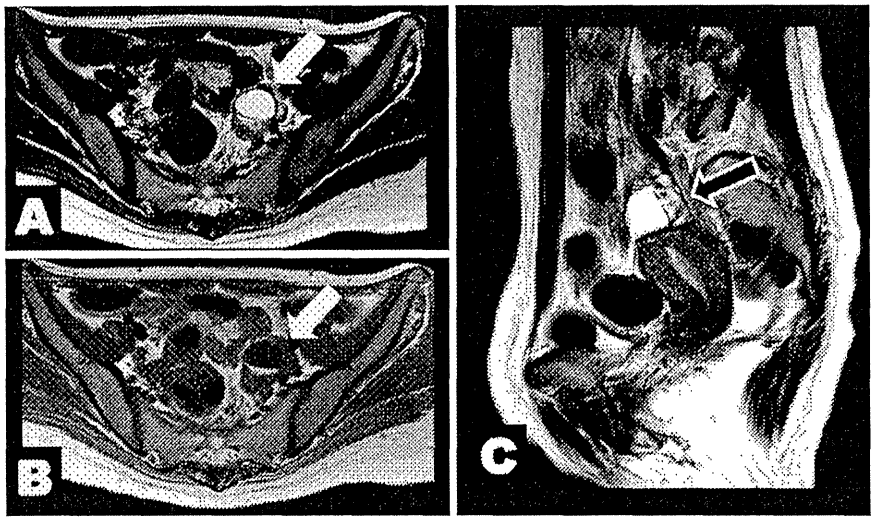

Figure 3. An ovarian lesion on pelvic MRI. A) Axial T2-weighted imaging. B) Axial T1-weighted imaging. C) Sagittal T2-weighted imaging. A small mass (26 mm in long diameter) was found in the left ovary (arrows).

thalmoplegia and lower limb muscle weakness were attenuated concurrently. Three months after admission, ocular movements, muscle strength and muscle stretch reflexes in the lower extremities were normalized. MNCV was normal in the peroneal (45.5 m/s) and the tibial nerve (46.9 m/s) on Day 177. Amplitudes of F-wave were also normal in the tibial nerve. The electrophysiological alternations from the early stage to the recovery stage suggested a mild degree of demyelinating neuropathy in the lower limbs. Neurological deficits were ameliorated completely. She refused surgical resection of the left ovarian tumor. We have investigated the patient carefully at the outpatient departments of neurology and gynecology.

Discussion

We reported a distinct patient with GBS-like condition of ophthalmoplegia and lower limb muscle weakness during the course of anti-NMDAR encephalitis. In addition, the present patient had marked hyponatremia and a transient splenial MRI lesion.

In general, NMDARs are ligand-gated cation channels and can play a crucial role in synaptic transmission and plasticity. The receptors are heteromers of NR1 subunits binding glycine and NR2 (A, B, C or D) subunits binding glutamate (16). NR1 and NR2 combine to express receptor subtypes with distinct pharmacological properties, localization and the ability to interact with intracellular messengers. Overactivity of NMDARs causing excitotoxicity is an underlying mechanism of epilepsy, dementia and stroke whereas these hypoactivity induces neuropsychiatric symptoms of schizophrenia (17-19). In 100 cases reported by Dalmau et al. (3) and 44 cases reported by Irani et al. (6), the common early clinical features included seizures, confusion, amnesia, behavioral changes and psychosis. The later distinctive aspects revealed conscious disturbance, involuntary movements and dysautonomia. The present patient experienced no involuntary movements and epileptic seizures during her entire clinical course, although hypothermia and hyponatremia were present. Hypothermia was described in only three (3%) of 100 patients with anti-NMDAR encephalitis (3). On the other hand, as a possible etiology of hyponatremia, syndrome of inappropriate secretion of ADH (SIADH) or cerebral sodium wasting syndrome (CSWS) was suspected in

Table. Previous and Present Cases of Anti-NMDAR Encephalitis and Peripheral Nerve Involvement

Reference Number (Reported years)	Age/sex	Tumor	Interval between anti-NMDAR encephalitis and peripheral nerve diseases	Anti-NMDAR antibodies	Serum antibodies to gangliosides	Treatment	Prognosis
11 (2011)	19 years/man	Absence	Anti-NMDAR encephalitis on Day 37 of GBS	Anti-NR1/NR2B antibodies	Negative	IVIg, mPSL	Sequelae
12 (2011)	23 years/woman	Absence	Anti-NMDAR encephalitis on Day 2 of MFS	Anti-GluRε 2, anti-NR1/NR2B antibodies	Anti-GQ1b IgG, anti-GT1a IgG	IVIg, mPSL	Good
Present case	26 years/woman	Ovarian teratoma	Ophthalmoplegia on admission and flaccid paraplegia on Day 7 of anti-NMDAR encephalitis	Anti-GluRε 2-NT2, anti-GluR ε 2-CT1, anti-GluR ζ 1-NT, anti-GluRδ 2-NT, anti-NR1/NR2B antibodies	Negative	IVIg, mPSL	Good

GBS: Guillain-Barré Syndrome, IVIg: intravenous immunoglobulin, MFS: Miller Fisher syndrome, mPSL: methylprednisolone, ND: not described, NMDAR: N-methyl-D-aspartate receptor

the present patient. The volemic state has been pointed out as the most crucial factor for the differential diagnosis of both syndromes. The plasma volume is normal or increased in SIADH patients whereas that is decreased in CSWS patients. The urine volume is normal or decreased in SIADH patients. CSWS patients have polyuria and dehydration symptoms (20). The present patient had normal CVP and urine volume without dehydration signs. These laboratory findings supported the diagnosis of SIADH rather than CSWS. Dilutional hyponatremia due to SIADH was not mentioned in previous review and case series reports of anti-NMDAR encephalitis (1-6). Interestingly, SIADH is uncommon in GBS patients. A previous study suggested that a mild to severe degree of SIADH occurred in 24 of 50 patients (48%) at some stages of GBS (21). The peripheral nervous system is rarely affected in patients with anti-NMDAR encephalitis (11, 12). The previous cases are summarized in Table.

In a case reported by Tojo et al. (11), a 19-year-old man developed limb muscle weakness and dysesthesia at 2 weeks after flu-like symptoms of cough and rhinorrhea. MNCV was decreased in the median and the tibial nerve with conduction block. No sensory nerve action potentials and F-waves were elicited. The patient was diagnosed with GBS. Psychomotor agitation was present on the 37th hospital day. Immunoreactivity against heteromers of NR1/NR2B subunits was positive in the serum and CSF samples. No serum IgG antibodies to GM1 or GQ1b were detected. In another case, a 23-year-old woman had an antecedent respiratory infection. One week later, she developed diplopia and unsteady gait. On the 2nd hospital day, mental and behavioral changes were noted. MNCV and compound muscle action potentials were normal. F-wave amplitudes were decreased in the median and the tibial nerve. Serum levels of IgG antibodies to GQ1b and GT1a were increased. IgM and IgG antibodies to GluRε2 and NR1/NR2B were detected in serum and CSF samples. The coexistence of MFS and anti-NMDAR encephalitis was considered. In the present case, the distinct neurological profile revealed extraocular and leg muscle paralysis with lower limb areflexia. The present and two previous patients experienced prodromes of respiratory or gastrointestinal infection. High frequency of preceding infection has been reported in patients with GBS and anti-NMDAR encephalitis. Whether there is the similar pathogenesis or incidental co-morbidity between these diseases remains unclear. Parainfectious common autoimmune reactions can trigger the development of anti-NMDAR encephalitis and acute demyelinating neuropathy.

