Case Reports in Neurology

Case Rep Neurol 2014;6:291–296

DOI: 10.1159/000371442
Published online: December 24, 2014

1662–680X/14/0063–0291$39.50/0
www.karger.com/crn

Karger Open access

Anti-Glutamate ε2 Receptor Antibody-Positive and Anti-N-Methyl-D-Aspartate Receptor Antibody-Negative Lobar Encephalitis Presenting as Global Aphasia and Swallowing Apraxia

Yuki Hayata[a] Kensuke Hamada[a] Yasuhisa Sakurai[a] Izumi Sugimoto[a]
Toru Mannen[a] Yukitoshi Takahashi[b]

[a]Department of Neurology, Mitsui Memorial Hospital, Tokyo, and [b]National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

Key Words
Anti-glutamate receptor antibodies · Aphasia · Lobar encephalitis · N-methyl-D-aspartate receptor encephalitis · Swallowing apraxia

Abstract
Background: Little is known about the difference between anti-N-methyl-D-aspartate receptor (NMDAR) antibody-positive encephalitis and anti-glutamate receptor (GluR) antibody-positive encephalitis. ***Objectives:*** To characterize anti-GluR antibody-positive encephalitis. ***Methods:*** We report a 33-year-old man with nonparaneoplastic anti-GluR ε2, ζ1 and δ2 antibody-positive and anti-NMDAR antibody-negative encephalitis, using neuropsychological tests and imaging studies including magnetic resonance imaging and single photon emission computed tomography (SPECT) with a ^{99m}Tc-ethylcysteinate dimer. ***Results:*** The patient exhibited global aphasia and swallowing apraxia (inability to transfer food to the pharyngeal cavity without sialorrhea). He was treated with 3 courses of corticosteroid pulse therapy and had recovered markedly 3 weeks after onset. Magnetic resonance diffusion-weighted images revealed hyperintensity in the bilateral frontal and left parietal cortices. Seven months later, a small area of hyperintensity in the left supramarginal gyrus remained. SPECT revealed hypoperfusion in extensive regions of the bilateral frontal lobes and left supramarginal gyrus. Thirteen months later, blood flow reduction was restricted to diffuse

Yasuhisa Sakurai, MD, PhD
Department of Neurology
Mitsui Memorial Hospital
1, Kanda-Izumi-cho, Chiyoda-ku, Tokyo 101-8643 (Japan)
E-Mail ysakurai-tky@umin.ac.jp

KARGER

Case Reports in Neurology

Case Rep Neurol 2014;6:291–296
DOI: 10.1159/000371442

areas in the frontal lobes. ***Conclusions:*** Frontal lobar encephalitis without medial temporal involvement, marked cognitive impairment with a relatively preserved level of consciousness, and a favorable response to corticosteroid therapy, with nearly reversible cortical damage, may characterize anti-GluR antibody-positive encephalitis.

Introduction

Autoimmune encephalitis associated with antibodies against N-methyl-D-aspartate-type glutamate receptors (anti-NMDAR encephalitis) was first reported by Dalmau et al. [1] in 2007. Clinical features are acute limbic encephalitis with personality and behavioral change, catatonia, memory loss, seizures, dyskinesia, and autonomic dysfunction [2–5]. The disease most often involves young women and accompanies ovarian teratoma. However, 40% of patients do not have a detectable tumor, and men are also affected [2]. The clinical manifestation of nonparaneoplastic anti-NMDAR encephalitis (without ovarian teratoma) is similar to that of paraneoplastic anti-NMDAR encephalitis (with ovarian teratoma) [6]. In many cases, the medial temporal lobes and cerebral cortex are affected on MRI [2]. On the other hand, patients with anti-glutamate receptor (GluR) ε2 (NR2B) antibody have been reported to show an association with nonherpetic acute limbic encephalitis (NHALE), Rasmussen's encephalitis, and chronic forms of epilepsia partialis continua [7, 8]. Although anti-NMDAR antibody and anti-GluR ε2 antibody could be simultaneously detected in NHALE [6, 9], some patients had anti-NMDAR antibody but did not have anti-GluR antibody [10], and others vice versa [11]. Little is known about the clinical difference between anti-NMDAR antibody-only encephalitis and anti-GluR antibody-only encephalitis.

We herein report a man with anti-GluR antibody but without anti-NMDAR antibody, presenting with predominantly frontal lobar encephalitis, and discuss the clinical significance of this type of non-paraneoplastic anti-GluR encephalitis.

Case Report

A left-handed, 33-year-old man, an office worker who had graduated from university, presented with progressive speech disturbance in February 2013. He was noted to have difficulty finding words in the office and made grammatical errors on writing e-mails. He was referred to and admitted to our hospital 2 days after disease onset. On neurological examination, the patient exhibited fluctuating consciousness disturbance and difficulty saying words: he could only say 'yes'. He did not obey some simple verbal commands such as eye closing or tongue protrusion. When asked to perform dictation, he repeatedly wrote down a character that was a part of our oral command. He was diagnosed with global aphasia. Once he had raised his arms, he kept them raised until we forced him to stop (catalepsy). No neck stiffness or Kernig's sign was noted.

Laboratory findings were unremarkable. Lumbar puncture showed cerebrospinal fluid (CSF) lymphocytic pleocytosis (cells: 51/mm^3, protein: 35 mg/dl), and an elevated IgG index (1.32, normal <0.7). HSV-IgM, HZV-IgM, and HIV antibodies were all negative. Antibodies to N-terminals of NMDA-type GluR including GluN2B (ε2, NR2B) and GluN1 (ζ1, NR1) [7], and those to the N-terminal of GluD2 (δ2) were all positive, and the antibody to the NMDAR NR1/NR2 complex (Dalmau's method) [1] was negative in both the CSF and serum. Magnetic resonance imaging (MRI) performed 2 weeks after onset revealed hyperintensity in diffusion-weighted images in the bilateral frontal and left parietal cortices (fig. 1). Electroen-

cephalography (EEG) showed diffuse semirhythmic 1- to 2-Hz δ waves with a small amount of 10-Hz α waves superimposed on the δ waves in P-O, which was similar to the 'extreme delta brush' in anti-NMDAR encephalitis [12].

On admission, the patient was able to take meals. However, oral intake decreased gradually, and he could not swallow purposely at 6 days after onset. Even if the patient put water in his mouth, the swallowing reflex did not occur, and water finally leaked out through the corners of his mouth. Although sialorrhea was not noted, he choked on his saliva at 10 days after onset, suggesting that voluntary oral transport of the trapped saliva was interrupted. As a result, he was dehydrated and required an intravenous drip. The patient exhibited bulging eyes, became mute and inattentive (he sometimes turned his eyes away while the doctor talked to him), with forced grasping that was more pronounced in the left hand. He was restless in the evening, and tried to leave the bed despite the infusion tube, and so required sedation with intravenous haloperidol. Suspecting herpetic encephalitis, we first administered intravenous acyclovir (1,500 mg/day) from 5 to 7 days after onset, which was ineffective and discontinued because of drug-induced acute renal injury. From 7 to 9 days after onset, he developed a transient partial seizure on the right side of his face and extremities.

Taking the possibility of an autoimmune mechanism into account, we then administered a total of 3 courses of intravenous corticosteroid pulse therapy (methylprednisolone at 1,000 mg/day for 3 days) from 10 to 25 days after onset, and subsequently gave him oral prednisolone at 30 mg/day that was tapered and discontinued for 6 weeks. Immediately after the first pulse therapy, the patient was able to repeat a syllable following the doctor's example and responded properly to yes-no questions, such as 'Are you Mr. (patient's name)?' He was able to take meals by himself 16 days after onset and spoke some sentences correctly 20 days after onset. EEG performed 23 days after onset showed a moderate amount of 10-Hz α waves with occasional 6- to 7-Hz θ waves.

SPECT with a ^{99m}Tc-ethylcysteinate dimer (ECD-SPECT) performed 3 weeks after onset revealed, for the mean cerebral blood flow (CBF), a reduced blood flow in both hemispheres [early picture (EP) method, left 32.8, right 32.2 ml/100 g/min] with the Patlak plot method and, for the regional CBF, significant hypoperfusion (uncorrected $p < 0.001$, by Statistical Parametric Mapping version 2) in the bilateral frontal convexity and mesial frontal gyri, and the left supramarginal gyrus (fig. 2).

Neuropsychological Assessment

The patient's cognitive function was evaluated for the first time 21 days after onset. The Mini-Mental State Examination (MMSE) score was 24.7/30: mental arithmetic (serial 7) and auditory comprehension (3-step command) were impaired. The Frontal Assessment Battery (FAB) score was 13/18. The Western Aphasia Battery (Japanese edition) conducted 27 days after onset revealed that spontaneous speech was dysfluent (5/10), with stuttering, halting, and occasional phonemic paraphasia and phonetic distortion (e.g., [handan] → [hannan]), suggesting slight apraxia of speech. Auditory comprehension (9.35/10), repetition (9.2/10), naming (9.3/10), reading (9.2/10), and writing (9.85/10) were minimally impaired. Overall, his language profile was rated as slight Boca's aphasia with apraxia of speech. The Wechsler Adult Intelligence Scale-III conducted 4 weeks after onset revealed a nearly normal cognitive function: verbal IQ 84, performance IQ 80, and working memory 76. The digit span forward score was 4. The Wechsler Memory Scale-Revised conducted 33 days after onset revealed a normal memory function (verbal memory 110, visual memory 101). However, retrograde amnesia for the 3 weeks from onset to recovery remained.

The patient returned to work 2 months after onset. The MMSE score at this time was 29/30, the FAB score was 16/18 with word fluency of 7 words/min. Stuttering, halting speech, phonemic paraphasia, and phonetic distortion disappeared 3 months after onset. However, the working memory remained lower (digit span forward, 5) after 1 year. MRI performed 7 months after onset revealed a small area of hyperintensity in the left parietal cortex (fig. 1). In the follow-up SPECT performed 13 months after onset, the reduced blood flow recovered to the normal range (EP, left 46.9, right 46.9 ml/100 g/min) and the regional hypoperfusion was restricted to the diffuse areas of the frontal lobe (fig. 2).

Discussion

The patient presented with global aphasia, swallowing disturbance, abnormal behavior [catalepsy (maintaining a forced posture) and nocturnal delirium], and partial seizure. Global aphasia was characterized by scanty speech and motor perseveration in writing, which resolved to apraxia of speech a few days after corticosteroid pulse therapy.

