teratoma in anti-NMDAR encephalitis remain limited [5, 19].

We performed immunohistological analysis of ovarian teratomas from anti-NMDAR encephalitis patients and non-encephalitis controls to clarify differences in NMDAR distribution and lymphocyte infiltration.

Methods

Standard Protocol Approvals and Patient Consent

Prior to the initiation of this study, informed consent was obtained from each patient following a clear explanation of its purposes and methods. Ethics approval for this study was granted by the Saga University Ethics Committee.

Patients and Controls

Patients with ovarian teratomas hospitalized at Saga University Hospital between January 2004 and February 2010 were investigated in this study. All clinical data were obtained from Saga University Hospital medical records, and all formalin-fixed paraffin-embedded ovarian teratoma tissue blocks were obtained from the Department of Pathology, Saga University Faculty of Medicine. The clinical and laboratory parameters of patients with encephalitis in this study were as follows: age; symptoms; disease severity; laboratory data (thyroid functions, anti-thyroglobulin Abs, antinuclear Abs, anti-DNA Abs, Abs against several viruses including herpes simplex virus (HSV), CSF cell count and protein, immunoglobulin G in the CSF, and polymerase chain reaction testing for HSV DNA in CSF); radiological examinations, and electroencephalography. Exclusion criteria were as follows: an ovarian teratoma containing no neuronal tissue, and inappropriate tissue conditions for this study.

Detection of the Anti-NMDAR Antibody in the Serum and CSF

Methods for detecting the anti-NMDAR Ab have been described previously [8]. In brief, cDNA encoding NR1 and NR2B was ligated into expression vectors and transfected into human embryonic kidney (HEK)-293 cells in medium containing 10 mM MK-801 using Lipofectamine (Invitrogen, Carlsbad, Calif., USA). Twelve hours after transfection, HEK-293 cells were fixed in 4% paraformaldehyde in 0.1 M phosphate-buffered saline (pH 7.4) for 20 min. After non-specific binding was blocked with 10% goat serum in phosphate-buffered saline, these cells were incubated with patient sera (1:40) or CSF (1:2) overnight at 4°C and then with fluorescein isothiocyanate-conjugated rabbit anti-human immunoglobulin G (BD Biosciences, San Jose, Calif., USA) for 30 min at room temperature. SlowFade gold anti-fade reagent (Molecular Probes, Inc., Eugene, Oreg., USA) was applied to the slides and staining was observed under fluorescence microscopy.

Immunohistochemical Study of Ovarian Teratoma

Sections cut from formalin-fixed paraffin-embedded tissue blocks were used. The primary Abs used were NR1-C2 (dilution 1:100; Frontier Institute, Hokkaido, Japan), NR2B (dilution 1:100; Frontier Institute), SMI-31 (dilution 1:500; Convance, Emeryville, Calif., USA), ionized calcium-binding adaptor molecule 1 (IBA-1) (dilution 1:200; Abcam, Cambridge, Mass., USA), glial fibrillary acidic protein (GFAP) (dilution 1:100; Dako Cytomation, Glostrup, Denmark), Neurofilaments (dilution 1:100; Dako Cytomation), CD3 (prediluted; Nichirei Biosciences, Tokyo, Japan), CD4 (dilution 1:20; Nichirei Biosciences), CD8 (dilution 1:100; Dako Cytomation), and CD20 (dilution 1:100; Dako Cytomation). Slides were microwave-heated in ethylenediaminetetraacetic acid (pH 8) for antigen retrieval. The Envision+® System (Dako Cytomation) was used for the secondary Ab. Slides were visualized using diaminobenzidine tetrahydrochloride and nuclei were counterstained with hematoxylin. The Autostainer plus® automatic stainer (Dako Cytomation) was used to stain all Abs [2, 6]. The degree of staining for NMDA receptor Abs (NR1 and NR2B) was graded as follows: 0, no staining; focal (+), <30% cell staining; patchy (++), 31–60% cell staining, and diffuse (+++), >60% cell staining. To estimate the number of lymphocytes, a standard 3-point scoring system was used: low (–), intermediate (+), or high (++). The immunohistological results were independently scored by one pathologist and two neurologists.

Results

Twenty-six patients with ovarian teratomas were included in this study. These patients were divided into two groups: encephalitis group, 3 encephalitis patients with ovarian teratomas, and non-encephalitis group, 23 ovarian teratoma patients with no evidence of encephalitis. Four patients in the non-encephalitis group were excluded due to a lack of neural tissues in the ovarian teratoma (n = 2) or because of an insufficient sample state (n = 2).

Clinical Characteristics of Patients with Encephalitis

The mean age of the encephalitis group was 24.3 years (range 18–33) and that of the non-encephalitis group was 30.3 years (range 18–49). Clinical, laboratory, and radiological characteristics in the encephalitis group are shown in table 1.