With respect to the radiological hallmarks of anti-NMDAR encephalitis, the brain MRI findings were unremarkable in 45 of 100 patients described by Dalmau et al. (3). The remaining 55 patients had T2- or FLAIR-hyperintense lesions in the hippocampus, the cerebellum, the cerebral cortex, the frontobasal and insular regions, the basal ganglia and the brainstem. The most common lesion was found in the medial temporal lobes. The lesion of the corpus callosum was reported in 4 patients. Follow-up MRI was normal in most of patients (3). Otherwise, transient splenial lesion (TSL) was described in a variety of diseases or conditions, including encephalopathy, epileptic seizure and antiepileptic medication (22-24). However, there are no literatures of the diffusion-restricted TSL in patients with anti-NMDAR encephalitis. Brain DWI and ADC map findings have not been noted in patients with this type of encephalitis. In the present patient, the nonspecific encephalitic condition and SIADH may have contributed to the transient restriction of water diffusivity in the callosal splenium.

In conclusion, we highlighted GBS-like deficits, SIADH and TSL in a patient with anti-NMDAR encephalitis. Physicians should pay more attention to the cranial and the peripheral motor nerve involvement. Further clinico-immunological examination is needed to elucidate the full spectrum of anti-NMDAR encephalitis or its partial overlapping with other neurological autoimmune diseases.

The authors state that they have no Conflict of Interest (COI).

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Association of Acute Cerebellar Ataxia and Human Papilloma Virus Vaccination: A Case Report

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Neuropediatrics

Abstract

Introduction We report the case of a patient who developed symptoms of acute cerebellar ataxia (ACA) after administration of the human papilloma virus (HPV)-16/18 vaccine.

Patient and Method This patient developed symptoms of ACA, including nausea, vertigo, severe limb and truncal ataxia, and bilateral spontaneous continuous horizontal nystagmus with irregular rhythm, 12 days after administration of the HPV-16/18 AS04-adjuvanted cervical cancer vaccine. After this, the patient received methylprednisolone pulse and intravenous immunoglobulin (IVIG) therapies as well as immunoadsorption plasmapheresis.

Results Severe ACA symptoms did not improve after methylprednisolone pulse and IVIG therapies, but the patient recovered completely after immunoadsorption plasmapheresis.

Conclusion This temporal association strongly suggests that ACA was induced by the vaccination.

Keywords
- acute cerebellar ataxia
- human papilloma virus vaccination
- immunoadsorption plasmapheresis therapy

Introduction

Acute cerebellar ataxia (ACA) is a common neurologic disorder characterized by acute-onset truncal ataxia and gait disturbances, occasionally in combination with nystagmus. It may develop after viral infections, particularly, varicella.[1] ACA has also been linked to vaccination against varicella zoster virus (VZV)[2] and hepatitis B.[3] However, no previous reports described of an association between ACA and the human papilloma virus (HPV)-16/18 AS04-adjuvanted cervical cancer (HPV-16/18) vaccine. We report the case of a patient who developed ACA after administration of the HPV-16/18 vaccine (Cervarix; GlaxoSmithKline Biologicals, Rixensart, Belgium).

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Case Report

The female patient was the first child of healthy, nonconsanguineous Japanese parents with an unremarkable family history. Her delivery was uneventful, and she had good health and normal development as a child. At the age of 2 years, she was infected with varicella but recovered without complications. At that time, she was not vaccinated against VZV and hepatitis B virus.

At the age of 12.5 years, she suddenly developed nausea, vertigo, severe limb and truncal ataxia, and persistent nystagmus without fever. Twelve days before her symptom onset, she had received the HPV-16/18 vaccine. No prodromal infectious diseases were reported 2 months before the vaccination. At symptom onset, she was examined by an otolaryngologist and an ophthalmologist; their evaluations were normal. Her symptoms persisted, and she was referred to our hospital 20 days after symptom onset.

On admission, her physical examination was unremarkable. Neurologic examinations revealed bilateral spontaneous continuous horizontal nystagmus with irregular rhythm that was not inhibited by visual fixation. Finger-nose and heel-knee-shin tests revealed severe limb ataxia with terminal intention tremor and dysmetria. She was able to sit unaided but could not stand unsupported. Her deep tendon reflexes were mildly increased in bilateral upper and lower extremities. She showed no disturbance of consciousness, convulsions, pathologic reflexes, dysarthria, facial or limb sensory loss, facial or limb weakness, cranial nerve impairment, other involuntary movements such as myoclonic jerks, or behavioral changes such as irritability.

The following laboratory tests were normal: complete blood cell count; coagulation and fibrinolysis; blood chemistry; C-reactive protein; blood glucose; blood ammonia; α-fetoprotein; neuron-specific enolase; total serum immunoglobulin G (IgG, 1,111 mg/dL), IgA (151.0 mg/dL), and IgM (262.0 mg/dL) levels; complement; antiganglioside autoantibodies (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and Gal-C); anti-triosephosphate isomerase antibody; antiglutamate receptor δ2 antibody; anticardiolipin IgG; anti-β_2-glycoprotein-1 antibody; antinuclear antibody; anti-single-stranded DNA antibody; anti-double-stranded DNA antibody; plasma and urine amino acids; blood lactate and pyruvate; urinalysis; and urinary vanillylmandelic acid and homovanillic acid. The patient was seropositive for IgG against VZV but negative for IgM. The presence of antibodies against the Epstein-Barr virus suggested previous infection. Cerebrospinal fluid examination was normal, including white blood cell count (2/μL), total protein (29 mg/dL), glucose, IgG index, lactate, pyruvate, oligoclonal bands, and myelin basic protein. Bacterial and viral cultures of cerebrospinal fluid were also negative. Brain magnetic resonance (MR) imaging, MR angiography, single-photon emission computed tomography, abdominal computed tomography, whole body gallium-67 scintigraphy, echocardiography, electrocardiogram, electroencephalogram, motor and sensory nerve conduction velocity, and auditory brainstem responses revealed no abnormalities.

She was diagnosed with ACA after clinical and laboratory findings ruled out other known causes of cerebellar ataxia, including posterior fossa tumor, neuroblastoma, cerebrovascular disease, acute labyrinthitis, and metabolic disorders. ACA is usually self-limiting; however, her symptoms were severe and did not improve spontaneously. Therefore, three courses of intravenous methylprednisolone pulse therapy (1,000 mg/d for 3 consecutive days) were administered starting on day 25. Intravenous immunoglobulin (IVIG) therapy was then administered at 400 mg/kg for 5 consecutive days starting on day 44. However, neither limb and truncal ataxia nor the severe continuous horizontal nystagmus improved, and she was barely able to watch television, read, or stand without support.