The swallowing disturbance was voluntary in nature: he had difficulty transporting food to the pharyngeal cavity. In contrast, he swallowed saliva automatically; therefore, he did not exhibit sialorrhea. This automatic-voluntary dissociation in swallowing is characteristic of apraxia. It was clear that the patient did not initiate bolus transfer with a lack of lingual movement during the oral stage. Therefore, the symptom can be diagnosed as swallowing apraxia [13].

It is noteworthy that our patient presented with frontal lobar encephalitis. As described earlier, nonherpetic anti-NMDAR encephalitis usually involves the limbic cortex and is associated with several psychiatric symptoms [2–5]. On the other hand, the clinical features of anti-GluR antibody-positive encephalitis (GluR encephalitis) are similar to those of NMDAR encephalitis with ovarian tumor, except that paraneoplastic NMDAR encephalitis necessitates a longer hospitalization period [6]. It is suggested that in these patients with GluR encephalitis, anti-NMDAR antibody was also positive.

One problem is that in many reported cases of nonparaneoplastic anti-GluR encephalitis, anti-NMDAR antibody was not examined. Thus, the clinical difference between anti-NMDAR encephalitis and anti-GluR encephalitis remains unknown. It is suggested that our patient with lobar encephalitis without medial temporal involvement, marked cognitive impairment with a relatively preserved level of consciousness, and a favorable response to corticosteroid therapy, with nearly reversible cortical damage, characterizes anti-GluR antibody-only encephalitis.

It should also be noted that the lesion was difficult to detect on MRI, whereas the extent of the lesion was easily identifiable on SPECT. This discrepancy suggests that neuronal damage was too mild to produce cytotoxic edema, and only a small area of the left supramarginal gyrus remained permanently injured. This reversible cortical damage may be another characteristic of anti-GluR antibody-only encephalitis.

Disclosure Statement

The authors declare that they have no conflict of interest.

References

1 Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, et al: Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
2 Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR: Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–1098.
3 Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R: Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.
4 Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, Friese MA, Galea I, Kullmann DM, Beeson D, et al: N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133:1655–1667.
5 Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, et al: Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–165.
6 Takahashi Y, Yamazaki E, Nishimura S, Tsunogae H, Niwa K, Dalmau J, Imai K, Fujiwara T: Acute limbic encephalitis and NMDA type-glutamate receptor (in Japanese). Rinsho Shinkeigaku 2008;48:926–929.
7 Takahashi Y, Kubota Y, Yamasaki E, Matsuda K: Rasmussen encephalitis and non-herpetic acute limbic encephalitis (in Japanese). Rinsho Shinkeigaku 2008;48:163–172.
8 Takahashi Y, Mori H, Mishina M, Watanabe M, Kondo N, Shimomura J, Kubota Y, Matsuda K, Fukushima K, Shiroma N, et al: Autoantibodies and cell-mediated autoimmunity to NMDA-type GluRε2 in patients with Rasmussen's encephalitis and chronic progressive epilepsia partialis continua. Epilepsia 2005;46(suppl 5):152–158.
9 Takahashi Y: Epitope of autoantibodies to N-methyl-D-aspartate receptor heteromers in paraneoplastic limbic encephalitis. Ann Neurol 2008;64:110–111, author reply 111–112.
10 Ishiura H, Matsuda S, Higashihara M, Hasegawa M, Hida A, Hanajima R, Yamamoto T, Shimizu J, Dalmau J, Tsuji S: Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. Neurology 2008;71:1921–1923.
11 Yamamoto F, Yamaguchi T, Tamaoka A: Case report; a case of anti-glutamate receptor antibody positive limbic encephalitis with positive various autoantibodies (in Japanese). Nihon Naika Gakkai Zasshi 2013;102:2057–2059.
12 Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D: Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012;79:1094–1100.
13 Logemann JA: Evaluation and Treatment of Swallowing Disorders, ed 2. Austin, Pro-Ed, 1998.

Case Reports in Neurology

Case Rep Neurol 2014;6:291–296

DOI: 10.1159/000371442

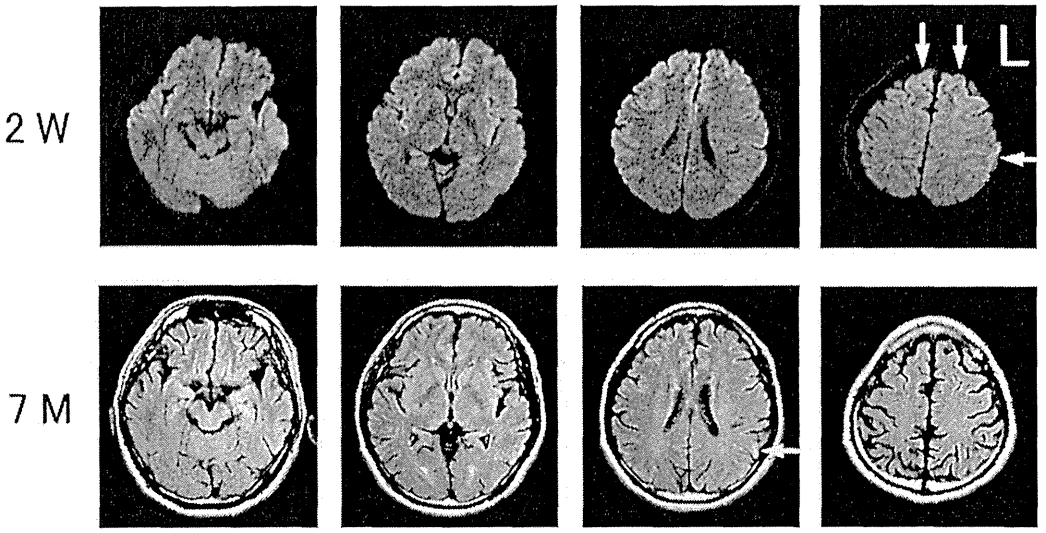

Fig. 1. MRI 2 weeks after onset (2 W) and 7 months later (7 M). Diffusion-weighted axial imaging performed 2 weeks after onset (upper panels) revealed hyperintensity in the bilateral frontal and left parietal cortices (arrows). Fluid-attenuated inversion recovery axial images obtained 7 months after onset (lower panels) revealed a high signal intensity in a small area of the left parietal cortex (arrow).

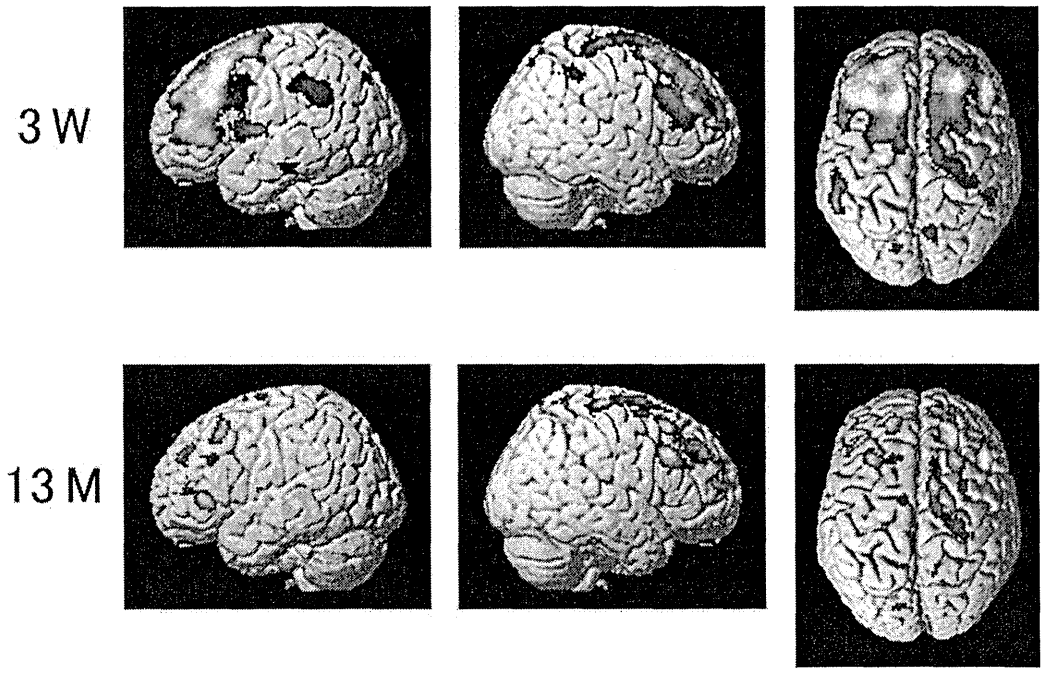

Fig. 2. ^{99m}Tc-ECD-SPECT images 3 weeks (3 W) and 13 months (13 M) after onset. ^{99m}Tc-ECD-SPECT using a 2-sample t test [patient vs. healthy subjects aged between 20 and 39 years (n = 28), uncorrected $p < 0.001$] in Statistical Parametric Mapping version 2 revealed hypoperfusion in the bilateral frontal convexity, mesial frontal gyri, and left supramarginal gyrus 3 weeks after onset (upper panels). Regional blood flow reduction was restricted to diffuse areas in the frontal lobes 13 months later (lower panels).

ELSEVIER

Brain & Development 36 (2014) 645–652

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

Anti-NMDAR autoimmune encephalitis

Kazushi Miya [a], Yukitoshi Takahashi [b], Hisashi Mori [c,*]

[a] *Department of Pediatrics, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan*
[b] *Division of Pediatrics, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka 420-8688, Japan*
[c] *Department of Molecular Neuroscience, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan*

Received 14 August 2013; received in revised form 7 October 2013; accepted 10 October 2013

Abstract

The *N*-methyl-D-aspartate receptor (NMDAR) is involved in normal physiological and pathological states in the brain. Anti-NMDAR encephalitis is characterized by memory deficits, seizures, confusion, and psychological disturbances in males and females of all ages. This type of encephalitis is often associated with ovarian teratoma in young women, but children are less likely to have tumors. Anti-NMDAR encephalitis is a neuroimmune syndrome in patients with autoantibodies recognizing extracellular epitopes of NMDAR, and the autoantibodies attenuate NMDAR function through the internalization of NMDAR. Following the initial symptoms of inflammation, the patients show the various symptoms such as memory loss, confusion, emotional disturbances, psychosis, dyskinesis, decrease in speech intelligibility, and seizures. About half of these patients improved with immunotherapy including high-dose intravenous corticosteroids and intravenous immunoglobulins is administrated to these patients, but the patients who had no improvement with these therapy require further treatments with rituximab or cyclophosphamide. It is necessary to detect anti-NMDAR antibodies at early stages, because the prognosis of these patients may be improved by early treatment. Recovery is slow, and the patients may have some disturbances in their motor function and cognition. The pathologic mechanism underlying the development of anti-NMDAR encephalitis has been elucidated gradually, but the optimal treatment has not yet been clarified. Further studies are required to clarify in detail the mechanism underlying anti-NMDA encephalitis and to develop effective treatments.