Briefly, 2 of the 3 patients (cases 1 and 2) in the encephalitis group exhibited the typical clinical symptoms of anti-NMDAR encephalitis, including initial psychosis, subsequent central hypoventilation, intractable seizures, dysautonomia, and prominent orofacial dyskinesia. In contrast, 1 patient (case 3) exhibited psychosis mimicking limbic encephalitis, but never showed central hypoventilation, seizure, or orofacial dyskinesia. The presence of anti-neuronal Abs against NR1/NR2 heteromers of NMDAR was confirmed in both the serum and CSF; therefore, 3 patients in the encephalitis group were diagnosed with anti-NMDAR encephalitis. In contrast, ovarian teratoma patients in the non-encephalitis group showed no neurological or psychological symptoms according to their medical records.

Table 1. Clinical, laboratory, and radiological characteristics of patients with anti-NMDAR encephalitis

	Case 1 (severe group)	Case 2 (severe group)	Case 3 (mild group)
Age, years	24	34	18
Duration between disease onset to ovarian teratoma resection	70 days (hyperkinetic phase)	17 days (hyperkinetic phase)	20 days (psychotic phase)
Mechanical respiratory assistance	+	+	-
CSF findings			
Cells/ml	114	37	7
Protein, mg/dl	218	27	13
Anti-NMDAR antibody			
Serum	+	+	+
CSF	+	+	+
Abnormal head MRI findings	T2 hyperintensity (cerebrum)	T2 hyperintensity (cerebrum and cerebellum)	T2 hyperintensity (cerebellum)
Treatment			
Ovarian teratoma resection	+	+	+
Corticosteroids	+	+	+
Intravenous immunoglobulin	+	+	-
Plasma exchange	+	+	-

Histopathological and Immunohistochemical Findings in Ovarian Teratoma

Neural tissues were demonstrated in all teratoma samples from the encephalitis and non-encephalitis groups according to cell morphology and varying degrees of immunostaining for anti-SMI-31 Ab (a neuron-specific marker), anti-GFAP Ab (an astrocyte-specific marker), and anti-IBA-1 Ab (a microglia-specific marker) (fig. 1a–d, 2a–d). The presence of NMDAR in neuronal tissues was also revealed. In the encephalitis group, all neuronal tissues showed positive staining by anti-NR1 and anti-NR2 Ab with (++) intensity (fig. 1e, f). In contrast, the intensity of staining for anti-NR1 and anti-NR2 Ab-positive neural tissues in ovarian teratomas in the non-encephalitis group varied from (-) to (+++) (fig. 2e, f). Immunohistochemical data for neuronal tissue staining and the presence of NMDAR in the encephalitis and non-encephalitis groups are summarized in table 2.

Inflammatory cell infiltration around neural tissues was also observed in both the encephalitis group (n = 3) and non-encephalitis group (n = 2). Interestingly, inflammatory cell infiltration was observed in only 2 of 19 patients in the non-encephalitis group, whereas all 3 patients in the encephalitis group showed varying degrees of inflammatory cell infiltration. Both CD4-positive T lymphocytes and CD8-positive T lymphocytes were observed close to neural tissues (fig. 2g, h), and a predominance of CD4+ T-lymphocyte infiltration was observed in 4 of the 5 patients showing inflammatory cell infiltration (80%; all 3 patients in the encephalitis group and 1 of 2 patients in the non-encephalitis group) (fig. 2g, h). The presence of CD20-positive B lymphocytes was also observed around neural tissues in teratomas in the encephalitis and non-encephalitis groups. The state of B-lymphocyte infiltration was markedly denser in the encephalitis group than in the non-encephalitis group (fig. 1i, 2i). In addition, B-lymphocyte infiltration appeared to be adjacent to the site of NR1- and NR2B-positive neuronal tissues. This characteristic B-lymphocyte infiltration was observed among patients showing typical clinical features such as initial psychosis, subsequent central hypoventilation, intractable seizures, dysautonomia, and prominent orofacial dyskinesia. Immunohistochemical data for lymphocyte infiltration in the encephalitis and non-encephalitis groups are summarized in table 3.

Discussion

Immunotherapies such as intravenous methylprednisolone pulse therapy, intravenous immunoglobulin administration, and plasma exchange are well recognized as first-line treatments for anti-NMDAR encephalitis in the acute clinical phase. These therapeutic strategies strongly suggest that immunological pathogenesis lies in anti-NMDAR encephalitis. In addition, concerning anti-NMDAR en-