Immunoadsorption plasmapheresis (IA) therapy was administered seven times a month starting on day 65. Plasma was separated from the cellular component using a membrane-type plasma separator (OP-05; Asahi Medical, Tokyo, Japan) and then passed through a TR 350 unit (Asahi Medical) to remove autoantibodies. After only two IA treatments, nystagmus began to stop intermittently during visual fixation, and both dysmetria and intention tremor began to improve. After 19 IA treatments (day 134), her symptoms abruptly and completely disappeared with the total serum IgG level reduced to 354 mg/dL. From day 220, the intermittent nystagmus without ataxia was observed again. Thereafter, the symptoms became continuous, and the total serum IgG level had increased to 899 mg/dL on day 325. The following laboratory tests were normal: complete blood cell count, coagulation and fibrinolysis, blood chemistry, C-reactive protein, blood glucose, blood ammonia, neuron-specific enolase, urinalysis, and cerebrospinal fluid examination, including white blood cell count, total protein, glucose, lactate, pyruvate, oligoclonal bands, and myelin basic protein on day 328. Her brain MR imaging was normal. One course of intravenous methylprednisolone pulse therapy was not effective; therefore, IA was started again on day 332. After five IA treatments her nystagmus was completely suppressed, with the total serum IgG level reduced to 503 mg/dL on day 347. Although she complained of mild headache and nausea almost every night after IA therapy, no other side effects, such as infection, hypotension, or arrhythmia, were evident.

Discussion

Our patient developed ACA 12 days after administration of the HPV-16/18 vaccine. Guillain-Barré syndrome (GBS) is reported to be a frequent complication of a quadrivalent HPV-6/11/16/18 vaccine (Gardasil).[4] However, her clinical symptoms and diagnostic test results were apparently different from the manifestations of GBS.

The mean age at ACA presentation was reported to be 4.8 ± 3.8 years, with 70% of afflicted children aged 2 to 5 years.[5] The latency from the prodromal illness to ACA onset was reported to be 9.9 ± 7.9[1] or 8.8 ± 7.4 days.[5] Souayah et al reported the distribution of time interval between quadrivalent HPV-6/11/16/18 vaccine and the occurrence of GBS showed a peak within the first 2 weeks after vaccination.[4]

Although this is a single case report, the rare age at ACA onset and the strong temporal association with vaccination strongly suggests that ACA was induced by the HPV-16/18 vaccine.

Although the pathogenesis of ACA remains unclear, an autoimmune process triggered by molecular mimicry has been proposed. No significant antibodies are detected in this patient; however, the effectiveness of IA suggests that some unknown antibodies were involved in the pathophysiology of ACA. The HPV-16/18 vaccine contains the major capsid L1 protein of HPV-16/18,[6] which has a sequence similar to certain human cell-adhesion molecules, enzymes, transcription factors, and neuronal antigens.[7] Further research on molecular mimicry between human proteins and HPV16 L1-derived peptide may provide important information on the pathologic mechanism of ACA.

HPV is an epitheliotropic double-stranded DNA virus that infects up to 80% of all women.[8] About 5 to 10% of adult women do not clear the virus and therefore develop persistent infection. Infection by high-risk HPV types is the single most important factor in the development of cervical cancer. The HPV-16/18 vaccine is highly effective in protecting women against HPV-16/18 infection and associated cervical lesions.[6,9] Our patient recovered fully; therefore, such rare instances of ACA after HPV-16/18 vaccination should not deter women from immunization.

In our patient, truncal ataxia and nystagmus remained unchanged after methylprednisolone pulse and IVIG therapies. These symptoms were reported to be more common in ACA patients exhibiting subsequent disability,[1] so IA was performed. This treatment course resulted in complete abrogation of symptoms in association with serum IgG levels. IA has been proposed for neurologic autoimmune diseases like GBS[10] because IA does not require supplementation of fresh frozen plasma and albumin, which carry a risk of infection and allergic reactions. To our knowledge, there are no previous reports describing IA in a patient with ACA. The rapid improvement from the initiation of the therapy and a full clinical recovery suggest that the IA may have shortened the course of the disease. The first case presented here indicates that IA is worth considering for treatment of severe ACA that does not respond to steroid or IVIG therapy.

In conclusion, ACA might be a rare side effect of the HPV-16/18 vaccine. This case also indicates that IA is a possible treatment for severe ACA unresponsive to steroid or IVIG therapies.

Acknowledgment

We sincerely thank Prof. Kousaku Ohno for his experienced comments throughout this case study.

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Clinical Observations

Acute Cerebellitis Following Hemolytic Streptococcal Infection

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ABSTRACT

BACKGROUND: Acute cerebellitis is a rare inflammatory syndrome in children, with either infectious or autoimmune etiologies. **PATIENT:** We describe a 7-year-old girl with a presentation of cerebellitis following group A streptococcal infection. **RESULTS:** Magnetic resonance imaging showed diffuse symmetrical swelling and edema of the cerebellum resulting in compression of the fourth ventricle and hydrocephalus. Autoantibodies against glutamate receptor δ2 were detected in the cerebrospinal fluid, suggesting that the cerebellum might be injured by postinfectious immunologic reaction. The most common causes of cerebellitis are acute viral infection, postinfection, and following vaccination. No examples of acute cerebellitis following group A streptococcal infection have been documented. **CONCLUSION:** Our report demonstrates that group A streptococcal can lead to acute cerebellitis.

Keywords: cerebellitis, hemolytic streptococcal infection, autoantibodies against glutamate receptor δ2

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Introduction

Acute cerebellitis is an inflammatory syndrome that is often accompanied by fever, nausea, headache, and an altered mental status in conjunction with acute onset of cerebellar symptoms.[1] Children with acute cerebellitis may or may not present with typical cerebellar signs; therefore, neuroimaging may be the most useful method of demonstrating cerebellar involvement. The characteristic magnetic resonance imaging (MRI) findings are diffuse cortical swelling and high intensity of the cerebellum on T2-weighted (T2-W) images. The most common causes are acute viral infection, postinfection, and vaccination. Frequently involved infectious agents include varicella zoster, Epstein-Barr virus, rubella, pertussis, diphtheria, and coxsackie viruses. Cerebellitis was caused by direct invasion of the pathogen, effect of cytokine release, or secondary immune response.[2] Glutamate receptor δ2 is predominantly expressed in cerebellar Purkinje cells and some cases of cerebellitis associated with anti-glutamate receptor δ2 antibodies have been reported.[2,3] Here, we report a child with acute cerebellitis following group A streptococcal infection. Anti-glutamate receptor δ2 antibody was detected in cerebrospinal fluid (CSF). Our patient demonstrates that group A streptococcus may be considered in addition to the more common infective agents.

Case report

A previously normal 7-year-old Japanese girl experienced gait disturbance and slow speech 7 days after a mild upper respiratory infection with symptoms of sore throat and rhinorrhea. She was treated with antibiotics because group A streptococcal antigen was detected in throat swab specimen. There was no family history of neurological disorders and her psychomotor development was normal. Despite an initial diagnosis of acute cerebellar ataxia, her symptoms gradually worsened and she was admitted to a nearby hospital 5 days after the onset. Brain computed tomography on admission showed swelling of the cerebellum and mild hydrocephalus. Seven days after the onset, she was transferred to our hospital because symptoms did not improve. On admission, she was alert (Glasgow coma scale; E3 V5 M6) and irritable. She had dizziness without nystagmus, hypotonia of upper and lower extremities, and could not sit by herself. Deep tendon reflex was normal and finger-nose test was poor. Heart rate was 122 beats/minute,

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respiratory rates were 18 breaths/minute, and body temperature was 37.5°C. Blood examination was normal and CSF analysis revealed 86 cells/mm^3 (polynuclear/mononuclear cells = 2/84), protein 36 mg/dL, and glucose 72 mg/dL. Anti-streptolysin O antibody was elevated to 1264 IU/mL (range: 0-244 IU/mL). Bacterial cultures of blood, CSF, and throat swab were all negative.