Keywords: Encephalitis; *N*-Methyl-D-aspartate receptor; Autoantibody

1. Introduction

The *N*-methyl-D-aspartate receptor (NMDAR) is critically involved in normal neural network formation, synaptic plasticity, and higher brain functions such as learning and memory [1,2]. A highly active NMDAR is composed of multiple glutamate-binding GluRε (NR2, GluN2) subunits and a glycine/D-serine-binding GluRζ1 (NR1, GluN1) subunit [3]. The hyperactivation of NMDAR has been shown to mediate acute neuronal death and chronic neurodegeneration [4]. In contrast, the hypoactivation of NMDAR is involved in the development of psychiatric states [5,6]. The NMDAR subunits are widely distributed throughout the brain including the limbic system. In situ hybridization analyses, the GluRζ1 (NR1, GluN1) subunit mRNA distributes ubiquitously in the brain. The GluRε1 (NR2A, GluN2A) subunit mRNA is expressed postnatally and widely in the brain. The GluRε2 (NR2B, GluN2B) subunit mRNA is found throughout the entire embryonic brain, but its expression becomes restricted to the forebrain at postnatal stages. The GluRε3 (NR2C,

* Corresponding author. Address: Department of Molecular Neuroscience, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani 2630, Toyama 930-0194, Japan. Tel.: +81 76 434 7230; fax: +81 76 434 5015.
E-mail address: hmori@med.u-toyama.ac.jp (H. Mori).

0387-7604/$ - see front matter © 2013 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.braindev.2013.10.005

GluN2C) subunit mRNA appears postnatally and predominantly in the cerebellum. The GluRε4 (NR2D, GluN2D) subunit mRNA is abundantly expressed in the diencephalon and the brainstem at embryonic and neonatal stages [3].

Limbic encephalitis is an inflammation of the limbic system, which includes the hippocampus, thalamus, hypothalamus, and amygdala. The symptoms of limbic encephalitis are memory deficits, seizures, confusion, and psychological disturbances. In 1960, the disease was first described as subacute encephalitis affecting the limbic areas by Brierley et al. [7]. Subsequently, it was mainly reported as paraneoplastic limbic encephalitis associated with lung carcinoma and malignancies in the ovary, breast, stomach, uterus, kidney, bladder, and colon [8]. The report suggested that limbic encephalitis is caused by autoimmunity against limbic system antigens, similarly to Eaton–Lambert syndrome. In 2001, Buckley et al. reported the cases of two patients with limbic encephalitis in whom the antibodies to voltage-gated potassium channels (VGKCs) were detected in their serum samples [9]. Later, the true target antigen of the antibodies to VGKCs has been shown to be leucine rich glioma inactivated 1 (LGI1) and contactin associated protein 2 (CASPR2) [10]. Furthermore, anti-NMDAR NR2 subunit autoantibodies were detected in some patients with acute encephalitis including those with limbic encephalitis in 2003 [11]. From these reports, the role of immunity and inflammatory processes in epilepsy or encephalitis became the focus of interest.

In 2007, the concept that anti-NMDAR encephalitis associated with ovarian teratoma, a severe, potentially lethal, treatment-responsive disorder, is mediated by autoantibodies against NMDAR was proposed by Dalmau et al. [12]. However, an increasing number of cases have been reported for both men and women from children to adults of advanced age, with and without tumors [13–18]. Recently, the spectrum of the neuroautoimmune syndromes has greatly expanded by the discovery of new antigen-specific antibodies. These syndromes are suggested to categorize (1) classical paraneoplastic syndromes associated with antibodies to intracellular antigens such as Hu, Ma2, collapsin-responsive mediator protein-5 (CRMP5), Yo or amphiphysin and (2) autoimmune encephalitis associated with antibodies to cell surface or synaptic antigens such as NMDAR, gamma aminobutyric acid receptor (GABAR-B), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), LIG1 or CASPR2, based on the underlying immunopathogenesis and responsiveness to immunotherapy [19,20]. In this report, we present the case of a girl with anti-NMDAR encephalitis and review the clinical presentations, diagnosis, and evidence supporting autoimmune mechanisms of this syndrome.

2. Case presentation

A 7-year-old previously healthy Japanese girl had a cough and low-grade fever. 5 days later, she sought her mother frequently and complained of anxiety. A week later, she was brought to our hospital owing to

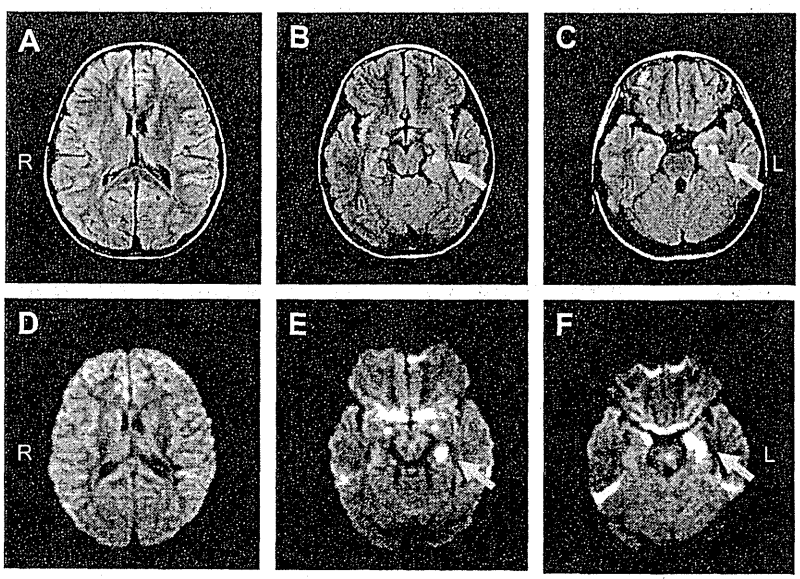

Fig. 1. MR images of a patient with anti-NMDAR encephalitis. Axial FLAIR images (panels A–C) and diffusion-weighted (DW) images (panels D–F) of a 7-years-old girl with anti-NMDAR encephalitis. Arrows in panels B, C, E, and F show hyperintensities in the left medial temporal lobe on FLAIR and DW images.

vomiting and her state of confusion. She had a temperature of 38.0 °C without focal neurologic deficits or meningeal signs. Her white blood cell count and serum C reactive protein level were slightly elevated. Cerebrospinal fluid (CSF) analysis revealed a lymphocytic pleocytosis of 296 nucleated cells/mm^3 with 90% lymphocytes and normal glucose and protein levels. Treatments with acyclovir and dexamethasone were started for presumed viral encephalitis. Her blood and CSF bacterial cultures showed negative results. Viral cultures and polymerase chain reaction analysis of CSF for herpes simplex virus also showed negative results. Thus, these treatments were stopped. Brain computerized tomography (CT) and magnetic resonance imaging (MRI) findings were normal. Electroencephalography (EEG) revealed diffuse slowing of waves, but no epileptic discharges.

Two days after admission, her state of confusion worsened and she spoke incomprehensible words, "blue, blue, blue" or "green, green, green" to her parents. She was treated with intravenous methylprednisolone, which did not improve her neurological states. She refused to take anything by mouth, necessitating nutritional support using a nasogastric tube. She demonstrated orofacial dyskinesias and involuntary movements of the right upper extremity on arousal. A week later, a second brain MRI with fluid attenuation inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) revealed hyperintensities in the left medial temporal lobe (Fig. 1). A course of intravenous immunoglobulins (2 g/kg) was completed with no response. She began to develop symptoms of dyskinesias, stereotyped motor automatisms, and spastic rigidity. We had to administer sedatives and antipsychotic medications, because she was awake during nighttime and slept during daytime and her serum creatinine kinase level increased owing to her involuntary movements.

Two months later, she showed gradual improvements in her motor and cognitive functions. 3 months after her admission, she could take food by mouth and walk a short distance by herself. After her discharge, her serum was found to be positive for anti-NMDAR antibodies (Fig. 2) and we diagnosed her as having anti-NMDAR encephalitis. Presently, she goes to school cheerfully, but has some cognitive problems, such as mild memory disturbance and learning disabilities.

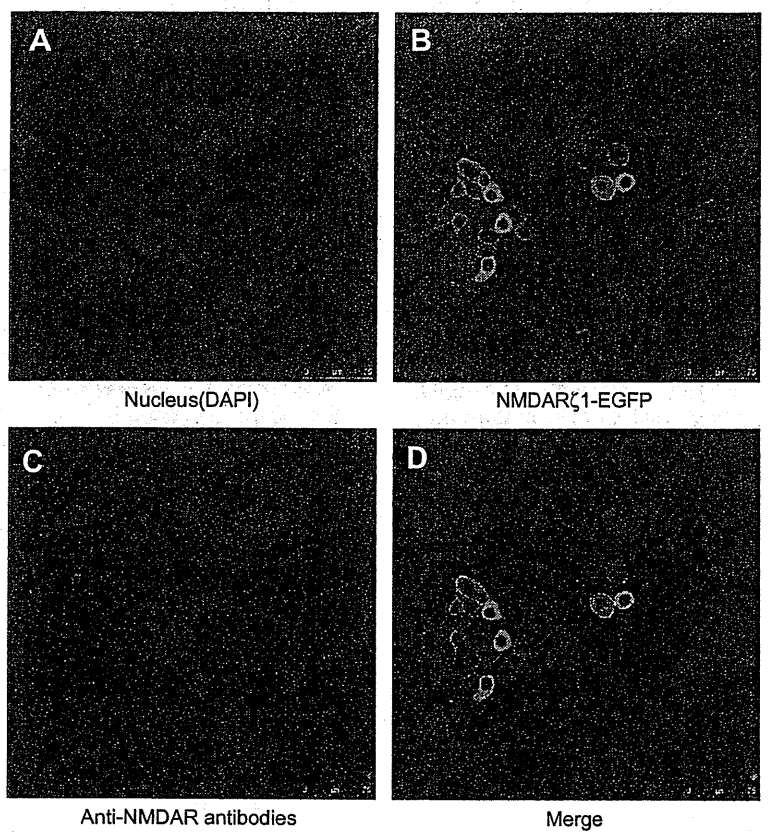

Fig. 2. Immunostaining of HEK 293T cells transfected with NMDAR ζ1-EGFP/ε2 subunits with serum from the 7-years-old girl with the anti-NMDAR encephalitis. Signals of nuclei DAPI (blue, A), fluorescence signals of NMDAR ζ1-EGFP (green, B), and immunofluorescence signals of autoantibodies in serum (magenta, C) from the patient. Panel D shows the merged image of these signals. Scale bar: 75 μm.