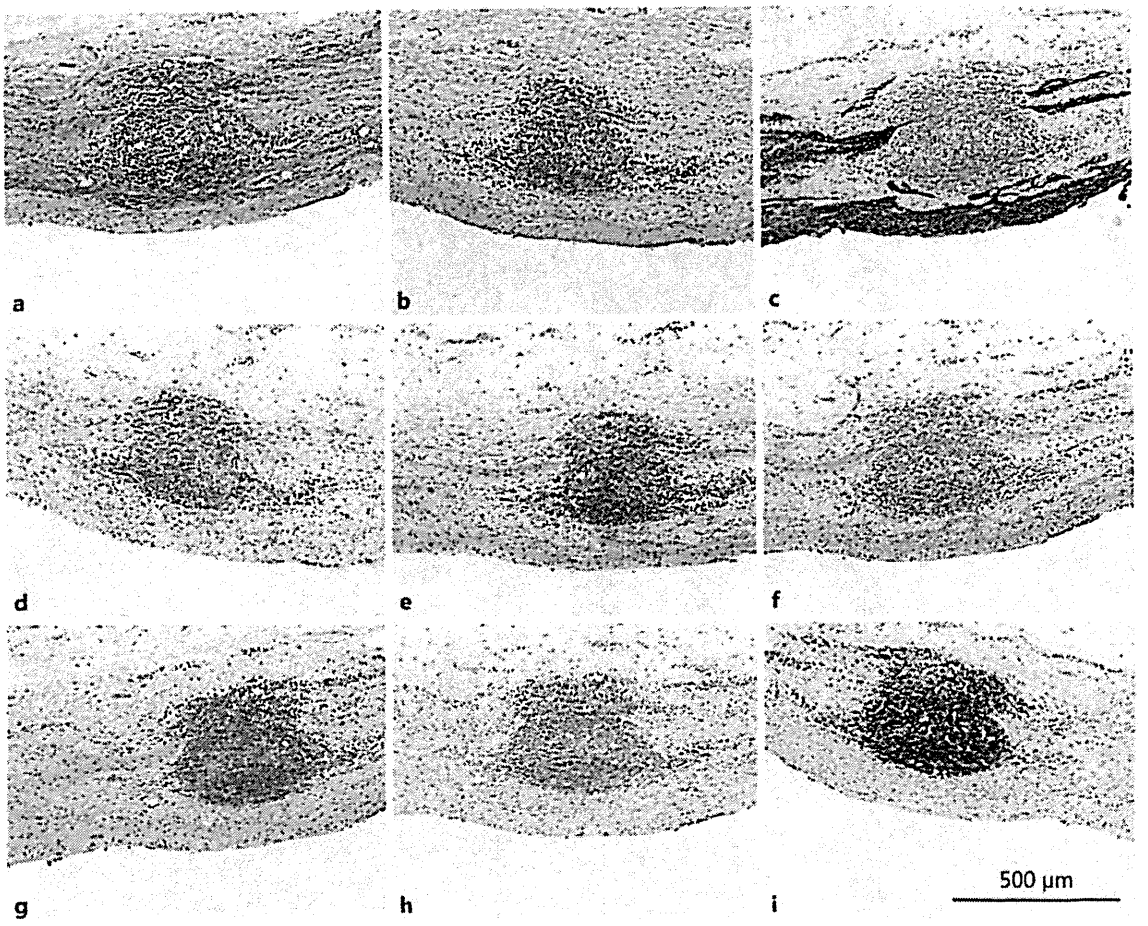

Fig. 1. Histopathological and immunohistochemical findings in ovarian teratomas with encephalitis (case 1). Neuronal tissues in the ovarian teratoma were demonstrated based on cell morphology (**a**). Immunostainings using anti-SMI-31 Ab (**b**), anti-GFAP Ab (**c**), and anti-IBA-1 Ab (**d**) confirmed the presence of several neuronal compartments in neuronal tissues. The presence of NMDAR in neuronal tissues was also demonstrated using anti-NR1 (**e**) and anti-NR2 Ab (**f**). Lymphocyte infiltration was revealed around neuronal tissues. CD4+ T lymphocytes (**g**) and CD8+ T lymphocytes (**h**) were observed around neuronal components. CD20-positive B lymphocytes were also observed around neuronal tissues with dense infiltration in the encephalitis group (**i**).

cephalitis complicated by ovarian teratoma, there have been reports that resection of the teratoma resulted in rapid and marked improvements in the condition, suggesting an involvement of ovarian teratoma in immune responses [7–12]. Ovarian teratoma appears to contribute to the pathogenesis of anti-NMDAR encephalitis [13–15]. Recent studies have shown that neuronal tissues in ovarian teratomas in anti-NMDAR encephalitis patients expressed NR2B and/or NR2A, and B- and T-lymphocyte infiltration has also been reported in the ovarian teratoma [2, 8]. In general, however, information on inflammatory cell infiltration in ovarian teratomas in patients with anti-NMDAR encephalitis is limited, and all except one report have described findings in the clinical recovery phase.

Similar to our results, Dabner et al. [19] reported pathological differences in ovarian teratomas between patients with anti-NMDAR encephalitis and non-encephalitis controls. Diffuse lymphoplasmacytic infiltrates were observed within the neurological matrix of ovarian teratomas in patients with anti-NMDAR encephalitis. Our study revealed the presence of neuronal tissues in ovarian teratomas in the encephalitis and non-encephalitis groups. NR1 and NR2B, as subunits of NMDAR, were also detected in neuronal tissues in both groups, which suggests that the presence of NMDAR itself is not a specific finding for anti-NMDAR encephalitis with ovarian teratoma. In addition, denser inflammatory cell infiltration around neural tissues in ovarian teratomas was observed in the encephalitis group.