MRI demonstrated swelling and diffuse high intensity in the cerebellum and cerebral ventricular dilation on diffusion-weighted imaging (DWI), not obvious on T1-, T2- weighted or fluid-attenuated inversion-recovery (FLAIR) (Fig 1A). Considering the treatable cerebellitis, she had been treated with intravenous immunoglobulin (1 g/kg/day for 1 day, one course), ceftriaxone, and acyclovir until infection of herpes simplex virus was ruled out. The next day, she received methylprednisolone pulse therapy (30 mg/kg/day for 3 days, one course). An electroencephalograph showed normal finding. Brain single-photon emission computed tomography (SPECT) revealed mild hypoperfusion in the cerebellum (Fig 1B). On day 12, MRI revealed high intensity in the cerebellum on T2-weighted image and FLAIR, further magnetic resonance spectroscopy (MRS) was performed to assess brain metabolism and showed the peak N-acetylaspartate/creatine ratio was 0.49 in the cerebellum (Fig 2). This low N-acetylaspartate/creatine ratio indicated neural cell damage. The ataxia gradually improved. MRI on day 23 revealed improvement of swelling and high intensity in the cerebellum on DWI, T2, and FLAIR. SPECT on day 36 revealed further decrease of blood flow in cerebellum. MRS on days 23 and 52 demonstrated improvement of N-acetylaspartate/creatine ratio (0.58 and 0.98, respectively). She could leave the hospital 1.5 months after admission, walking alone with normal gait, but a slight action tremor remaining. Anti-glutamate receptor δ2-N-terminal and C-terminal antibodies on day 7 were positive in CSF (enzyme-linked immunosorbent assay: optical density (OD) = 1.613, normal range 0.274 ± 0.147 standard deviation [SD] and optical density (OD) = 1.634, normal range 0.316 ± 0.171 SD, respectively), and anti-glutamate receptor δ2-C-terminal antibodies were positive in serum (enzyme-linked immunosorbent assay: OD = 1.500, normal range 0.580 ± 0.172 SD). Polymerase chain reaction for herpes simplex virus, adenovirus, and enterovirus in the CSF specimen was negative.

Discussion

Acute cerebellitis is characterized by rapid onset of cerebellar ataxia following an infection or vaccination. Although etiology remains unknown in many patients, varicella zoster virus, Epstein-Barr virus, mycoplasma, and rotavirus have been reported as causative pathogens of cerebellitis.[1,4] Recently, there have been reports of cerebellitis complicated with rotavirus infection, including chronological MRI/MRS and SPECT.[4,5] As previously reported, MRI-DWI sensitively showed swelling and high intensity in the cerebellum and was helpful for diagnosis of cerebellitis. Furthermore, MRS demonstrated low N-acetylaspartate/creatine ratio in the early stage in present case report. Decline in N-acetylaspartate indicates neural cell damage, though this change is not specific for cerebellitis.[4,6] N-acetylaspartate, which declined on day 23, increased on day 52. Decline of N-acetylaspartate was reversible, and improvement of cerebellar symptoms might be correlated with the recovery of N-acetylaspartate in the present patient. There are a few reports of perfusion-SPECT in assessing cerebellitis and acute cerebellar ataxia. It has been reported that hypoperfusion might indicate a post-infectious autoimmune response, whereas hyperperfusion might reflect the immune-mediated demyelination of cerebellitis.[7,8]

Glutamate receptor δ2 is predominantly expressed in cerebellar Purkinje cells, which play a crucial role in cerebellar functions.[3] Anti-glutamate receptor δ2 autoantibody has also been reported in patients with acute cerebellar ataxia and acute or chronic cerebellitis.[2,3,9] In a patient with acute cerebellitis, anti-glutamate receptor δ2 antibody in serum was detected at an early stage, which is different from our patient.[2] Although the exact mechanism is unclear, it was suggested that acute cerebellitis might be caused by some autoimmune reaction because anti-glutamate receptor δ2 antibody was positive in CSF. Although it could not be excluded, the possibility of cross-reactivity of anti-streptolysin O antibody and anti-glutamate receptor δ2 antibody was also considered the possibility of association with postinfectious immune reaction and pathophysiology of cerebellitis. The neuronal cells damage resulting from immune reaction may be prevented by early therapeutic intervention, including intravenous immunoglobulin and steroids. It has been reported that high-dose steroids at an early stage improves cerebellar swelling and clinical prognosis.[9] Because acute cerebellitis occurs during various clinical courses, appropriate treatment must be applied for each patient. Most patients will recover without administration

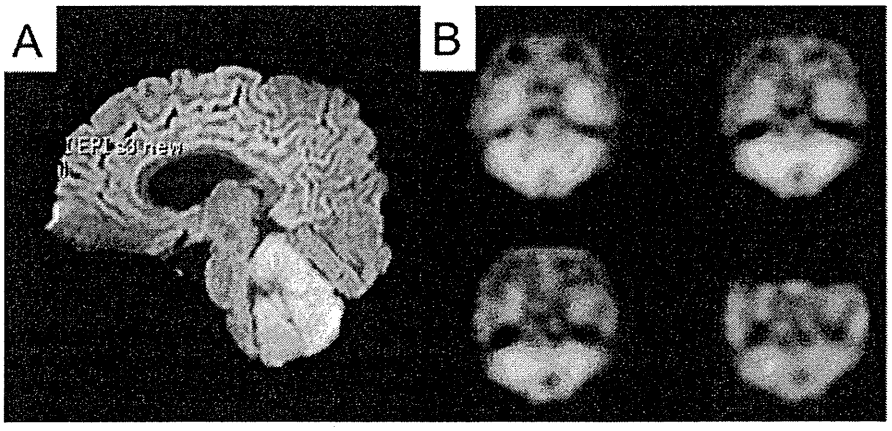

FIGURE 1.
(A) Magnetic resonance imaging–diffusion-weighted imaging revealed swelling and high intensity in the cerebellum. (B) Single-photon emission computed tomography demonstrated mild hypoperfusion in the left cerebellum compared with in cerebral cortex.