3. Clinical features

The exact incidence of anti-NMDAR encephalitis is unclear. The antibodies to NMDAR were detected in 4% of patients with encephalitis by a multicenter, population-based prospective study in England [21]. In another study, anti-NMDAR antibodies were detected in 1% of patients with encephalitis of unknown etiology admitted to the intensive care unit [15]. In a study in the United Kingdom and Europe, 11.1% of patients suspected of having encephalitis were positive for anti-NMDAR antibodies [22]. In the California Encephalitis Project, 4% of patients with encephalitis of uncertain etiology aged <30 years were positive for anti-NMDAR antibodies [23]. From these studies, anti-NMDAR encephalitis is not rare, and may be misdiagnosed as an unidentified encephalitis or a psychiatric disorder [16,24–26]. Initially described as paraneoplastic encephalitis associated with ovarian teratoma, young female patients often had ovarian teratoma [12,17,22]. The other tumors were sex-cord stromal tumor, neuroendocrine tumor, teratoma of the mediastinum, small cell lung cancer, and lymphoma [17,18,22]. Recent reports of the expression of the NMDAR in some tumors and its role in tumor invasion are interesting [27–29]. Many cases in children are less likely to have tumors [13,14,18]. Anti-NMDAR encephalitis commonly occurs in young females, but has been reported in males and females of all ages (from 8 months to 85 years) [13,16,18,22].

Prodromal symptoms such as fever, headache, upper respiratory symptoms, vomiting, and diarrhea are observed in 48–86% of patients within 2 weeks before hospital admission [14,17,30]. The initial symptoms of anti-NMDAR encephalitis are evenly distributed between psychotic and neurologic. However, the severity and sequence of the symptoms such as memory loss, confusion, emotional disturbances, psychosis (delusions and hallucinations), dyskinesis, decrease in speech intelligibility, and seizures vary [14,17,18]. During the course of the disorder, 76–77% of patients have seizures, most commonly tonic–clonic seizures [14,17]. Patients presenting with psychosis are often treated with antipsychotic agents [16,24–26]. Sequentially, dyskinesis (especially orofacial), involuntary movement, spastic rigidity, echolalia, ataxia, refractory seizures, and decreased level of consciousness are observed [14,17,30,31]. Some patients develop drastic involuntary movements and spastic rigidity, and have high levels of creatine kinase [17,31]. Days–weeks later, autonomic instability often causes cardiac arrhythmia, hypotension, and central hypoventilation, requiring intubation or pacemakers [14,17]. Patients show gradual improvement in motor and cognitive functions. The median duration of hospitalization is in the range of 2–2.5 months (range, 1–14 months) [17,30].

Results of conventional investigations including examination of CSF, brain imaging, and EEG are nonspecific for anti-NMDAR encephalitis. CSF analysis revealed lymphocytic pleocytosis in many cases (68–91%), oligoclonal banding and increased CSF protein level within the first few days after the onset of neurological symptoms [17,22,30]. EEG demonstrated epileptic discharge or slowing of waves [17,22,30]. A unique electrographic pattern "Extreme delta brush" may be associated with a more prolonged illness [30,32]. There are some reports that EEG showed generalized rhythmic delta activity with a nonconvulsive status epilepticus [33,34]. In MRI, few patients showed hyperintensities on T2-weighted sequences or FLAIR images of the medial temporal lobes, corpus callosum, or cerebral cortex [17,18,22,30]. The results of brain PET were limited, but all the patients showed abnormal frontotemporal, occipital, and cerebellar hypermetabolism [22,35]. The identification of anti-NMDAR antibodies is critical for the diagnosis of anti-NMDAR encephalitis, because other clinical examination results are nonspecific.

4. Detection of anti-NMDAR antibodies

The laboratory approach to the detection of anti-NMDAR antibodies involves indirect or direct examinations. Indirect immunofluorescence on cryopreserved sections or primary cell cultures of the rodent brain may be a good screening test in patients suspected of having autoimmune encephalitis regardless of having autoantibodies for brain antigens or not [12,22]. The lysates of human embryonic kidney (HEK) cells ectopically expressing NR1 or NR1–NR2 heteromers and the peptide of the NMDAR subunit were used in in vitro enzyme-linked immunosorbent assay (ELISA) [17]. A cell-based assay is an immunoassay of culture cells (i.e., HEK cells) transfected with the complementary DNA (cDNA) representing the single or assembled NR1–NR2 subunits [12,36]. The cell-based assay is a more specific and sensitive evaluation system for detecting autoantibodies recognizing conformational extracellular epitopes of NMDAR [12,36].

Rapid quantitative evaluation systems for detecting autoantibodies against extracellular epitopes of NMDAR are necessary, because paraneoplastic anti-NMDAR encephalitis has a better prognosis after tumor resection and immunotherapy (corticosteroids, intravenous immunoglobulins, or plasma exchange) [12,17,18]. Thus, the establishment of cells stably expressing functional NMDAR is desirable. However, Ca^{2+} influx through NMDAR activated by glutamate and glycine present in a culture medium is toxic to nonneurons [37]. We reported a method to rapidly analyze the presence and function of autoantibodies against NMDAR using cultured cells (HEK293T) that stably expressed mutant NMDAR with decreased Ca^{2+}

permeability on a heterologous cell surface [36]. The level of the anti-NMDAR antibody in serum of the patients is significantly higher than that in the CSF [13,22,38].

5. Treatment and prognosis

A randomized controlled trial of the treatment for anti-NMDAR encephalitis has not been reported. When the patients were diagnosed as having anti-NMDAR encephalitis, the immunotherapy including high-dose intravenous corticosteroids, intravenous immunoglobulins, plasma exchange, cyclophosphamide, azathioprine, mycophenolate mofetil, tacrolimus, methotrexate, and monoclonal antibodies (e.g., rituximab) was used in sequence or in combination [14,17,18]. Although a few patients recovered to their normal state with supportive care alone, most of the patients required further treatments such as tumor resection and immunotherapy [17,18,39]. Thus, Dalmau et al. proposed that the tumor (an ovarian teratoma or a testicular tumor) should be removed when present [39]. When tumor is not present, they prefer the first-line therapy with intravenous immunoglobulins, methylprednisolone, plasma exchange [40],

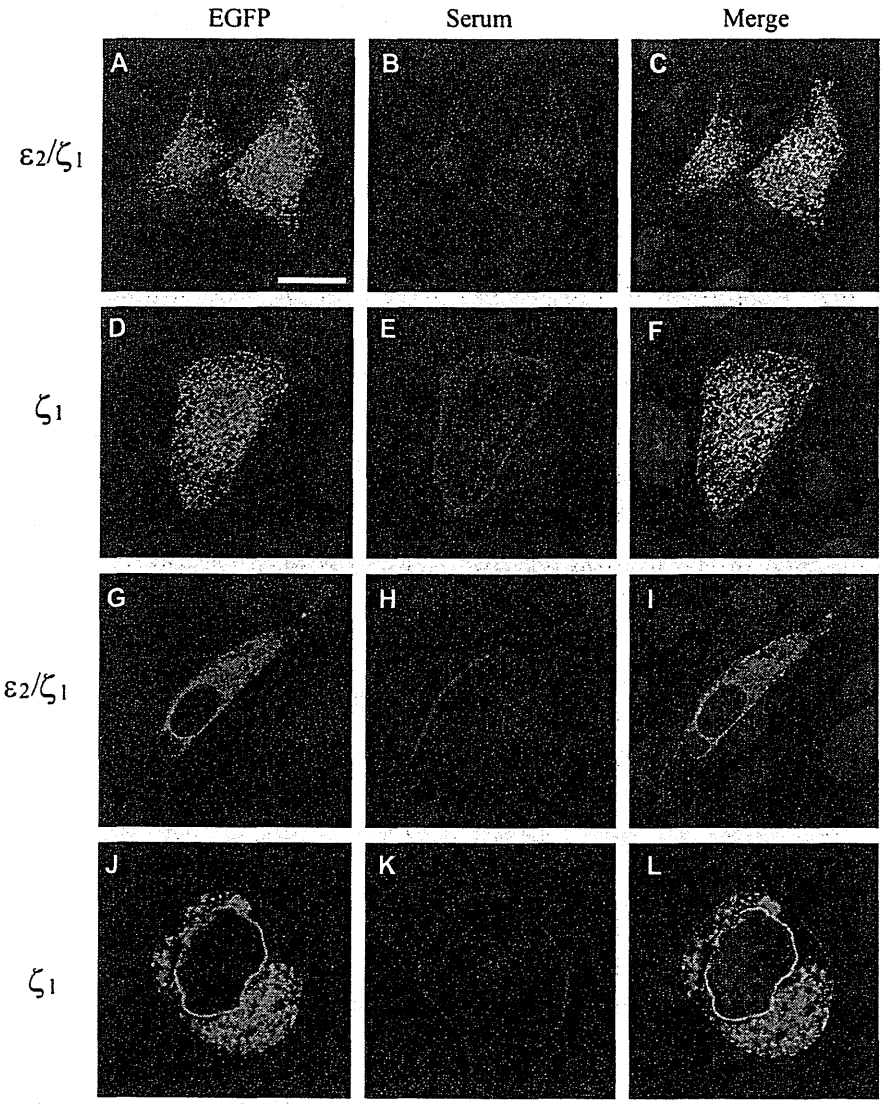

Fig. 3. Internalization of cell surface NMDAR subunits in Chinese hamster ovary (CHO) cells induced by patient's antibodies (reproduced from [36]). The ε2/ζ1-(A–C and G–I) and ζ1- (D–F and J–L) subunit-transfected CHO cells were incubated with the patient's antibodies at 37 °C (A–F) or 4 °C (G–L) then fixed and observed by confocal laser microscopy. The fluorescence signal of EGFP (green; A, D, G, and J) and the immunofluorescence signals of the antibodies in the serum (magenta; B, E, H, and K) samples from patients were detected and merged with the signal of DAPI (blue; C, F, I, and L). Scale bar: 25 μm.

or their combinations. If no response is observed after 10 days, they prefer to start the second-line therapy with rituximab [41] or cyclophosphamide [42]. The patients who did not improve with the first line immunotherapy may have better outcome due to the second line immunotherapy [18]. For patients showing a good response, the treatment shifts to supportive care and tumor surveillance. The level of anti-NMDAR antibodies in CSF and serum usually decreases when patients show substantial clinical recovery [15,17,22,43].