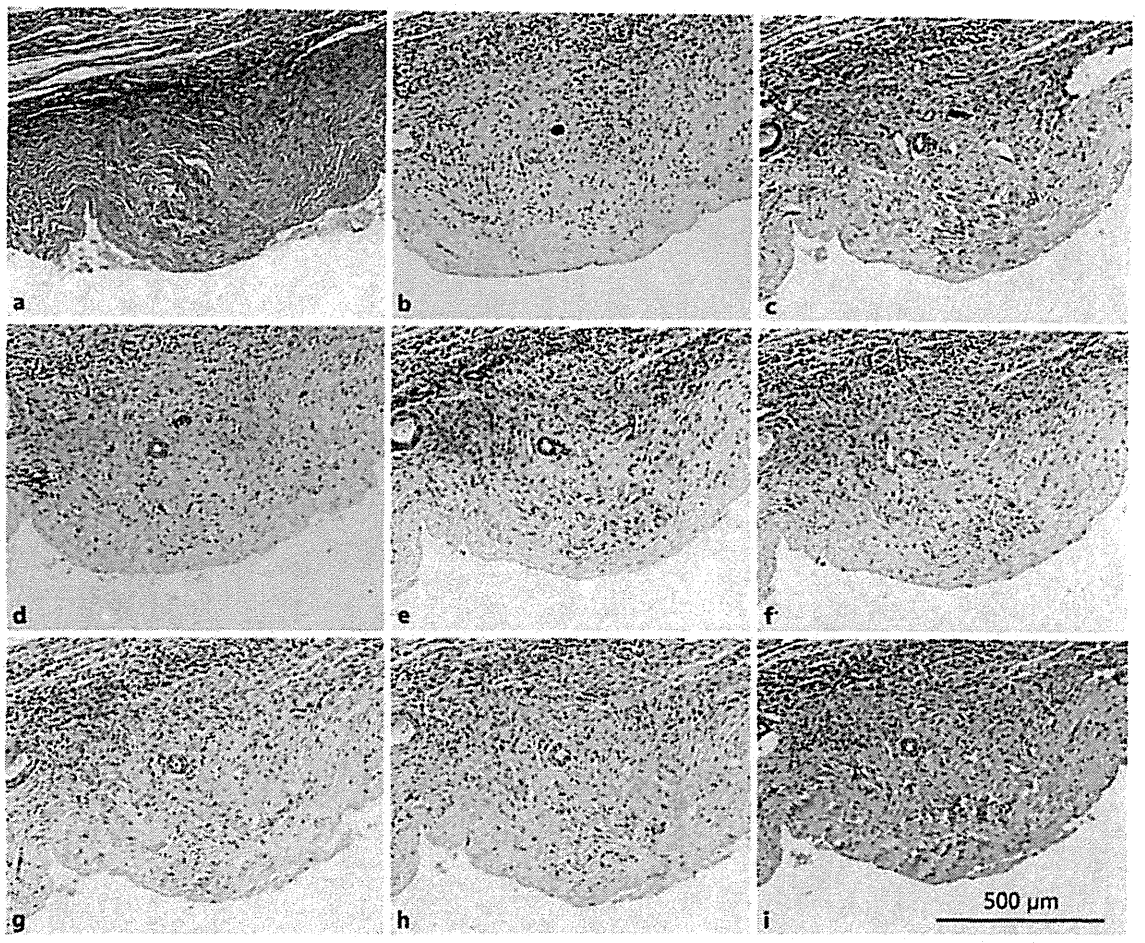

Fig. 2. Histopathological and immunohistochemical findings in ovarian teratomas with non-encephalitis. Neuronal tissues in the ovarian teratoma were demonstrated based on cell morphology (**a**). Immunostaining using anti-SMI-31 Ab (**b**), anti-GFAP Ab (**c**), and anti-IBA-1 Ab (**d**) confirmed the presence of several neuronal compartments in neuronal tissues. The presence of NMDAR in neuronal tissues was also demonstrated using anti-NR1 (**e**) and anti-NR2 Ab (**f**). Lymphocyte infiltration was revealed around neuronal tissues. CD4+ T lymphocytes (**g**) and CD8+ T lymphocytes (**h**) were observed around neuronal components. CD20-positive B lymphocytes were found around neuronal tissues with no or slight infiltration in the non-encephalitis group (**i**).

Furthermore, another study showed NR2B-related immunoreactivity in the cytoplasm of oocytes in normal ovaries. Taking these findings together, the presence of NMDAR itself is necessary, but not a sufficient condition in anti-NMDAR encephalitis. However, these results do not deny the importance of neuronal elements in an ovarian teratoma in the immunopathogenesis of anti-NMDAR encephalitis because differences in lymphocyte infiltration were also observed between ovarian teratomas in the encephalitis and non-encephalitis groups in this study.

In contrast with the ubiquitous presence of NMDAR in the ovary with or without encephalitis, the frequency and mode of lymphocyte infiltration differed markedly between the encephalitis and non-encephalitis groups. In particular, dense infiltration of CD20+ B lymphocytes around NR1- and NR2B-positive neuronal tissues represents a unique finding because this mode of infiltration was only observed in patients in the encephalitis group. This characteristic B-lymphocyte infiltration supports the immunopathogenesis of anti-NMDAR encephalitis against neuronal elements in ovarian teratomas, and differences in B-lymphocyte reactions against neuronal elements such as NMDAR could depend on some genetically predisposed individuals. Therefore, an ovarian teratoma may represent a site of antigen presentation for anti-NMDAR encephalitis patients with ovarian teratomas.

