contrast, MRI is not always helpful in establishing diagnosis because there are no specific neuroradiological abnormalities in AERRPS. Hyperintensities in limbic structures on MRI, which were observed in six patients in our series, are presumably due to refractory SE. This finding is consistent with a recent report on a Taiwanese series (10).

Clinical entities resembling AERRPS have also been reported elsewhere outside Japan. Kramer et al. (11) reported five cases of refractory SE which is presumably caused by encephalitis of unknown origin. In their report, they identified the preceding febrile illness, persistent seizures despite induced burst suppression coma, and negative results for the cause of seizures, as common features. They postulated that this severe refractory type of SE is due to relatively mild encephalitis. Mikaeloff et al. (12) reported 14 cases of 'devastating epileptic encephalopathy in school-age children', which is characterized by prolonged SE following non-specific febrile illness without any latent period. These cases are slightly different from AERRPS because they are limited to the cases with school-age onset and perisylvian involvement. These facts clearly demonstrate that the clinical entities similar to AERRPS are distributed all over the world.

Limbic encephalitis (LE) is characterized by limbic seizures, short-term memory loss, and psychiatric symptoms (13). Recent studies have revealed that acute non-paraneoplastic LE is related to the anti-voltage-gated potassium channel antibody (14, 15) or antibodies that reacted with the *N*-methyl-D-aspartate receptor (16, 17). AERRPS can be distinguished from LE for the following reasons. First, psychiatric disorders and memory impairment are uncommon and seldom present as initial predominating features in AERRPS. Second, no case has been described in which AERRPS was presumably caused by a neoplasm. Third, AERRPS, but not LE, shows a uniformly unfavorable outcome with neurological sequelae. Nevertheless, there is a report of an atypical clinical presentation of paraneoplastic LE with pharmacoresistant epilepsy lacking memory loss or psychiatric symptoms (18). Hence, there is a possibility of some overlap between AERRPS and LE.

The process of epileptogenicity in AERRPS is not well understood. Epilepsy secondary to encephalitis is reported to occur after a latent period of 3.82 ± 3.7 years (1). In contrast, there is no definite seizure-free period in AERRPS. We hypothesize that extraordinary epileptogenicity prolongs seizures even after the acute phase and therefore makes the initiation of epilepsy inconspicuous.

The etiology of AERRPS remains to be clarified. In the present study, several lines of evidence supported the hypothesis that some of AERRPS are associated with CNS inflammation. First, unlike epilepsy, neurological manifestations are preceded by febrile illness and are accompanied by persistent fever. Second, the levels of neopterin, which are known to be up-regulated in macrophage activation syndrome, are elevated in CSF; however, others seem to be irrelevant to the inflammatory process. Not all the patients showed increased mononuclear cells or elevated CSF protein concentration. In the previous reports, Kramer et al. maintained an 'inflammatory' theory (11), whereas Mikaeloff et al. objected to this (12). Taken together, it is possible that AERRPS and similar disorders are caused by multiple etiologies with a common clinical phenotype.

The involvement of the inflammatory process permits us to speculate that a specific infectious agent causes AERRPS; however, this is unlikely because extensive viral studies were all negative. Another possibility is an autoimmune mechanism. It is intriguing that the serum or CSF of some patients with AERRPS was positive for antibodies against GluRε2. Ito et al. first reported a patient with AERRPS who had this antibody (19). This antibody is not specific to AERRPS but is found in patients with various neurological diseases, including intractable epilepsy, Rasmussen encephalitis, and other forms of encephalitis (8). However, the early appearance (0–20 days after onset) of antibodies against GluRε2 in CSF suggests that GluR autoimmunity contributes to the onset of encephalitis (20).

In conclusion, a novel clinical syndrome designated AERRPS is characterized by definite hallmarks. AERRPS is currently defined solely by its clinical characteristics, and thus further investigation into its pathomechanisms is necessary.

Acknowledgements

We thank Drs Shihoko Kimura-Ohba, Takahito Inoue, Sawa Yasumoto, Katsuya Yamamoto, Masaru Takayanagi, Jun Tohyama, Kimio Minagawa, Kazuhiro Haginoya, Eiji Hattori, Shinichi Hirabayashi, Akihisa Okumura, Tamami Yano, Kenji Yokochi, Rie Miyata, Hisashi Kawashima, Masahiro Kikuchi, Susumu Miyake, Mana Kurihara, Takeshi Miyamoto, Akimitsu Watanabe and Toshihiko Nishida, for providing clinical information of their patients. This work was supported by a research grant for nervous and mental disorders from the Ministry of Health, Labour and Welfare, Japan (grant number 17A-11).