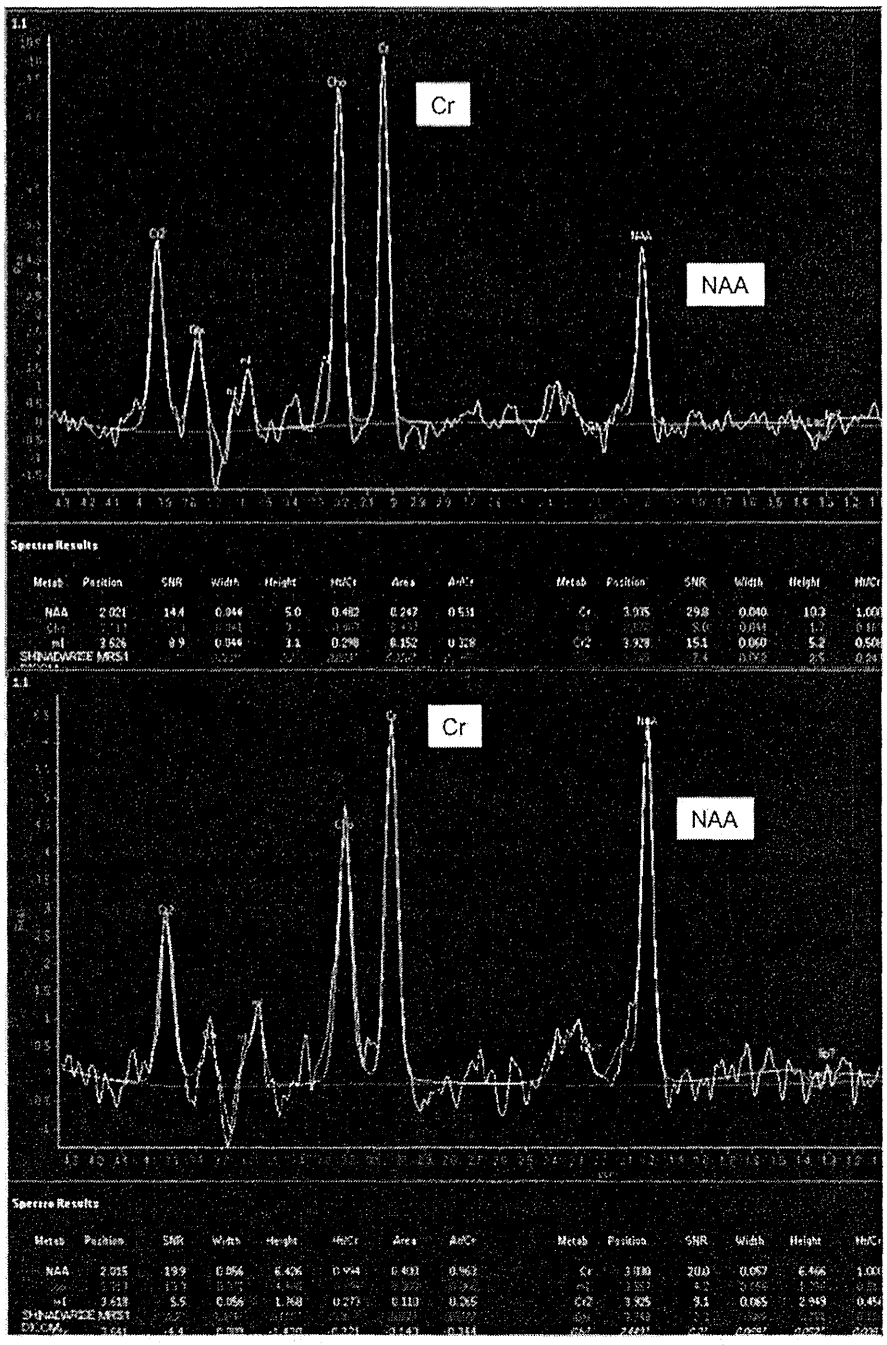

FIGURE 2.
MRS showed the N-acetylaspartate (NAA)/creatine (Cr) ratio in the cerebellar hemisphere was 0.49. Although data are not shown, they showed a similar result in the cerebellar vermis (the NAA/Cr ratio = 0.53).

of any specific treatments or steroids. In some literature, management of acute cerebellitis has been reported. Steroids are a first-line treatment when signs are moderate or severe. Further, severe headache or disturbed consciousness with cerebellar swelling on neuroimaging should be treated with steroids. If brainstem compression is developing, appropriate surgical intervention should be undertaken. Although the accurate role of steroids remains unclear, the appropriate treatment including high-dose steroids should be initiated in a life-threatening instance with hydrocephalus or brainstem involvement, as reported previously.[10] Hence, it is necessary to make a diagnosis more quickly and accurately, depending on the evaluation of clinical course and MRI/MRS. The dilation of cerebral ventricular and compression of the brainstem improve in this girl, suggesting that intravenous

immunoglobulin and steroid treatment might be effective. Further investigations are needed to clarify the role of autoantibodies, especially in relation to the pathogenesis of cerebellitis.

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The human genome consists of our species, the hereditary code of life. This newly revealed text was 3 billion letters long, written in a strange and cryptographic four-letter code. Such is the amazing complexity of the information carried within each cell of the human body, that a live reading of that code at a rate of one letter per second would take thirty-one years, even if reading continued day and night. Putting these letters out in regular font size on normal bond paper and binding them together would result in a tower the height of the Washington Monument. For the first time on that summer morning this amazing script, carrying within it all of the instructions for building a human being, was available to the world.

Francis S. Collins
The Language of God

短　報

伝染性単核球症に続発し脳脊髄液に抗グルタミン酸受容体δ2抗体をみとめた急性小脳失調症

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要旨：症例は18歳の女性である．伝染性単核球症（IM）で入院し病状は軽快傾向にあったが，第4病日に歩行時のふらつき，めまい，悪心が急性に出現した．神経学的所見では四肢体幹の小脳性運動失調をみとめた．脳脊髄液検査，頭部画像所見や神経伝導検査に異常はなく，急性小脳失調症（ACA）と診断し，ステロイドパルス療法をおこない数日で軽快した．本例は脳脊髄液の抗グルタミン酸受容体δ2（GluRδ2）抗体が陽性であり，IM後のACAとの関連について考察した．

（臨床神経 2013;53:555-558）
Key words：伝染性単核球症，急性小脳失調症，Epstein-Barrウイルス，抗グルタミン酸受容体δ2抗体

はじめに

先行感染やワクチン接種後に急性に小脳性運動失調を発症する急性小脳失調症（acute cerebellar ataxia; ACA）の病態は未解明で，従来の多くの症例報告で病態を特定しかねていた．今回，われわれは伝染性単核球症（infectious mononucleosis; IM）にひき続き発症したACA例を経験し，脳脊髄液で抗グルタミン酸受容体δ2（GluRδ2）抗体が陽性であったことから発症機序について考察した．

症　例

症例：18歳の女性
主訴：歩行時のふらつき，めまい，悪心
既往歴・家族歴：特記すべきことなし．

現病歴：2011年5月中旬に咽頭痛，上腹部痛および食欲低下が出現し増悪した．6日後に近医を受診し，身体所見で白苔をともなう扁桃肥大，頸部リンパ節腫大，血液検査で異型リンパ球の出現や肝障害をみとめ，IMがうたがわれ対症療法が開始された．上腹部痛と食欲低下がいちじるしいため発症8日目（第1病日）に消化器内科に入院した．入院時に身体所見で扁桃肥大，肝脾腫を，血液検査で末梢血への異形リンパ球の出現と肝機能障害をみとめ，血清抗体価によりEB（Epstein-Barr）ウイルス初感染のIMと診断された．入院後は対症療法がおこなわれ各症状は軽快傾向にあったが，第4病日に歩行時のふらつき感やめまいが急性に出現し，悪心も増悪したため，第5病日に神経内科を受診した．

一般身体所見（第5病日）：特記すべき異常をみとめず．

神経学的所見（第5病日）：意識は清明で，高次脳機能，脳神経，運動系，感覚系に特記すべき異常をみとめず，髄膜刺激徴候もみとめなかった．協調運動系は指鼻試験，反復拮抗運動，踵膝試験で四肢の小脳性運動失調が著明で，体幹失調のため座位や立位の保持も困難であった．