Table 2. Histopathological and immunohistochemical findings of ovarian teratoma in patients with anti-NMDAR encephalitis and non-encephalitis group

	Encephalitis group (n = 3)	Non-encephalitis group (n = 19)
Neuronal tissues staining, %		
SMI-31	100	100
GFAP	100	100
IBA-1	100	100
NMDAR staining, n (%)		
NR1 no stain (-)	0 (0)	1 (5)
Focal (+)	0 (0)	4 (18)
Patchy (++)	3 (100)	5 (25)
Diffuse (+++)	0 (0)	9 (45)
NR2B no stain (-)	0 (0)	5 (26)
Focal (+)	0 (0)	7 (42)
Patchy (++)	3 (100)	3 (16)
Diffuse (+++)	0 (0)	3 (16)
Lymphocyte infiltration, %	3 (100)	2 (10)

Table 3. Lymphocyte infiltration around neuronal tissues in the ovarian teratoma in patients with or without anti-NMDAR encephalitis

	T lymphocyte				B lymphocyte CD20
	CD3	CD4	CD8		
Encephalitis group					
Case 1	(+)	(+)	(+)	CD4 predominance	(++)
Case 2	(+)	(+)	(+)	CD4 predominance	(++)
Case 3	(+)	(+)	(+)	CD4 predominance	(+)
Non-encephalitis					
Group 1	(+)	(+)	(+)	CD4 = CD8	(+)
Group 2	(+)	(+)	(+)	CD4 predominance	(+)

(+) = Intermediate lymphocytes infiltration; (++) = highly lymphocytes infiltration.

Further investigations, such as differences in HLA constellations or microRNA expression profiles, are needed to clarify individual differences in genetic backgrounds.

On the other hand, systemic viral infection or mild inflammation affecting the ovary may create a trigger for NMDAR recognition, or the ovary itself may be important even in anti-NMDAR encephalitis patients without ovarian teratomas as a site of antigen exposure because NMDAR is present even in the ovary itself.

Although the number of patients in this study was small, the results, which showed differences in lymphocyte infiltration in ovarian teratomas between the anti-NMDAR encephalitis and non-encephalitis groups, suggest the importance and contribution of immunological mechanisms involving NMDAR to ovarian teratomas in anti-NMDAR encephalitis.

Acknowledgments

The authors are grateful to members of the Pathology Department in Saga University Faculty of Medicine for their helpful suggestions about ovarian pathology. Immunopathological analysis was contributed by Dr. Masatoshi Yokoyama and measurements of anti-NMDAR Abs in the serum and CSF were contributed by Dr. Yukitoshi Takahashi and Keiko Tanaka. This study was supported in part by grants from the Ministry of Health, Labour and Welfare, Japan.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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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

(Intern Med 52: 2811-2815, 2013)
(DOI: 10.2169/internalmedicine.52.1065)

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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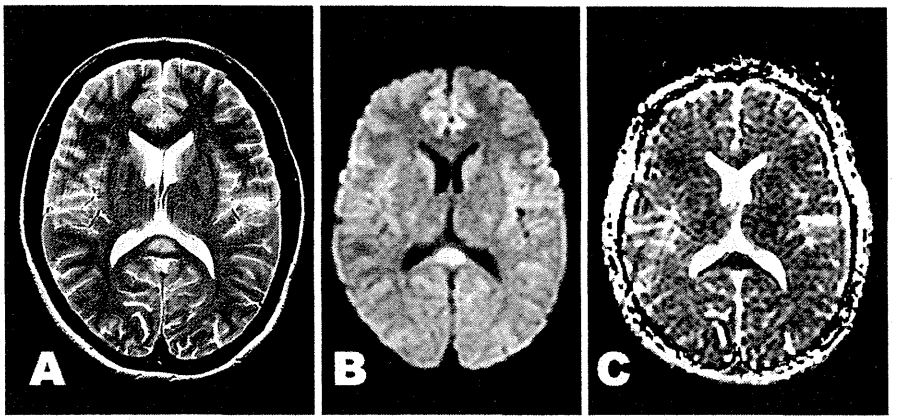

Figure 1. A transient splenial lesion on MRI. A) T2-weighted imaging. B) DWI. A hyperintense lesion was found in the callosal splenium. C) The ADC map showed a hypointense splenial lesion.

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-

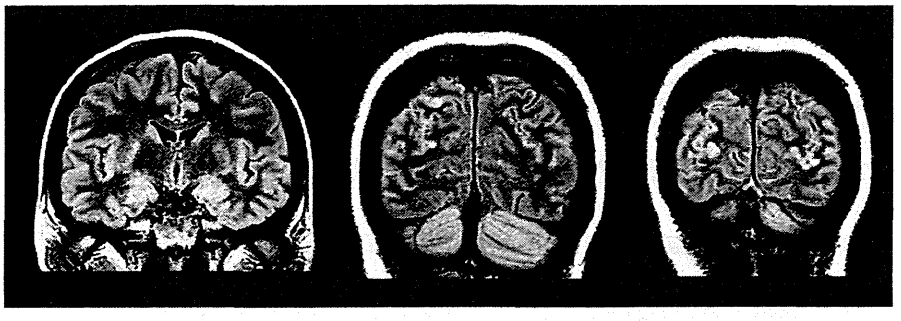

Figure 2. Hippocampal and cerebral subarachnoid lesions on MRI. FLAIR imaging showed hyperintense lesions in the medial temporal lobes and the cerebral subarachnoid region.