Supporting information

Additional Supporting Information may be found in the online version of this article:
Table S1. Clinical features.

Table S2. Laboratory, EEG, and MRI findings.
Table S3. Treatment and Outcome.

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Journal of the Neurological Sciences 294 (2010) 127–130

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Short communication

Twenty-one-year course of adult-onset Rasmussen's encephalitis and bilateral uveitis: Case report

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ARTICLE INFO

Article history:
Received 19 September 2009
Received in revised form 22 March 2010
Accepted 22 March 2010
Available online 5 May 2010

Keywords:
Rasmussen's encephalitis
Adult
Longitudinal course
Anti-glutamate receptor antibody
GluR ε2
NR2B
Uveitis
Interferon

ABSTRACT

We report the longitudinal history of a 48-year-old, right-handed woman with Rasmussen's encephalitis (RE) who presented with seizures and cerebral atrophy confined to the left hemisphere, as well as with bilateral uveitis, during her 21-year disease course. Neurological symptoms included recurrent partial seizures with secondary generalized convulsions, reduced visual acuity of the left eye with optic atrophy, right hemianopsia, right hemiplegia and aphasia. MRI T2-weighted images revealed progressive atrophy and high signal intensity lesions localized in the left cerebral hemisphere. An interictal electroencephalogram showed slowing of background activities to 4–7 c/s and epileptiform discharges in the left hemisphere. Anti-glutamate receptor (GluR) ε2 IgG and IgM antibodies were detected in her serum. Our diagnosis was RE. Intravenous administration of high-dose methylpredonisolone immediately ameliorated her condition. Use of interferon β-1b, as well as immunosuppressants, appeared to reduce seizure frequency, prevented exacerbation of her other central nervous system symptoms and slowed development of brain hemiatrophy. Her case is notable because it was complicated with bilateral uveitis and managed favorably by immunotherapy.

1. Introduction

Rasmussen's encephalitis (RE) is a chronic condition, usually beginning in childhood, which leads to severe hemispheric cerebral atrophy and intractable partial seizures [1]. Heterogeneous autoantibodies, such as anti-glutamate receptor (GluR) subtype 3 [2,3] and GluR ε2 [4] (the latter also classified as NMDA receptor 2B (NR2B)), have been detected in association with RE. Only two reports so far have described the long term courses of RE patients [5,6]. We report the longitudinal history of a patient with RE who presented with relapsing white matter lesions and eventual cerebral atrophy confined to the left cerebral hemisphere together with corresponding neurological symptoms, recurrent partial seizures and bilateral uveitis, as well as serum anti-GluR ε2 (NR2B) antibodies over a clinical course of 21 years.

2. Case report

A 27-year-old, right-handed woman was transferred to our hospital because of generalized convulsions that occurred soon after having her first child. She had no previous history of illness. Two days later, she experienced visual disturbance including concentric visual field defect and reduced visual acuity of the left eye. Brain MRI high T2 signal intensity revealed lesions in the white matter of the left cerebral hemisphere. Prednisolone and anti-epileptic drugs were administered and tapered off in 2 year's time. Her longitudinal clinical course is summarized in Fig. 1.

At age 30, generalized convulsions occurred 6 months after the birth of her second child, and MR images showed new white matter lesions confined to the left hemisphere. The anti-epileptic drugs, phenytoin, phenobarbital and prednisolone again were prescribed.

At age 31 she experienced another episode of generalized convulsions. Again new white matter lesions were present in the left cerebral hemisphere.

The 4th reoccurrence was at age 33 with pain in the left eye and episodes of nausea. One month later she experienced motor aphasia, alexia and visual hallucinations. On T2-weighted images high signal intensity white matter lesions were presented adjacent to the frontal horn of the lateral ventricle and temporal lobe in the left hemisphere (Fig. 2A lower). Gadolinium DTPA enhanced the cortical and subcortical lesions of the frontal horn and temporal lobe (Fig. 2A upper). High-dose intravenous methylprednisolone was begun, her symptoms disappearing gradually in a month's time. Ophthalmological examination detected no abnormality in the retina or optic disc.