Recovery may take 2 years or longer, and the patient may not always return to their former levels of motor function and cognition [14,17,18,44,45]. In a cohort of 252 patients, 81% experienced complete or near-complete recovery (Modified Rankin scale scores of 1–2) and 10% (14/252) died [18]. Relapses have been reported to occur in 20–30% of patients [14,17,18,22,46], and the occurrence is higher in patients without immunotherapy [18,46]. This finding suggests the benefit of early immune suppression and tumor resection.

6. Pathology

The clinical features of anti-NMDAR encephalitis correspond to the state caused by the change in the activity of NMDAR. Anti-NMDAR encephalitis is considered to be antibody-mediated because anti-NMDAR antibodies are detected in the serum or CSF of most patients, anti-NMDAR encephalitis has a better prognosis after tumor resection and immunotherapy, and antibody levels are related to clinical outcomes [15,17,22,43]. Furthermore, the reversibility of the disorder, irrespective of the duration of symptoms, suggests an immune-mediated neuronal dysfunction rather than irreversible degeneration [17,47].

These features indicate that anti-NMDAR antibodies do not mediate neuronal death by hyperactivation of NMDAR or complement or cytotoxic T-cell mechanisms, but that these antibodies recognize extracellular epitopes of NMDAR and change NMDAR functions. The mechanisms underlying the pathogenic effects were proposed, including attenuation of NMDAR function by internalization and degradation of NMDAR by anti-NMDAR antibodies associated with paraneoplasms, such as ovarian tumors [36,39,47]. The internalization of NMDAR with anti-NMDAR antibodies was suggested by a biochemical study and a study using primary cultured neurons [36,47]. We detected the immunofluorescence signals of autoantibodies in the cytoplasm in addition to the membrane in cells expressing NMDAR (Fig. 3) [36]. The antibodies in patients with anti-NMDAR encephalitis lead to the loss of surface NMDAR by antibody-mediated internalization, resulting in the attenuation of NMDAR function [39,47]. In anti-NMDAR encephalitis, autoantibodies crossreacting with NMDAR are produced against tumors or pathogens (*Mycoplasma pneumonia* [14], influenza viruses A and B, *Chlamydophilia pneumoniae*, *Bordetella pertussis*, *Bordetella parapertussis* [15], and Epstein–Barr virus [48]). Anti-NMDAR antibodies may be produced in subarachnoid space, because the patients with NMDAR encephalitis had significant B-cell expansion in CSF and infiltration of plasma cells around vessels or in CSF [17,49–51]. This intrathecal production of autoantibody may be important factor associated with poor prognosis or resistant to first-line immunotherapy with intravenous immunoglobulins, methylprednisolone, plasma exchange. On the other hand, it is also considered that the leakage of antibodies from vessels into the brain occurs in the patients,

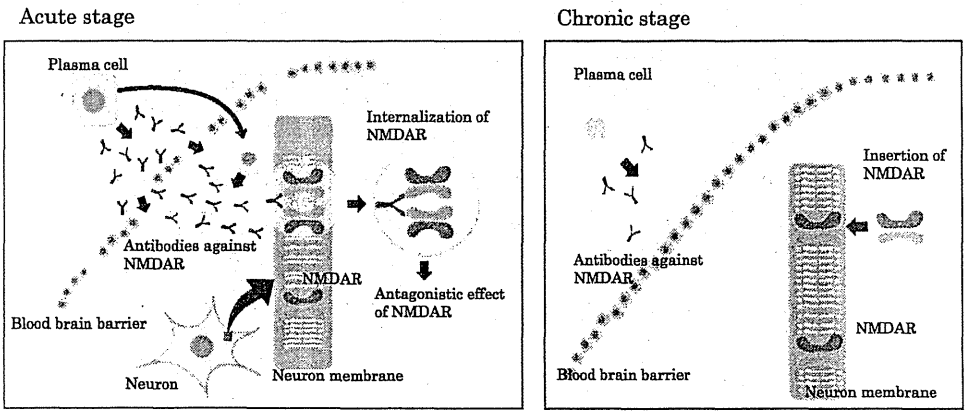

Fig. 4. Schematic models of the possible mechanism underlying the development of anti-NMDAR autoimmune encephalitis. At the acute stage, autoantibodies against NMDAR leak into CSF through the disruption of the blood–brain barrier. Intrathecal production of anti-NMDAR antibodies are also suggested. Anti-NMDAR antibodies induce the internalization of NMDAR. The decrease in the expression level of neuronal surface NMDAR results in neuronal hypoactivity. At the chronic stage, after the level of anti-NMDAR antibodies produced by plasma cells decreases and the blood–brain barrier is restored, the level of anti-NMDAR antibodies in CSF decreases. The NMDAR is expressed on the neuronal surface again, and neuronal functions recovers.

because there are some reports that the anti-NMDAR antibody levels in serum are significantly higher than that in CSF [13,22,38]. Finally, anti-NMDAR antibodies in CSF disrupt the interactions between EPHB2R and NMDARs [52], which results in the attenuation of NMDAR function through the internalization of NMDAR (Fig. 4). At the chronic stage, after the level of anti-NMDAR antibodies produced by plasma cells decreases and the blood–brain barrier is restored, the level of anti-NMDAR antibodies in CSF decreases. The NMDAR is expressed on the neuronal surface again, and neuronal functions recovers (Fig. 4).

7. Conclusion

Anti-NMDAR encephalitis with central nerve or psychiatric symptoms is detected in a significant percentage of patients with acute encephalitis. The early and precise examination for the presence of anti-NMDAR antibodies is necessary, because the prognosis of these patients may be improved by early treatment. The pathologic mechanism underlying the development of anti-NMDAR encephalitis has been elucidated gradually in in vitro studies, but the optimal treatment has not yet been clarified. Further studies are required including those of additional cases and animal models of anti-NMDAR encephalitis to clarify in detail the mechanisms underlying the development of anti-NMDA encephalitis.

Acknowledgments

We thank Dr. Shiho Takano for establishment of cell-based assay detecting anti-NMDAR antibodies. This work was supported by a grant from the Ministry of Health and Labour Sciences Research Grants for Comprehensive Research on Disability Health and Welfare (H24).

References

[1] Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 1993;361:31–9.
[2] Komuro H, Rakic P. Modulation of neuronal migration by NMDA receptors. Science 1993;260:95–7.
[3] Mori H, Mishina M. Structure and function of the NMDA receptor channel. Neuropharmacology 1995;34:1219–37.
[4] Lancelot E, Beal MF. Glutamate toxicity in chronic neurodegenerative disease. Prog Brain Res 1998;116:331–47.
[5] Gunduz-Bruce H. The acute effects of NMDA antagonism: from the rodent to the human brain. Brain Res Rev 2009;60:279–86.
[6] Coyle JT, Tsai G, Goff D. Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. Ann NY Acad Sci 2003;1003:318–27.
[7] Brierley J, Corsellis J, Hierons R, Nevin S. Subacute encephalitis of later adult life. Mainly affecting the limbic areas. Brain 1960;83:357–68.
[8] Newman NJ, Bell IR, McKee AC. Paraneoplastic limbic encephalitis: neuropsychiatric presentation. Biol Psychiatry 1990;27:529–42.
[9] Buckley C, Oger J, Clover L, Tuzun E, Carpenter K, Jackson M, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol 2001;50:73–8.
[10] Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain 2010;133:2734–48.
[11] Takahashi Y, Mori H, Mishina M, Watanabe M, Fujiwara T, Shimomura J, et al. Autoantibodies to NMDA receptor in patients with chronic forms of epilepsia partialis continua. Neurology 2003;61:891–6.
[12] Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
[13] Dale RC, Irani SR, Brilot F, Pillai S, Webster R, Gill D, et al. N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. Ann Neurol 2009;66:704–9.
[14] Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11–8.
[15] Pruss H, Dalmau J, Harms L, Holtje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010;75:1735–9.
[16] Day GS, High SM, Cot B, Tang-Wai DF. Anti-NMDA-receptor encephalitis: case report and literature review of an under-recognized condition. J Gen Intern Med 2011;26:811–6.
[17] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
[18] Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–65.
[19] Bien CG, Vincent A, Barnett MH, Becker AJ, Blumcke I, Graus F, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Brain 2012;135:1622–38.
[20] Davis R, Dalmau J. Autoimmunity, seizures, and status epilepticus. Epilepsia 2013;54:46–9.
[21] Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 2010;10:835–44.
[22] Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133:1655–67.
[23] Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California encephalitis project. Clin Infect Dis 2012;54:899–904.
[24] Tsutsui K, Kanbayashi T, Tanaka K, Boku S, Ito W, Tokunaga J, et al. Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. BMC Psychiatry 2012;12:37.
[25] Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein HG, Vielhaber S, et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial

diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA Psychiatry 2013;70:271–8.
[26] Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, et al. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. Br J Psychiatry 2011;199:508–9.
[27] Stepulak A, Luksch H, Gebhardt C, Uckermann O, Marzahn J, Sifringer M, et al. Expression of glutamate receptor subunits in human cancers. Histochem Cell Biol 2009;132:435–45.
[28] Li L, Hanahan D. Hijacking the neuronal NMDAR signaling circuit to promote tumor growth and invasion. Cell 2013;153:86–100.
[29] Prickett TD, Samuels Y. Molecular pathways: dysregulated glutamatergic signaling pathways in cancer. Clin Cancer Res 2012;18:4240–6.
[30] Armangue T, Titulaer MJ, Malaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis – clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013;162:850–6.
[31] Turner MR, Irani SR, Leite MI, Nithi K, Vincent A, Ansorge O. Progressive encephalomyelitis with rigidity and myoclonus: glycine and NMDA receptor antibodies. Neurology 2011;77: 439–43.
[32] Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012;79:1094–100.
[33] Goldberg EM, Taub KS, Kessler SK, Abend NS. Anti-NMDA receptor encephalitis presenting with focal non-convulsive status epilepticus in a child. Neuropediatrics 2011;42:188–90.
[34] Kirkpatrick MP, Clarke CD, Sonmezturk HH, Abou-Khalil B. Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptor antibody encephalitis. Epilepsy Behav 2011;20:392–4.
[35] Morooka M, Kubota K, Minamimoto R, Furuhata M, Abe T, Ito K, et al. 18F-FDG and 11C-methionine PET/CT findings in a case with anti-NMDA (NR2B) receptor encephalitis. Clin Nucl Med 2012;37:400–2.
[36] Takano S, Takahashi Y, Kishi H, Taguchi Y, Takashima S, Tanaka K, et al. Detection of autoantibody against extracellular epitopes of N-methyl-D-aspartate receptor by cell-based assay. Neurosci Res 2011;71:294–302.
[37] Anegawa NJ, Lynch DR, Verdoorn TA, Pritchett DB. Transfection of N-methyl-D-aspartate receptors in a nonneuronal cell line leads to cell death. J Neurochem 1995;64:2004–12.
[38] Suh-Lailam BB, Haven TR, Copple SS, Knapp D, Jaskowski TD, Tebo AE. Anti-NMDA-receptor antibody encephalitis: performance evaluation and laboratory experience with the anti-NMDA-receptor IgG assay. Clin Chim Acta 2013;421:1–6.
[39] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.
[40] Pham HP, Daniel-Johnson JA, Stotler BA, Stephens H, Schwartz J. Therapeutic plasma exchange for the treatment of anti-NMDA receptor encephalitis. J Clin Apher 2011;26:320–5.
[41] Ikeguchi R, Shibuya K, Akiyama S, Hino S, Kubo H, Takeda T, et al. Rituximab used successfully in the treatment of anti-NMDA receptor encephalitis. Intern Med 2012;51:1585–9.
[42] Kashyape P, Taylor E, Ng J, Krishnakumar D, Kirkham F, Whitney A. Successful treatment of two paediatric cases of anti-NMDA receptor encephalitis with cyclophosphamide: the need for early aggressive immunotherapy in tumour negative paediatric patients. Eur J Paediatr Neurol 2012;16:74–8.
[43] Seki M, Suzuki S, Iizuka T, Shimizu T, Nihei Y, Suzuki N, et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 2008;79:324–6.
[44] Leypoldt F, Gelderblom M, Schottle D, Hoffmann S, Wandinger KP. Recovery from severe frontotemporal dysfunction at 3 years after N-methyl-D-aspartic acid (NMDA) receptor antibody encephalitis. J Clin Neurosci 2013;20:611–3.
[45] Poloni C, Korff CM, Ricotti V, King MD, Perez ER, Mayor-Dubois C, et al. Severe childhood encephalopathy with dyskinesia and prolonged cognitive disturbances: evidence for anti-N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol 2010;52:78–82.
[46] Gabilondo I, Saiz A, Galan L, Gonzalez V, Jadraque R, Sabater L, et al. Analysis of relapses in anti-NMDAR encephalitis. Neurology 2011;77:996–9.
[47] Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 2010;30:5866–75.
[48] Xu CL, Liu L, Zhao WQ, Li JM, Wang RJ, Wang SH, et al. Anti-N-methyl-D-aspartate receptor encephalitis with serum anti-thyroid antibodies and IgM antibodies against Epstein–Barr virus viral capsid antigen: a case report and one year follow-up. BMC Neurol 2011;11:149.
[49] Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 2011;77:589–93.
[50] Camdessanche JP, Streichenberger N, Cavillon G, Rogemond V, Jousserand G, Honnorat J, et al. Brain immunohistopathological study in a patient with anti-NMDAR encephalitis. Eur J Neurol 2011;18:929–31.
[51] Dale RC, Pillai S, Brilot F. Cerebrospinal fluid CD19(+) B-cell expansion in N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol 2013;55:191–3.
[52] Mikasova L, De Rossi P, Bouchet D, Georges F, Rogemond V, Didelot A, et al. Disrupted surface cross-talk between NMDA and ephrin-B2 receptors in anti-NMDA encephalitis. Brain 2012;135:1606–21.

左半身の部分痙攣にて発症した抗N-methyl-D-aspartate（NMDA）受容体脳炎の1例

尾上　亮[1]・荒木　勇人[1]・髙橋　幸利[2]
島筒　和史[3]・中原　章徳[1]

Ⅰ．緒　　言

抗N-methyl-D-aspartate（以下NMDAと略す）受容体脳炎は，中枢神経系のNMDA受容体に対する細胞膜抗体の産生によって発症する辺縁系脳炎で，若年女性に好発する自己免疫性脳炎としてさまざまな研究・報告が見られるようになり，近年急速に認知されるようになっている。

今回われわれは，難治性の左上下肢の部分痙攣にて発症し，亜急性の経過で，アテトーゼ様の不随意運動・記憶障害・不隠・幻覚など精神症状，さらには低血圧・低換気症状により長期にわたり人工呼吸管理など集中治療を要した抗NMDA受容体脳炎の1例を経験したので，若干の文献的考察を加え報告する。

Ⅱ．症　　例

症　例：24歳，女性。

主　訴：痙攣。

既往歴：頭部外傷・先行感染・予防接種歴なし。そのほか，特記すべきものなし。

家族歴：特記すべきものなし。

現病歴：201X年4月27日に左下肢の部分痙攣が認められた。4月29日にも同様の発作あり，5月1日午後7時頃にも左上下肢の部分痙攣が生じたために近医を受診した。そこでは頭部CT・MRIで異常は認められなかった。帰宅後に再度全身痙攣が出現したため，当科に救急搬送された。

来院時現症：意識清明。血圧100/73 mmHg，脈拍98回／分，体温37.1℃，動脈血酸素飽和度96%。頭痛なし，嘔気・嘔吐なし，そのほか特記すべき神経脱落症状を認めなかった。

検査所見：来院時の血液生化学検査では特記すべき異常所見を認めなかった。頭部MRI検査は入院第1病日・第14病日・第21病日・第101病日に施行したがすべてにおいて特記すべき異常所見を認めなかった（図1）。血清での自己抗体・ウイルス抗体検査に関しては第24病日に行い，抗核抗体，リウマチ因子，抗ミトコンドリア抗体は陰性であった。可溶性IL-2レセプターは671 U/ml（正常221～496 U/ml）と軽度高値を認めた。サイトメガロウイルス抗体価，EBウイルス抗体価，単純ヘルペスウイルス抗体価，水痘帯状ヘルペスウイルス抗体，ムンプスウイルス抗体価，インフルエンザウイルス抗体価，HIV抗体価はすべて有意な上昇を認めなかった。第16病日の髄液検査では細胞数24/mm^3（単核球100.0%，多核球0.0%），糖61 mg/dl，蛋白22.3 mg/dl，CL 119.0 mEq/l，LDH 20 IU/l。第21病日の髄液検査では細胞数17/mm^3（単核球64.7%，多核球35.3%），糖72 mg/dl，蛋白23.8 mg/dlで，髄液単純ヘルペスPCRは陰性であった。胸部・腹部・骨盤部のCT検査では明らかな腫瘍性病変は認められなかった。

経過：図2に示す。入院当初は意識障害や発熱・頭痛は全くなく経過するものの，痙攣発作に関してはカルバマゼピンやバルプロ酸・レベチラセタムなどにてコントロールを試みたが，発作のコントロールは不良であった。第16病日ころより後弓反張様の伸展反応やアテトーゼ様の四肢の動きなどが出現した。第20病日より幻覚・記憶障害・不隠が出現し，四肢の不随意運動が増悪，さらに中枢性低換気による呼吸不全やプレショック状態を呈するようになり，

キーワード：抗NMDA受容体抗体（anti-N-methyl-D-aspartate receptor antibody），脳炎（encephalitis），自己免疫（autoimmune），部分痙攣（partial convulsion），卵巣奇形腫（ovarian teratoma）

[1]Ryo Ogami, [1]Hayato Araki, [2]Yukitoshi Takahashi, [3]Kazufumi Shimazutsu, [1]Toshinori Nakahara: A case of Anti-N-methyl-D-asparate receptor encephalitis with left sided partial convulsion as initial manifestation. [1]Department of Neurosurgery, Mazda Hospital. [2]Department of Pediatrics, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders. [3]Department of Surgery, Gion Ushita Hospital.
[1]マツダ病院脳神経外科
[2]国立病院機構静岡てんかん・神経医療センター小児科
[3]ぎおん牛田病院外科