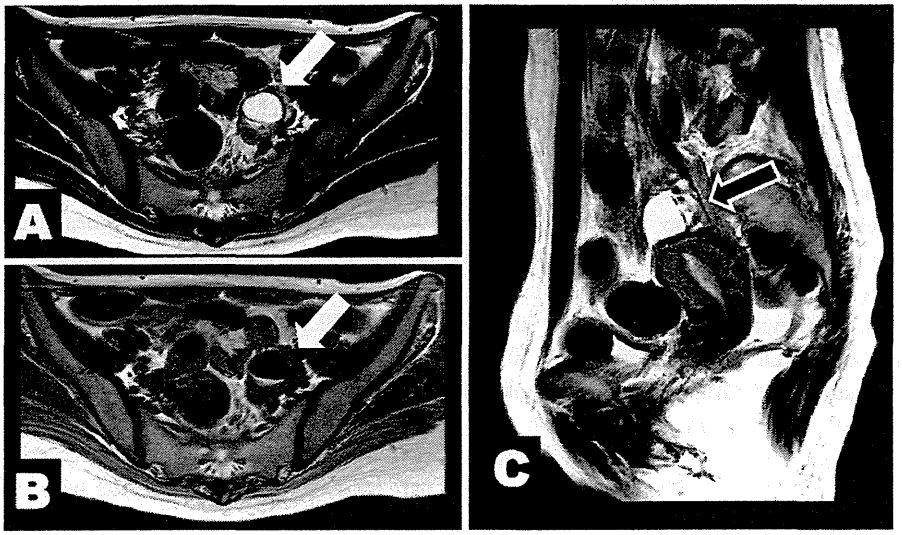

Figure 3. An ovarian lesion on pelvic MRI. A) Axial T2-weighted imaging. B) Axial T1-weighted imaging. C) Sagittal T2-weighted imaging. A small mass (26 mm in long diameter) was found in the left ovary (arrows).

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-GluRε 2-CT1, anti-GluRζ 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).

received
August 22, 2012
accepted after revision
January 2, 2013

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DOI http://dx.doi.org/10.1055/s-0033-1333873.
ISSN 0174-304X.

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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Pediatric Neurology 49 (2013) 497–500

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

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

Pediatr Neurol 2013; 49: 497-500

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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,

Article History:
Accepted December 2012.

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0887-8994/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2013.06.003

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

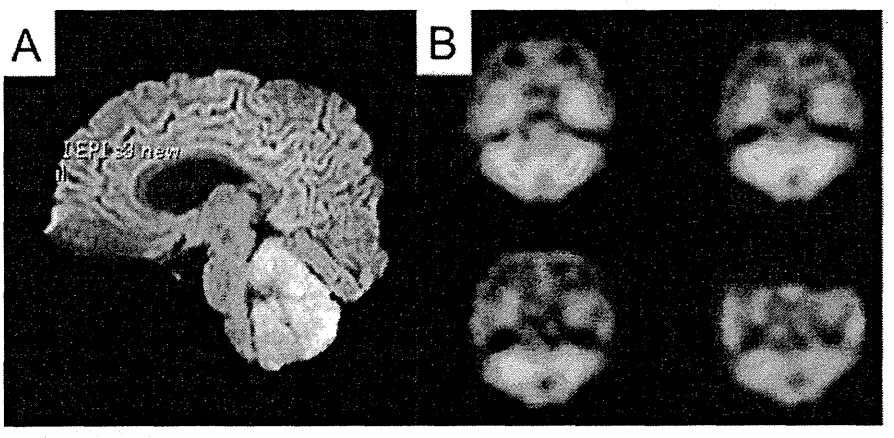

FIGURE 1.
(A) Magnetic resonance imaging–diffusion-weighted imaging revealed swelling and high intensity in the cerebellum. (B) Single-photon emission computed tomography demonstrated mild hypoperfusion in the left cerebellum compared with in cerebral cortex.