At age 35 her motor aphasia worsened and was accompanied by generalized convulsions. These were alleviated by a high dose of intravenous methylprednisolone followed by daily doses of per oral 10 mg prednisolone and 150 mg myzoribine as immunosuppressant. Aphasia again occurred after two months and was accompanied by

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doi:10.1016/j.jns.2010.03.016

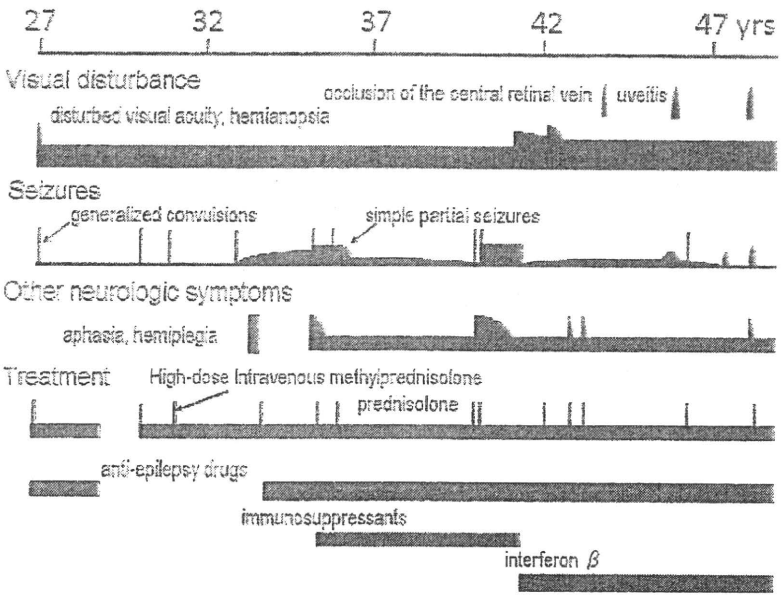

Fig. 1. Summary of the disease's clinical course.

nausea attacks, monoplegia of the right upper limb and pain in the left eye. These symptoms were alleviated by intravenous injections of methylprednisolone.

Four months later she had an aphasia episode followed by versive seizures then by generalized tonic–clonic convulsions. At that time, her physical condition was normal. Neurological examination found a severely diminished visual field in the left eye and an atrophic optic disc. Nominal aphasia and right hemianopsia also were present. Muscle strength in her right upper and lower extremities was slightly reduced. Deep tendon reflexes were increased in the right extremities, but there were no pathological reflexes. No sensory, cerebellar or autonomic disturbances were found. Routine hematological and urine examination results were negative. A CSF study gave normal cell counts of 2/μl, 43 mg/dl protein and 4.8 mg/dl IgG. Both the oligoclonal IgG band and myelin basic protein were negative. CSF IgG antibodies against herpes zoster virus, herpes simplex virus, cytomegalovirus and measles were negative. A serological test for syphilis also was negative. T2-weighted and FLAIR MR images showed an atrophic left hemisphere with high signal intensity lesions in the white matter adjacent to the left anterior horn of the lateral ventricle, the temporo-occipito-parietal deep white matter and the subcortical region of the left superior frontal sulcus (Fig. 2B), where lesions were enhanced partially by gadolinium DTPA. No spinal lesion was found. [^{1}H] MR spectroscopy of the atrophic lesion in the left hemisphere showed a decreased *N*-acetylaspartate peak. An electroencephalogram revealed slowing of background activities and focal spikes in the left hemisphere. High-dose intravenous methylprednisolone lessened these symptoms, but a daily dose of per oral prednisolone of up to 30 mg did not prevent exacerbation. An additional 50 mg/day of cyclophosphamide therefore was given for two years then replaced by a once weekly per oral administration of 75 mg methotrexate. After taking these immunosupressants for 5 years, her apparent symptom exacerbation subsided.

At age 40 she experienced generalized convulsions followed by repeated partial seizures lasting more than 30 min in her right face