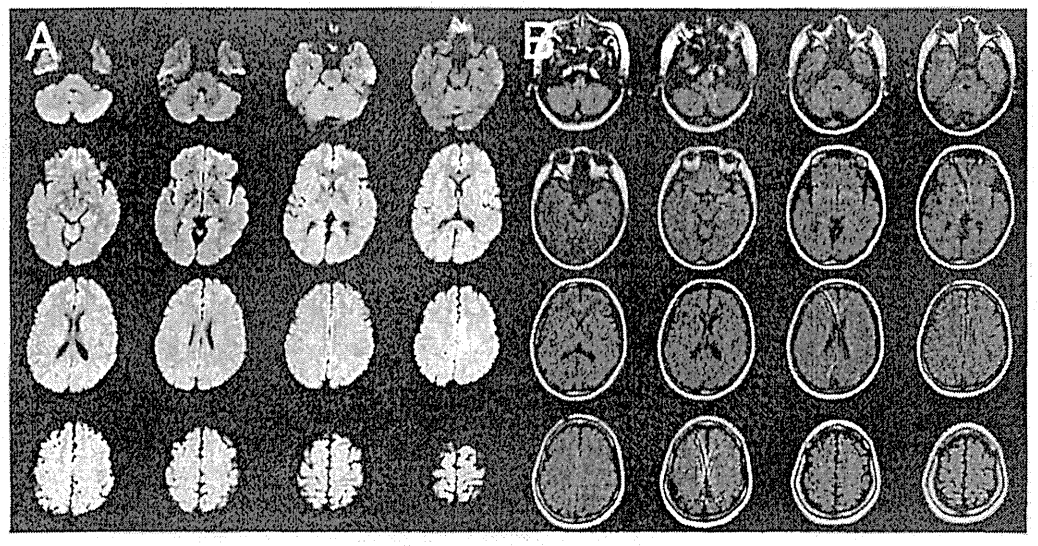

図 1　入院時 MRI（A：拡散強調画像，B：FLAIR 画像）
特記すべき異常所見を認めない。

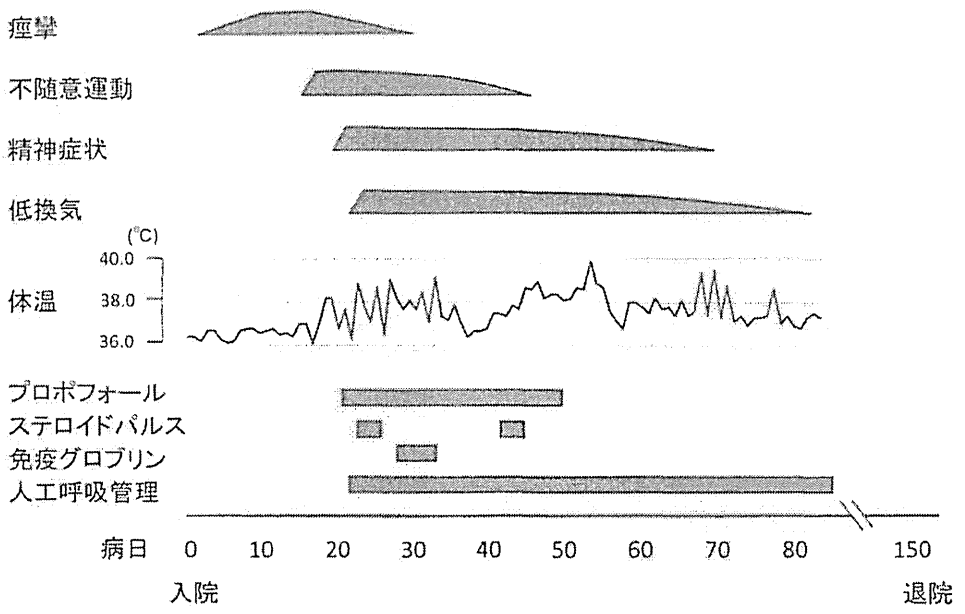

図 2　入院後臨床経過

第 21 病日よりプロポフォール持続鎮静下に気管挿管・人工呼吸管理を開始した。第 21 病日に採取した髄液中の IL-6 が 74.4 pg/ml と高値であり，さらに病状経過より，抗 NMDA 受容体脳炎などの自己免疫性脳炎の可能性を疑い，第 24 病日よりステロイドパルス（メチルプレドニゾロン 1,000 mg/day，3 日間）を，第 28 病日より免疫グロブリン大量療法（乾燥 pH4 処理人免疫グロブリン 20 g/day，5 日間）を施行した。第 16 病日に採取した髄液および第 21 病日に採取した血清の抗グルタミン酸受容体（GluR）抗体を測定したところ，髄液・血清ともに GluR ε2 抗体・GluR ζ1 抗体・GluR δ2 抗体において陽性であった。これらにより，抗 NMDA 受容体抗体脳炎と診断した。第 42 病日よりステロイドパルス 2 クール目施行。第 49 病日より持続鎮静を中止した。その頃より徐々に神経症状は改善。疎通性も認められるようになった。第 86 病日に人工呼吸器から離脱可能となった。独歩や経口摂取も可能となり，軽度の短期記憶障害のみが残存する状態で第 158 病日にリハビリ加療目的に転院となった。尚，入院時の胸腹骨盤部 CT では明らかな腫瘍性病変を認めなかったが，その後転院先で卵巣腫瘍の出現が認められている。

Ⅲ. 考　　察

NMDA受容体は，グルタミン酸受容体（GluR）のうち，イオンチャンネル型GluRに属し，中枢神経系内の興奮性シナプス伝達の中心的役割を担う分子で，必須となるGluRζ1（NR1）とGluRε1～4（NR2A～2D）あるいはGluRχ1～2（NR3A～3B）といったサブニットが四つ会合した4量体（複合体）構造をとり，イオンチャネルとして機能している[1),2)]。抗NMDA受容体脳炎では自己抗体が神経細胞表面に表出するNMDA受容体に結合して，細胞機能障害を生じると考えられている[3)]。

2007年にDalmauらは類似の臨床経過をたどる若年女性に好発する卵巣奇形腫に合併した脳炎を報告し，その中で，脳炎12症例中9例の血清および脳脊髄液において，NMDA受容体に対する抗体が陽性であり，病因となっていることを明らかにし，これらの一群を卵巣奇形腫関連傍腫瘍性抗NMDA受容体脳炎と名付けた[4)]。その後類似した臨床経過をたどる抗NMDA受容体抗体に関連した脳炎の報告が相次いで報告されるようになり，今日これらの脳炎は抗NMDA受容体脳炎として近年認知されるようになってきている。

抗NMDA受容体脳炎の臨床的特徴は，しばしば感冒様症状ののちに，幻覚・記憶障害・性格変化などの精神症状が生じ，その後痙攣・不随意運動・運動失調・意識障害，さらには致死的な不整脈・低血圧・低換気など自律神経症状が出現し，集中治療室での治療を要することも多い。経過は数ヵ月から数年の長期にわたるが，その転帰は比較的良好であることが多く，多くの場合社会的に自立可能となるまで改善する。また髄液検査や頭部MRI検査などの臨床検査上の異常所見に乏しいことも特徴の一つである。

Dalmauらの報告以前より本邦において，同様の臨床的特徴を有する脳炎の存在は「若年女性に好発する非ヘルペス性辺縁系脳炎（AJFNHE）」として知られており，Iizukaらは臨床的にAJFNHEと診断した4例の血清および髄液から，抗NMDA受容体抗体を検出し，3例に卵巣奇形腫を確認[5)]し，今日では抗NMDA受容体脳炎とAJFNHEはほぼ同一疾患であると考えられている。AJFNEに関してはKameiらにより全国疫学調査[6)]が行われており，発症頻度は年間0.33/10万人，女性が85%を占め，人工呼吸管理を71%の症例に要した。平均在院日数は平均180日（最長1,210日）と長期に及ぶものの，職場および家庭復帰率はそれぞれ46%および37%と比較的良好である。

抗NMDA受容体脳炎の診断に関しては，まだその疾患概念が新しいこともあり，まだ確立したものはない。現時点では特徴的な臨床的経過や血清および髄液中の抗NMDA抗体陽性所見および卵巣奇形腫の合併などの所見から総合的に診断されている。ただし，抗NMDA受容体抗体に関してはほかの神経疾患でも陽性となる場合[7)-9)]があり，抗NMDA受容体抗体の診断的意義やその作用に関してはさらなる病態解析の積み重ねが必要である。

今回われわれの症例では，頭痛・発熱などの感冒様の前駆症状を欠くものの，亜急性の経過で痙攣・精神症状・不随意運動が出現し，その後低換気・低血圧が生じ，遷延性の経過をたどったが，最終的には日常生活的にほぼ自立に近い状態まで改善したという臨床経過や，抗NMDA受容体抗体が髄液・血清ともに陽性であったこと，およびその後の経過で卵巣奇形腫の存在が明らかになったことなどから，卵巣奇形腫に関連した抗NMDA受容体脳炎であったと考えられる。

抗NMDA受容体脳炎の治療に関しては，合併する腫瘍に対する腫瘍摘出，ステロイド・免疫グロブリンの静注，血漿交換，リツキシマブ・シクロフォスファミドなどの免疫抑制薬の投与といった免疫療法，痙攣や精神症状に対する投薬コントロール，中枢性低換気に対する人工呼吸管理などといった支持療法が挙げられている[3),10)]。抗NMDA受容体脳炎は無治療では回復までに非常に長期間を要し，また再発する症例があることから[10)]，早期に診断の上，これらを適切に組み合わせて治療することが重要であると考えられる。

Ⅳ. 結　　語

比較的まれな抗NMDA受容体脳炎の1例を報告した。抗NMDA受容体脳炎は適切な治療により比較的良好な予後が期待できる疾患であり，その特徴的な臨床経過を念頭に置き，早期診断し適切な加療を行うことが重要であると考えられた。

文　　献

1）高橋幸利，向田壮一，池上真理子，ほか：【神経

疾患と自己抗体】抗GluR抗体と脳炎，神経内科：69: 350−358, 2008.
2) 高橋幸利，高山留美子，向田壮一，ほか：【抗NMDA受容体脳炎】抗NMDA受容体複合体抗体と抗グルタミン酸受容体ε2抗体，最新医学：64: 1520−1526, 2009.
3) Dalmau J, Gleichman AJ, Hughes EG, et al: Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies, Lancet Neurol: 7: 1091−1098, 2008.
4) Dalmau J, Tuzun E, Wu HY, et al: Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma, Ann Neurol: 61: 25−36, 2007.
5) Iizuka T, Sakai F, Ide T, et al: Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal, Neurology: 70: 504−511, 2008.
6) Kamei S, Kuzuhara S, Ishihara M, et al: Nationwide Survey of Acute Juvenile Female Non-Herpetic Encephalitis in Japan: Relationship to Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Internal Medicine: 48: 673−679, 2009.
7) Takahashi Y: Epitope of autoantibodies to N-methyl-D-aspartate receptor heteromers in paraneoplastic limbic encephalitis, Ann Neurol: 64: 110−111; author reply 111−112, 2008.
8) Takahashi Y, Mori H, Mishina M, et al: Autoantibodies and cell-mediated autoimmunity to NMDA-type GluRepsilon2 in patients with Rasmussen's encephalitis and chronic progressive epilepsia partialis continua, Epilepsia: 46 Suppl 5: 152−158, 2005.
9) 六反田拓，稲富雄一郎，米原敏郎，ほか：血清・髄液中抗グルタミン酸受容体抗体陽性が診断を混乱させたglioblastomaの1例，臨床神経学：48: 497−500, 2008.
10) 関　守：【抗NMDA受容体脳炎】抗NMDA受容体脳炎の治療，最新医学：64: 1585−1591, 2009.