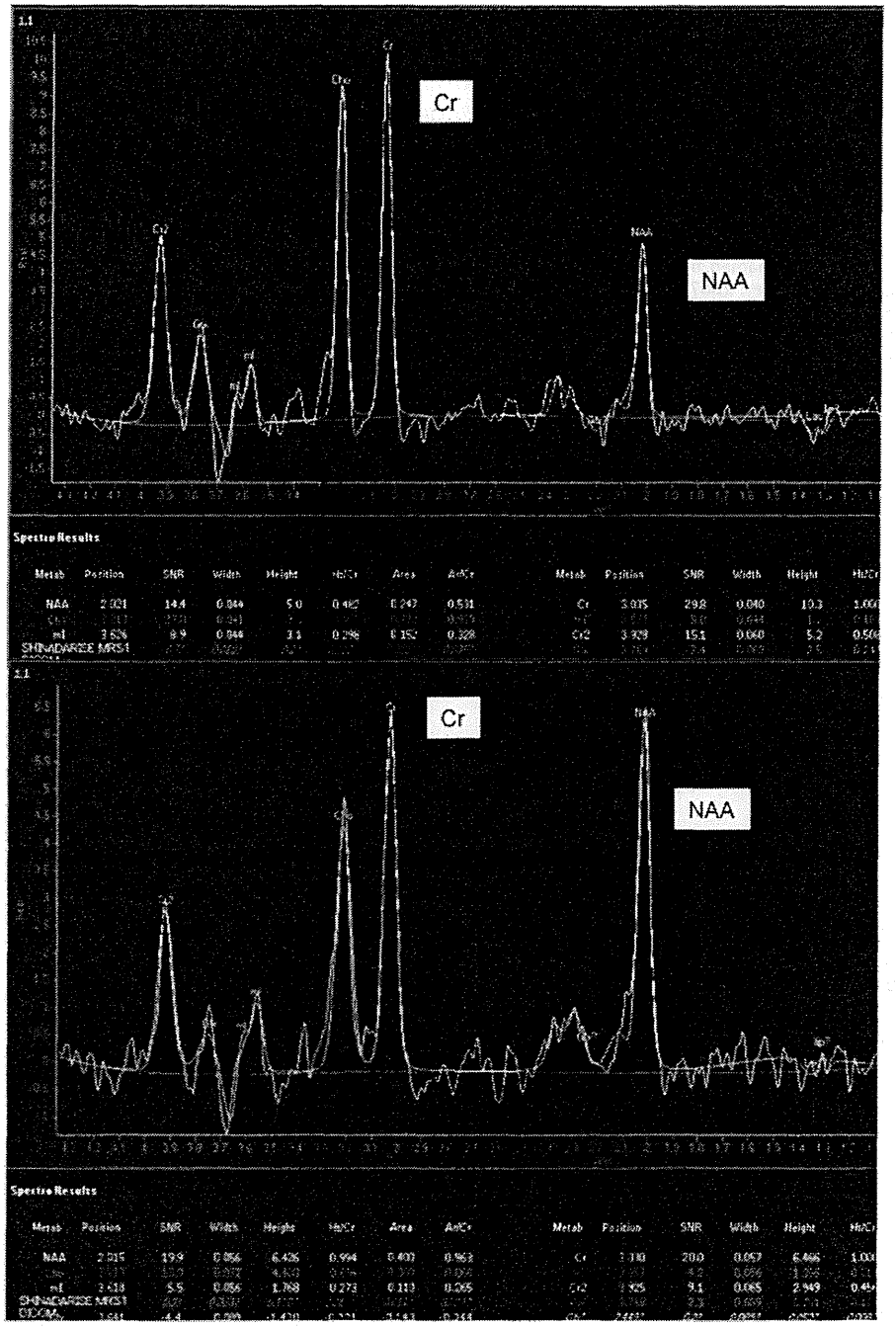

FIGURE 2.
MRS showed the N-acetylaspartate (NAA)/creatine (Cr) ratio in the cerebellar hemisphere was 0.49. Although data are not shown, they showed a similar result in the cerebellar vermis (the NAA/Cr ratio = 0.53).

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

ANNALS of Clinical and Translational Neurology
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BRIEF COMMUNICATION

Abnormal pupillary light reflex with chromatic pupillometry in Gaucher disease

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Funding Information
This study was supported by grants from the Ministry of Health, Labor and Welfare of Japan (H23-25 Nanji-Ippan-002).

Received: 3 September 2013; Revised: 20 December 2013; Accepted: 20 December 2013

***Annals of Clinical and Translational Neurology* 2014; 1(2): 135–140**

doi: 10.1002/acn3.33

Abstract

The hallmark of neuronopathic Gaucher disease (GD) is oculomotor abnormalities, but ophthalmological assessment is difficult in uncooperative patients. Chromatic pupillometry is a quantitative method to assess the pupillary light reflex (PLR) with minimal patient cooperation. Thus, we investigated whether chromatic pupillometry could be useful for neurological evaluations in GD. In our neuronopathic GD patients, red light-induced PLR was markedly impaired, whereas blue light-induced PLR was relatively spared. In addition, patients with non-neuronopathic GD showed no abnormalities. These novel findings show that chromatic pupillometry is a convenient method to detect neurological signs and monitor the course of disease in neuronopathic GD.

Introduction

Gaucher disease (GD) is the lysosomal storage disorder, caused by a deficiency of the lysosomal enzyme glucocerebrosidase (GBA), which catalyzes the degradation of glucosylceramide. GD phenotypes are clinically divided into three types: type 1 (GD1), the non-neuronopathic form; type 2 (GD2), infantile onset and rapid relentless neurological progression leading to death, usually by 2 years of age; type 3 (GD3), subacute neuronopathic, characterized by slower and more variable neurological progression.[1]

GD often involves the visual system and oculomotor deficits are the earliest symptoms identified in neuronopathic GD patients.[2] The most common manifestation is saccadic initiation failure, which has been variously labeled as "ocular motor apraxia" or "horizontal supranuclear gaze palsy."[3,4] These findings are pathognomonic and play an important role in diagnosis, whereas it is difficult to record saccades objectively in uncooperative patients and in children.