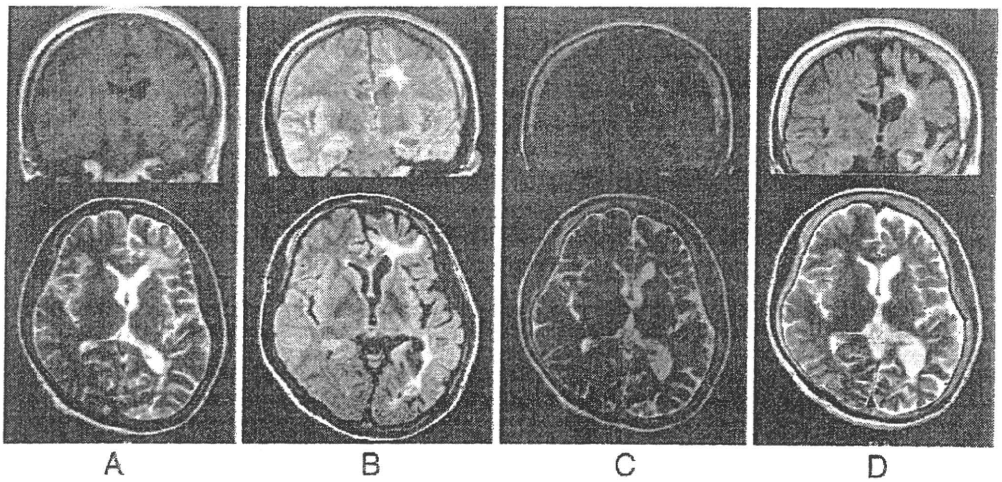

Fig. 2. Serial MR images of the patient. Obtained at ages 33 (A), 35 (B), 41 (C) and 48 (D). A: Lower: T2-weighted MR image showing high signal intensity in the white matter and brain atrophy confined to the left hemisphere. Degree of brain hemiatrophy determined as the hemispheric ratio (HR) = 0.91. Upper: Coronal T1-weighted MRI with gadolinium DTPA showing enhanced lesions in the cortex and subcortical white matter of the left temporal lobe. B: MR image showing progressive atrophy of the left hemisphere with a FLAIR-high signal white matter lesion adjacent to the anterior and posterior horns of the left lateral ventricle. HR = 0.86. C: High signal intensity on the T2-weighted image is less marked, but hemispheric atrophy has progressed slightly since age 35. HR = 0.78. D: Cerebral atrophy is still confined to the left hemisphere. HR = 0.79, the same value as at age 41.

and upper and lower extremities. This epilepsia partialis continua symptom was stopped by intravenous injection of diazepam. Her CSF had an increased protein level of 61 mg/ml and cell count of 7/μl. Electroencephalography detected asymmetrical background activities in the left hemisphere and focal spikes. Basic activities were 7–9 c/s alpha waves in the right hemisphere and 3–7 c/s slow waves in the left hemisphere (Fig. 3).

At age 41 she suffered worsened right hemianopsia, light visual acuity of the left eye, right hemiplegia and headache accompanied by reoccurring generalized convulsions and frequent partial seizures characterized by transient attacks of nausea lasting from several seconds to minutes. Brain MRI T2-weighted images showed progressive atrophy of the left hemisphere with high signal intensity lesions in the white matter adjacent to the anterior and posterior horns of the left lateral ventricle (Fig. 2C). These lesions were less prominent than those at age 35. Gadolinium DPTA did not enhance the lesions. Intravenous injection of a high dose of methylpredonisolone effectively alleviated her ocular symptoms. After injection, however, the frequency of nausea attacks increased from weekly to daily. Replacement of the immunosuppressant with a subcutaneous injection of 960 IU interferon β-1b every other day reduced seizure frequency, as well as lessened her right hemiplesia, within a month of the start of injection (Fig. 1).

At age 42 her right hemianopsia again worsened but soon was alleviated by intravenous injection of methylprednisolone.

At age 44 she complained of blurred vision in her left eye. An ophthalmologist found occlusion of the central retinal vein.

At age 46 a regular ophthalamological examination found bilateral uveitis which was alleviated by steroid eye drops. Several months later, generalized convulsions occurred followed by nausea and right face twitching for 20 min. This time anti-GluR ε2 IgG and IgM antibodies but no GluR δ2 antibodies were present in her sera.

At age 47 nausea attack frequency which lasted for a month increased from several times a month to several times a day.

At age 48 increased nausea attack frequency and uveitis again occurred with worsening of her right hemiplegia. MRI showed unihemispheric brain atrophy of similar degree to that at age 41 (Fig. 2D). Intravenous injection of methylprednisolone ameliorated the symptoms.

To evaluate temporal changes in the degree of brain hemiatrophy, we calculated the hemispheric ratio (HR) according to Bien et al. [6]. Spaces in both hemispheres were measured on the serial axial MR images as shown in Fig. 2, using the image processing software ImageJ (NIH, Bethesda, Maryland, USA). The ratio of the spaces of the left and right hemispheres was designated the HR. At age 33 the HR was 0.91 (Fig. 2A), at age 35 0.86 (Fig. 2B), at age 41 0.78 (Fig. 2C) and at age 48 0.79 (Fig. 2D).