検査所見：入院時の血液検査では，白血球数6,100/μl，うち19％が異形リンパ球であった．入院時の生化学・免疫学的検査では，GOT 331 U/l，GPT 355 U/l，LDH 655 U/lと上昇していた．EBウイルス関連の抗体価については，抗EBNA抗体は10倍，抗VCA-IgG抗体は2,560倍，抗VCA-IgM抗体は320倍であった．第11病日の血清では抗ガングリオシド抗体および抗GluRδ2抗体は陰性であった．脳脊髄液検査では，第6病日において細胞数1/μl，糖56 mg/dl，タンパク質46 mg/dlと異常をみとめず，EBウイルスDNAのPCR法および抗VCA（IgG，IgM）抗体も陰性であった．第11病日の検体では抗GluRδ2抗体が陽性であった．頭部MRI（T_1，T_2，拡散強調像）では異常をみとめず，末梢神経伝導検査（右正中，尺骨，腓骨，脛骨の各神経の運動・感覚神経伝導検査，F波，ならびに腓腹神経の感覚神経伝導検査）でも異常をみとめなかった．

経過（Fig. 1）：経過，現症，検査所見よりIMにともなう

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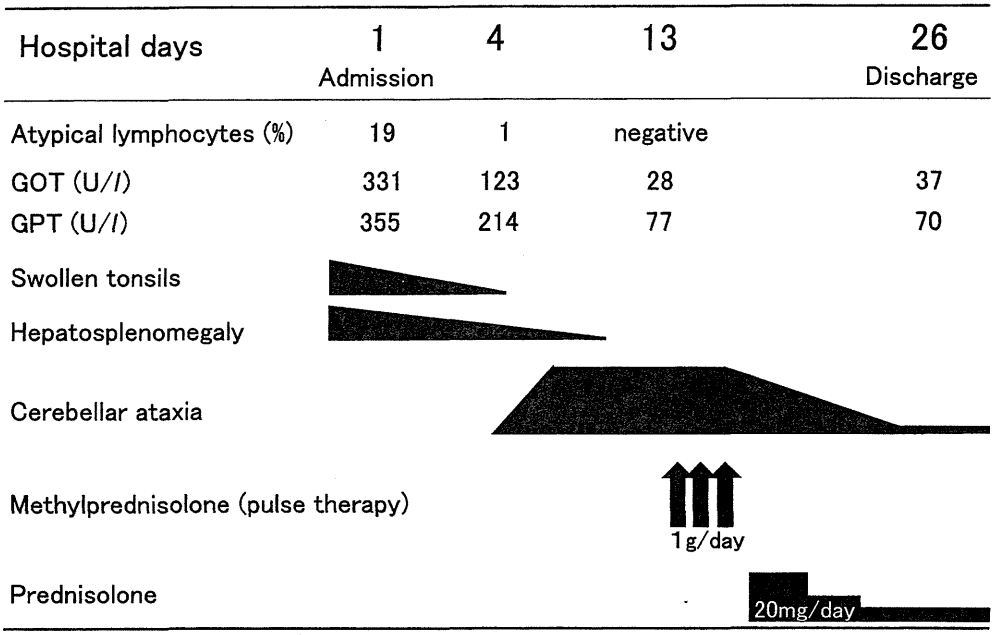

Fig. 1　Clinical course after admission.
The patient was admitted because of infectious mononucleosis. After the admission her condition improved. But on hospital day 4, she suddenly developed cerebellar ataxia in the trunk and four limbs. We diagnosed acute cerebellar ataxia and performed methylprednisolone pulse therapy. After this therapy, her cerebellar ataxia improved over a few days.

Table 1　Previously reported cases presenting cerebellar ataxia accompanied with anti-GluRδ2 antibody.

Case	Age (years)	Sex	Antecedent disease	Duration of the illness	Anti-GluRδ2 antibody		Abnormal MRI findings in the cerebellum
					Serum	CSF	
Sugiyama et al.[4] (2004)	3	M	Diarrhea, vomiting	More than 16 months	+	+	−
Usui et al.[5] (2011)	13	F	Vaccination (MR)	More than 9 months	+	+	−
Shimokaze et al.[6] (2007)	13	M	Unknown	Less than 3 weeks	+	−	+
Kubota et al.[7] (2008)	4	F	Vaccination (DPT)	20 months	−	+	−
Ichikawa et al.[8] (2009)	2	F	Respiratory infection	More than 9 months	+	unknown	−
Shiihara et al.[9] (2007)	1	M	Respiratory infection, Varicella	2 months	+	+	−
Present case	18	F	Epstein-Barr virus infection	3 weeks	−	+	−

CSF: cerebrospinal fluid, MR: measles and rubella, DPT: diphtheria, pertussis and tetanus.

ACAと診断し，第13病日からメチルプレドニゾロンパルス療法（1,000 mg/日を3日間，連日静注）をおこない，引き続いてプレドニゾロンを20 mg/日より漸減投与した．その結果，第18病日から症状は急速に改善し，第26病日に独歩で退院した．

考　察

ACAはワクチン接種や先行感染を機に突然の小脳症状が出現し，自然治癒傾向があると考えられている．またACAは，発症の誘因に各種の感染症やワクチン接種があること，症状が遷延する症例もあること，脳脊髄液や画像などの検査所見は症例毎に様々であることなど，病像が一様ではないことも指摘されている[1]．本例のようにEBウイルス感染がACA発症の誘因になりえること[1]が知られ症例報告も散見されるが，その発症機序はEBウイルスの直接浸潤説[2]や免疫介在説[3]が想定されているが不明である．本例では脳脊髄液中のEBウイルスDNAや抗VCA（IgM，IgG）抗体が陰性であり，EBウイルスの髄腔内への直接浸潤を示唆する根拠はえられなかったが，脳脊髄液に抗GluRδ2抗体をみとめた点が既報告にはない初の知見である．

抗GluRδ2抗体を検出したEBウイルス感染あるいはIM後のACA症例は過去に報告がないが，同抗体を検出した小脳障害例は過去に6例[4)〜9)]報告されている（Table 1）．いず

れも若年例で何らかの先行感染あるいはワクチン接種後に発症している点は本例と類似するが，症状の持続期間や血清および脳脊髄液中の抗体検出パターンは一定していない．さらに，抗GluRδ2抗体が小脳障害の結果として産生されるのか，小脳障害の要因であるのかについては結論がえられてはいないが，GluRδ2サブユニットがPurkinje細胞に発現し小脳機能に関与している[10]ことから，Purkinje細胞の障害と同抗体の産生には関連性が示唆される．抗GluRδ2抗体が小脳障害の結果産生されるとする説を支持するのは急性期に一過性に血清に同抗体を検出したShimokazeら[6]の報告で，炎症により小脳組織が障害され，GluRδ2サブユニットが遊離し，抗原提示された結果，2次的に同抗体が血清に出現したと考察している．Shimokazeらの症例[6]は本例および他の既報告5例[4)5)7)~9)]とことなり頭部MRIで小脳実質内に異常所見をともなっている点，本例および他の既報告4例[4)5)7)9)]とことなり脳脊髄液には同抗体をみとめない点が相違するため，本例とは病態がことなると思われる．一方，臼井ら[5]，Kubotaら[7]，Shiiharaら[9]は先行感染などを誘因とする免疫学的機序を介して誘導された抗GluRδ2抗体が小脳障害をきたしたと考察している．これらの3症例で同抗体が症状の持続期間にわたり検出されたことは，同抗体が主な病態を形成していたことを支持する．本例では経時的な抗GluRδ2抗体の検索をおこなえず，脳脊髄液中のみで同抗体が産生された理由を明確に説明しがたいが，ステロイド治療によりすみやかに治癒したことも考慮するとEBウイルス感染を契機とした免疫機序により同抗体が髄腔内で誘導されACAを発症した可能性が考えられる．ACA発症と先行感染および抗GluRδ2抗体との関連性を解明するために今後の症例蓄積が期待される．