In addition to these ocular manifestations, we noticed that some patients with neuronopathic GD have dilated pupils and reacted sluggishly to a broad-spectrum (white)

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light. Pupillary light reflex (PLR) can be measured noninvasively using a pupillometer, which uses an infrared camera to measure the pupil's reaction to light. Certain commercially available models allow for short testing times and minimal patient cooperation. Such devices are currently used in the clinic and in clinical research to measure retina, optic nerve, oculomotor, and brainstem functions.[5,6]

In this study, we evaluated pupil responses using chromatic pupillometry in GD patients to assess the incidence of PLR impairment and establish whether PLR is useful in the detection of neurological symptoms.

Subjects and Methods

Subjects

Data were acquired from 10 GD patients (one GD1 patient, five GD2 patients, and four GD3 patients) and 32 healthy controls (Control 1: $n = 30$, median age 23, range 22–37 years of age; Control 2: 4-year-old female; Control 3: 6-year-old female). The diagnosis of GD was confirmed by a deficiency of GBA activity in leukocytes or cultured fibroblasts and mutation analysis of the GBA gene. All GD patients underwent enzyme replacement therapy (imiglucerase, 60 IU/kg every 2 weeks) during the study. Moreover, they underwent general ophthalmological assessments and electrophysiologic studies (electroretinogram: ERG and visual evoked potential: VEP) to exclude other causes of visual impairment before PLR was assessed. All participants gave written informed consent to participation in the study, which had secured ethical approval from the institutional review board (Tottori University School of Medicine Ethics Committee Approval 2012).

Chromatic pupillometry

A binocular infrared pupillometer, Iriscoder Dual C10641 (Hamamatsu Photonics, Hamamatsu, Japan) was used for all experiments. This device is the same as that described by Ishikawa et al.,[7] and capable of recording PLR under blue (470 nm) and red (635 nm) LED light stimuli. The stimulation luminance is selectable from 10, 100, and 270 cd/m^2. For this experiment, we selected 1-sec blue and red stimuli of 100 cd/m^2. This protocol was based on the assumption that a high-intensity blue stimulus (100 cd/m^2, <480 nm) sensitizes intrinsically photosensitive retinal ganglion cells (ipRGCs), whereas a high-intensity red stimulus (100 cd/m^2, >620 nm) sensitizes L/M cones.[8,9]

Before recording, the subjects were asked to wear the goggles for 10 min for dark adaptation. In each series, the red stimulus was presented first, followed by the blue stimulus. PLR was measured in the same eye that received the light stimulation (closed-loop paradigm). One set of pupillary response tests consisted of three parts: 1 sec before stimulation, 1 sec during stimulation, and 3 sec after stimulation (a total of 5 sec). Figure 1 shows a representative normal pupil response.

Pupil recording and analysis

We evaluated the initial constriction rate (CR). CR was calculated using the following formula: CR (%) = (initial pupil diameter: D1 − minimum pupil diameter: D2)/D1 × 100. D1 was derived from the median size during the 1 sec just before the onset of each light stimulus, after dark adaptation. Negative constriction was defined as responses <5% to distinguish evoked pupil responses from random noise. Each procedure was tested twice after a minimum interval of 1 min without light stimulation. For each pupillometric variable, we used the average of all measurements for both eyes.

Results

The clinical characteristics and findings are provided in Figure 2 and Table 1. The graphic representation of the pupillary response to monochromatic light stimulation showed that red light-induced CRs (R-CRs) were markedly attenuated or absent in neuronopathic GD patients (Patients 2–10). Although R-CR was measured quantitatively in four patients (Patients 2, 3, 4, and 7), visibly

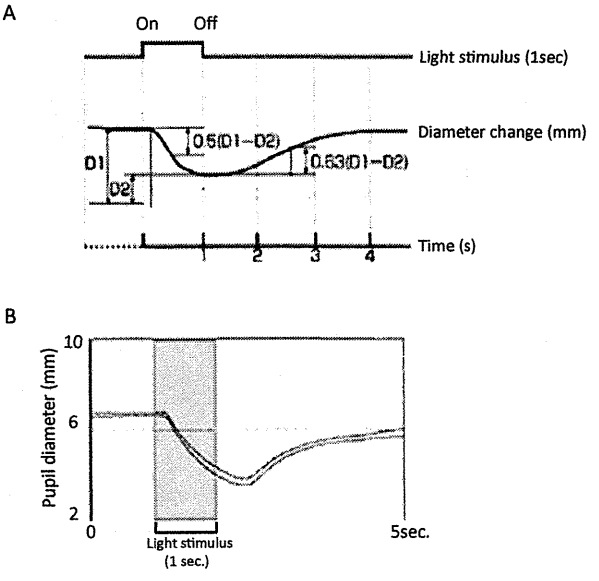

Figure 1. Example of a normal pupillary light reflex (PLR) profile. (A) PLR parameters. D1 = Initial pupil diameter (mm), D2 = Minimum pupil diameter (mm) after a pupillary reaction to light, CR = Initial constriction rate (%) = (D1 − D2)/D1 × 100 (B) Actual PLR recordings for both pupils.

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