（受付　2013−9−2）

脳と発達　2014；46：195―201

特集・第55回日本小児神経学会学術集会
シンポジウム10：難治性てんかんの病態を探る：分子遺伝学，病理，免疫，代謝異常，画像，電気生理

難治性てんかんの病態を探る

―脳炎後てんかんと免疫

髙橋　幸利　　山口　解冬

要旨　代表的な難治性てんかんとして，脳炎後てんかんの臨床，免疫，生化学的特徴を検討した．加療中の症例では，発作頻度は月単位で，知的障害，精神障害などを併存する症例が多く，脳炎急性期から数年経過した時期においても，発作・知的障害が進行悪化すると推測した．局在関連性てんかんでは髄液NMDA型GluR抗体が高値で，NMDA型GluR内在化，アポトーシス誘導作用等により，病態に影響していると推測され，matrix metalloproteinase-9の増加，tissue inhibitor of metalloproteinase-1の減少による血液脳関門障害も病態に影響していると推測された．

見出し語　脳炎後てんかん，NMDA型Glutamate receptor抗体，アポトーシス，血液脳関門，matrix metalloproteinase-9

はじめに

英国での9～93歳の525連続てんかん症例の発作予後調査では，63%が発作抑制され，6.5%が治療終結していたが，37%は難治に発作が継続していたとされ，てんかん症例の約40%が難治性てんかんと推定される[1]．1989国際てんかん分類でみると，West症候群，症候性局在関連性てんかん，Lennox-Gastaut症候群などで発作抑制に至れない難治性てんかん症例の比率が高く，2010年ILAEてんかん分類提案で見てみると，Dravet症候群，海馬硬化症を伴う内側側頭葉てんかん，Rasmussen症候群，進行性ミオクローヌスてんかんなども難治性てんかんとなりやすい．1993～1994年に当センターに入院した小児てんかん症例の集計では，症候性局在関連性てんかんが50.9%，症候性全般てんかんが35.2%で，数としては局在関連性てんかんが難治てんかんの多数を占め，原因としては脳炎や脳形成異常，周産期障害などが多い．その中で最も多かった脳炎（脳症を含む）を原因とすると推測されるてんかん症例で，難治化の要因について免疫，生化学的因子を主体に検討した．

国立病院機構静岡てんかん・神経医療センター小児科
連絡先　〒420-8688　静岡市葵区漆山886
国立病院機構てんかん・神経医療センター小児科
（髙橋幸利）
E-mail：takahashi-ped@umin.ac.jp
（受付日：2013．9．4）

Ⅰ　急性脳炎から脳炎後てんかん

我々の研究班（厚生労働科学研究，こころの健康科学研究事業）の後方視的調査では，日本では3,100人／年の急性脳炎発病があり，年齢別にみると1～10歳が多数を占めた．ミネソタでの調査では7.4人／年/10万人の発病率で，5～9歳と1歳未満が多く，日本に当てはめると7,500人／年の脳炎発病があることになる[2]．台湾での0～17歳の急性脳炎330例の後方視的調査では，16.4%（54/330）がてんかんを発病し，79.6%は脳炎から6カ月以内にてんかんと診断されていた[3]．脳炎急性期に，繰り返す発作，てんかん重積，重症意識障害，限局性の神経学的兆候が見られると，てんかんを発病しやすいと報告されている．脳炎後てんかんのてんかん原性メカニズム，発作原性メカニズムはいまだ未解明で，研究の進展が待たれる．

Ⅱ　脳炎後てんかんの特徴

1．てんかん分類

当センターにおいて筆頭著者が診療した連続症例（初診＋再診，2002年4月～2010年3月）で小児期発病のてんかん586例について，てんかんの病因と1989国際てんかん分類の関係を検討すると，脳炎によるてんかんでは，染色体異常（Fisher's exact test，p＝0.0005），遺伝子異常（p＝0.0436），皮質形成異常（p＝0.0263），仮死（p＝0.0081）によるてんかんに比べて，West症候群，Lennox-Gastaut症候群などの乳児てんかん性脳症（EE）の頻度が有意に低い（図1）．また，脳炎後てんかんは，染色体異常（Fisher's exact test，p＝0.0079），遺伝子異常（Fisher's exact test，p＜0.0001）に比べて，有意に

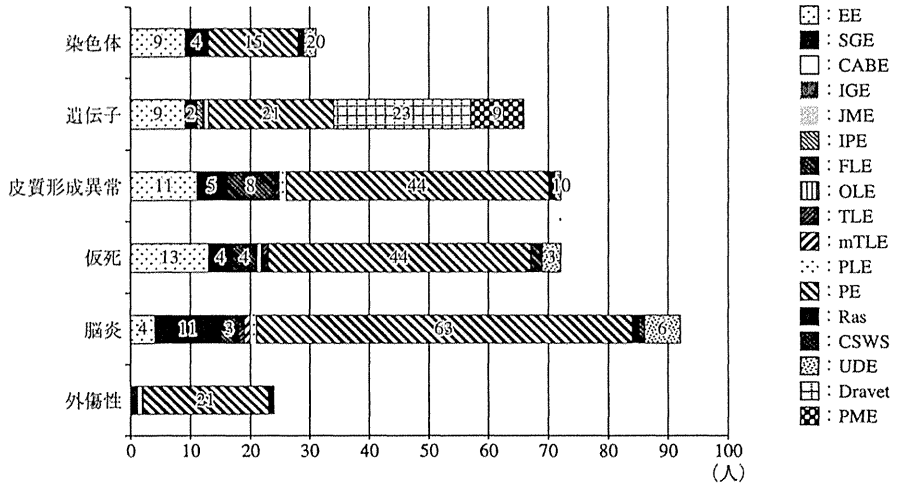

図1 小児難治性てんかん586例の病因とてんかん分類

横軸およびカラム内の数字は症例数を示す.

EE: epileptic encephalopathy (West syndrome, EIEE, Lennox-Gastaut syndrome, etc.), SGE: symptomatic generalized epilepsy, CABE: childhood absence epilepsy, IGE: idiopathic generalized epilepsy, JME: juvenile myoclonic epilepsy, IPE: idiopathic partial epilepsy, FLE: frontal lobe epilepsy, OLE: occipital lobe epilepsy, TLE: temporal lobe epilepsy, mTLE: mesial temporal lobe epilepsy, PLE: parietal lobe epilepsy, PE: partial epilepsy, Ras: Rasmussen syndrome, CSWS: epilepsy with continuous spike and wave complex during slow wave sleep, UDE: undetermined epilepsy, Dravet: Dravet syndrome, PME: progressive myoclonus epilepsy.

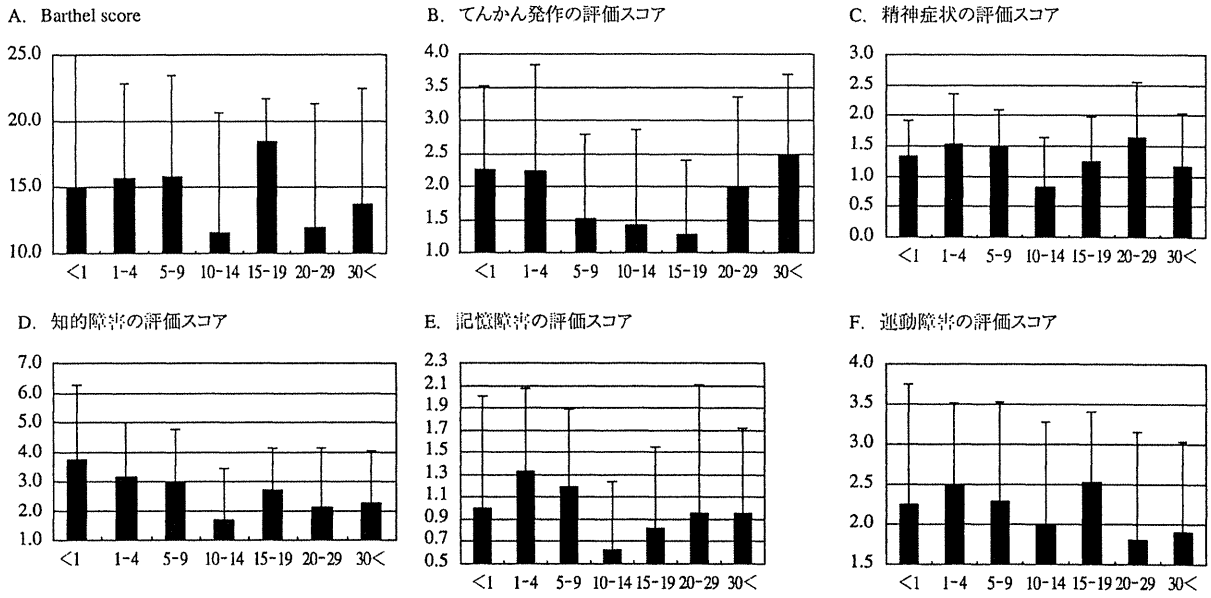

図2 脳炎後の罹病期間と脳炎後遺症

脳炎後てんかん慢性期199例の脳炎後の罹病期間と後遺症の程度を示す.

横軸は脳炎後の罹病期間（年）を，カラムは平均＋SDを示す．A：ADLはBarthel score（http://www.patient.co.uk/printer.asp?doc=40001654）に基づいて20点満点で評価した．B：てんかん発作の予後は，発作頻度によりスコア0（日単位），1（週単位），2（月単位），3（年単位），4（抑制）に分類，C：精神障害は0（精神症状のため日常生活が自立困難），1（精神症状はあるが日常生活は自立可能），2（精神症状はない）に，D：知的障害はIQまたはDQによりスコア0（IQ/DQ<19），1（IQ/DQ=34-20），2（IQ/DQ=49-35），3（IQ/DQ=69-50），4（IQ/DQ=79-70），5（IQ/DQ≧80）に，E：記憶障害はスコア0（記憶障害のため日常生活が自立困難），1（記憶障害はあるが日常生活は自立可能），2（記憶障害はない）に，F：運動障害はスコア0（四肢麻痺），1（障害があるが自力移動可能），2（支えなく歩行できるが走れない），3（運動障害はない）に後遺症の程度を分類した.