本論文の要旨は，第200回日本神経学会関東・甲信越地方会（2012年3月3日）にて発表した．

※本論文に関連し，開示すべきCOI状態にある企業，組織，団体はいずれも有りません．

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Abstract

A case of acute cerebellar ataxia following infectious mononucleosis accompanied by intrathecal anti-glutamate receptor δ2 antibody

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An 18-year-old woman was admitted because of sore throat and pain in the epigastric region. On admission, she presented with swollen tonsils and hepatosplenomegaly. Blood examinations revealed the presence of atypical lymphocytes, liver damage and anti-VCA IgM and IgG antibodies. These findings led to diagnosis of infectious mononucleosis. After admission, her condition improved, but on hospital day 4, she suddenly developed cerebellar ataxia in the trunk and four limbs. Cranial MRI findings were normal. Cerebrospinal fluid (CSF) collected on hospital day 6 showed normal cell counts and normal concentrations of protein and glucose. EB virus DNA and anti-VCA IgM and IgG antibodies were negative and glutamate receptor δ2 antibody was positive in CSF collected on hospital day 11. We diagnosed acute cerebellar ataxia (ACA) and performed methylprednisolone pulse therapy. After this therapy, her cerebellar ataxia improved over a few days. This is the first reported case of ACA after EB virus infection presenting with glutamate receptor δ2 antibody in CSF. The glutamate receptor δ2 subunit is expressed on cerebellar Purkinje cells. Therefore, the presence of the antibody may be associated with cerebellar dysfunction. In the present case, secondary immune reactions after EB virus infection may have produced the antibody.

(Clin Neurol 2013;53:555-558)

Key words: infectious mononucleosis, acute cerebellar ataxia, Epstein-Barr virus, anti-glutamate receptor δ2 antibody

神経内科，79(3)：354-362，2013

特集 抗体と神経疾患—最近の話題—

GluRε2抗体（NR2B抗体）—神経疾患における意義*

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Key Words：NMDA-type GluR, GluRε2, GluN2B, nonherpetic acute limbic encephalitis, Rasmussen syndrome

グルタミン酸受容体（GluR）

GluRは神経伝達物質であるグルタミン酸の受容体で，イオンチャネル型と代謝型が存在する[1)2)]．イオンチャネル型GluRは薬理学的にN-methyl-D-aspartate（NMDA）型，non NMDA型とorphanに分類され，non NMDA型はalpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid（AMPA）型とカイニン酸型に分類される．イオンチャネル型GluRには多数のサブユニットがあり，分子多様性が存在する（表1）．各サブユニットはN末が細胞外にあり，4つの膜貫通部分を経てC末は細胞内にある共通構造である（図1-A）．命名法が複雑で，マウスの遺伝子解析からの命名（GluRε1など）とラットの遺伝子解析からの命名（NR2Aな

表1 主なグルタミン酸受容体サブユニットの命名法，機能と発現部位

Sub-families	Nomenclature of subunits			Plasticity of synapse*	Learning & memory†	Neural pattern formation‡	Voluntary movement¶	Expression
	Mice	Rat	IUPHAR					
AMPA	α1-4	GluR1-4	GluA1-4					
Kainate	β1-3 γ1, γ2	GluR5-7 KA1, KA2	GluK1-5					
NMDA	ε1	NR2A	GluN2A	○	○			diffuse
	ε2	NR2B	GluN2B	○		○		Forebrain
	ε3	NR2C	GluN2C					Cerebellar granule cell
	ε4	NR2D	GluN2D				○	Thalamus, brain stem
	ζ1	NR1	GluN1					diffuse
	χ1	NR3A	GluN3A					
	χ2	NR3B	GluN3B					
GluRδ	δ1	δ1	GluD1					Inner hairy cell
	δ2	δ2	GluD2					Cerebellar Purkinje cell

* LTP, † Morris water maze, ‡ Brainstem trigeminal complex, ¶ Open field test, IUPHAR：International Union of Basic and Clinical Pharmacology.

* Antibodies to GluRε2（NR2B）—Significance in neurological diseases.

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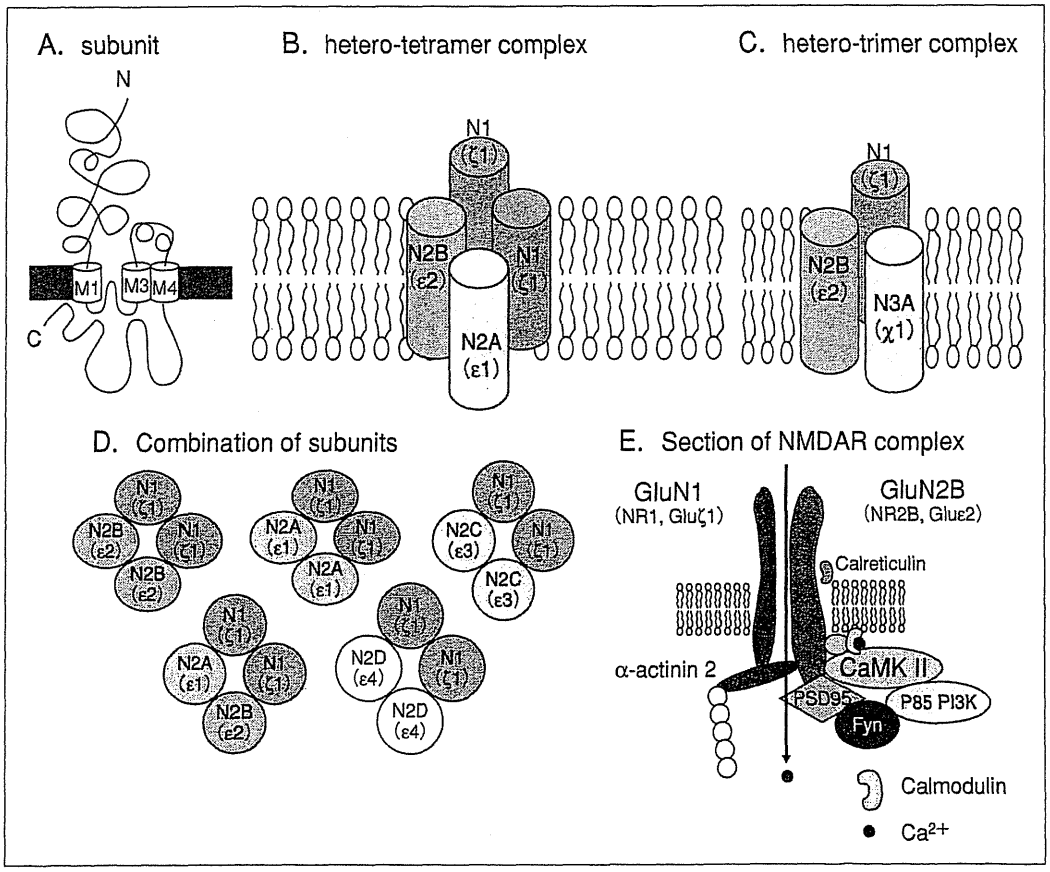

図1　NMDA型グルタミン酸受容体の構造

A：NMDA型グルタミン酸受容体のサブユニットの構造は，細胞外にあるN末から4つの膜貫通部位を経て，細胞内側にC末が存在する共通構造をとっている．B, C：NMDA型グルタミン酸受容体(NR)は，必須サブユニットであるGluN1(GluRζ1)(NR1)と，GluN2A-D(GluRε1-4)(NR2A-2D)あるいはGluRχ1-2(NR3A-B)といった可変サブユニットが4つ，稀には3つ会合した4量体，3量体構造をとっている(Mol Cell Neurosci 2001；48：308-20より引用)．D：4量体構造には，必須サブユニットと可変サブユニットの種々の会合パターンがあるとされている．E：NRの4量体，3量体構造からなる複合構造を断面で示す．各サブユニットのC末側にはシグナル伝達系の分子などが会合している．(Inactivation of NR1 by Ca-CaM：Cell 1996；84：745-55, Neuron 1998；21：443-53. Interaction with NMDA-R locks CaMK II：Nature 2001；411：801. Ca influx by anti-calreticulin antibodies：Neurosci Res 2000；36：285-90より引用)

ど)，2009年に改訂されたInternational Union of Basic and Clinical Pharmacology(IUPHAR)の命名法(GluN2Aなど)があり，ヒト，マウス，ラットの遺伝子配列にはかなり相同性がある．NMDA型GluRは，必須となるGluN1(ζ1)(NR1)と，GluN2A-D(ε1-4)(NR2A-2D)あるいはGluN3A-B(χ1-2)(NR3A-3B)といったサブユニットが4つまたは3つ会合した4量体または3量体構造(複合体)をとり(図1-B, C)，種々のサブユニット会合パターンがあるとされている(図1-D)．NMDA型GluRはイオンチャネルとしての機能のみならず，各サブユニットの細胞内のC末ドメインには種々の細胞内情報伝達分子が会合し，細胞内情報伝達にも関与する(図1-E)．GluRの生理的機能は多岐にわたり[1]，さらに中枢神経系疾患の病態にもGluRは深く関与している[3)4)]．

GluR抗体の測定法開発の歴史

GluRには上記のようにさまざまなサブファミリー，サブユニットがあるので，その自己抗体にもさまざまなものがあり，疾患とのかかわりが研究されてきた．

1994年にRasmussen症候群で，AMPA型GluRの一つのサブユニットであるGluA3(GluR3)に対する抗体が，フュージョン蛋白を用いたイムノブロット法およびGluR3をtransient transfection

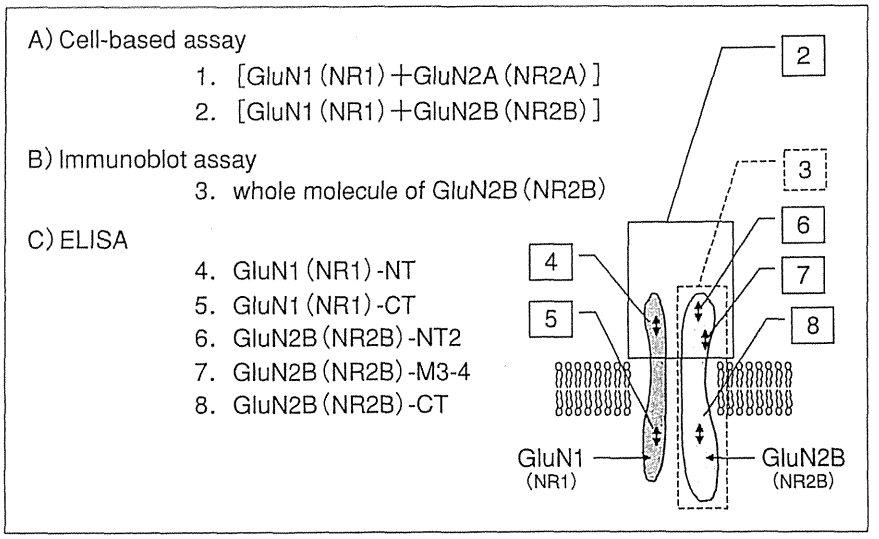

図2　NMDA型グルタミン酸受容体抗体測定法とその抗原部位

現在可能なNMDA型グルタミン酸受容体(NR)に対する抗体測定法とその抗原認識部位を示す．A：2種類のサブユニットを培養細胞表面に発現させて，実際の神経細胞表面と同じ複合体構造を作らせて抗原とするNMDA型GluR抗体(狭義のNMDAR抗体)，2の[GluN1(NR1)＋GluN2B(NR2B)]を発現させたHEK細胞を抗原とする抗体は，NR1 and or NR2Bの細胞外ドメインを抗原とする抗体である．B：GluN2Bサブユニット分子全長を遺伝子組み換えNIH3T3細胞内でテトラサイクリンシステムで合成し，その細胞ホモジネートを抗原としてイムノブロットで判定する抗体．GluRε2抗体と呼ばれ，GluN2B(ε2)全長分子を抗原として分子内のどこかを抗原とする抗体を検出する．C：サブユニットの一部のドメインの合成ペプチドを抗原としたELISAで検出する抗体．6のNR2B-NT2抗体は，GluN2B分子の細胞外N末のペプチドを抗原とする抗体である．

したHEK細胞を用いたcell-based assayで報告された[5]．この研究がGluR抗体と疾患との関連研究の始まりである．

われわれは，NMDA型GluRの一つのサブユニットであるGluN2B(GluRε2)をNIH3T3細胞中に遺伝子組み換えにより発現させ，細胞ホモジネートをポリアクリルアミド電気泳動(PAGE)後，ニトロセルロース膜に転写し検体と反応させ，二次抗体を用いてGluRε2抗体の有無を判定するイムノブロット法を確立した(図2-B)[6]．この抗体は日本では「GluRε2抗体」と呼ばれてきた．2002年に非ヘルペス性急性辺縁系脳炎(non-herpetic acute limbic encephalitis：NHALE)を含む脳炎症例でGluRε2抗体陽性例を報告し[7]，2003年にはRasmussen症候群でのデータを報告した[6]．

2007年になると，DalmauらはNMDA型GluRのGluN1とGluN2AまたはGluN2Bを発現するベクターをtransient transfectionしたHEK細胞の細胞外ドメイン立体構造を抗原とする，より生体に近い形での自己抗体測定法を開発し，卵巣奇形腫を伴う急性辺縁系脳炎における陽性例の報告を行った(図2-A)[8]．このcell-based assayにより検出される抗体(Dalmau抗体)は2種以上のサブユニットを同時に認識するとされていたが[8]，2008年になってDalmauらは，多くがGluN1(NR1)(GluRζ1)の細胞外ドメイン(N末25-380)をエピトープとしていると報告している[9]．この抗体は日本では「NMDA受容体抗体」，「NMDAR抗体」と呼ばれてきた．

これまでのNMDA型GluRに対する抗体測定法(イムノブロットによる抗GluRε2抗体やcell-based assayによりDalmau抗体)は定量性に困難があったが，2008年，われわれはGluN2B(NR2B)のN末細胞外ドメイン(NR2B-NT2)，膜貫通部M3-M4間の細胞外ドメイン(NR2B-M3-4)，C末細胞内ドメイン(NR2B-CT)のペプチドを合成し，ELISAによりGluN2B各ドメインに対する抗体を半定量測定する系を実用化し，抗体の量的変動から治療効果の判定が可能になった(図2-C)[10][11]．

2008年金沢医大の田中らは，GluN1とGluN2B