No systemic signs of inflammation or of collagen vascular disease, including increases in white blood cell count, erythrocyte sedimentation rate, serum anti-nuclear antibody titer, rheumatoid factor or angiotensin converting enzyme were found throughout the 21-year clinical course (see Fig. 3).

As for seizures, MRI showed generalized convulsions usually accompanied by the emergence of new cerebral lesions. Myoclonic seizure of the right face and/or upper and lower limbs, nausea or speech arrest lasting less than several seconds reoccurred. MRI detected no new neurological deficits or lesions. Sometimes, her seizures advanced from episodic nausea to aphasia then to numbness of the right upper limb. An intravenous high dose of methylprednisolone reduced seizure frequency. Interferon β-1b also was somewhat beneficial.

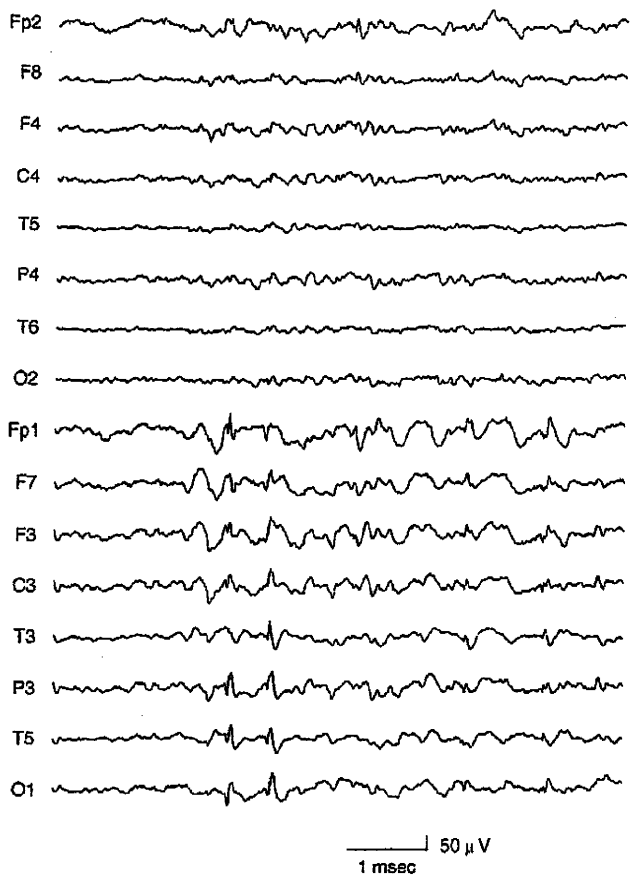

Fig. 3. EEG at age 40 showing widespread continuous slow-wave abnormalities over the left hemisphere accompanied by small spikes in the left temporal region.

3. Discussion

We present the case of a patient who suffered recurrent partial seizures. CNS lesions were confined to the left hemisphere and left optic nerve with corresponding neurologic deficits that included reduced left visual acuity with optic atrophy, right hemiplegia, hemianopsia and aphasia. She also presented bilateral uveitis. Given the hemisphere-localized nature of her cerebral lesions, the reoccurrence of seizures and detection of serum anti-GluR ε2 antibodies, RE was diagnosed based on the published diagnostic criteria [7]. Anti-GluR ε2 antibodies have been found in the CNS in various diseases: RE, limbic encephalitis and epilepsy [18,19]. The mechanism by which these antibodies produce brain damage is not, however, understood. In the case of RE, why inflammation usually is unihemispherical has yet to be clarified.

Multiple sclerosis (MS), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), as well as cerebral vasculitis were considered in making the differential diagnosis. Involvement of the optic nerve and the beneficial effect of immunotherapy are consistent with MS but not with the description of RE. Notably, all the lesions present on the serial MR images were confined to the left cerebral hemisphere over the entire 21-year course of illness. Our search of the electronic database turned up a single report of a patient with MS whose lesion was confined to one hemisphere [8]. A notable symptom of our patient is the reoccurrence of partial seizures. MS symptoms vary depending on the location and extent of the demyelinating lesions. Of possible symptoms, seizure is rare in MS. Our patient experienced seizures as the initial symptom of her disease and frequently as the initial symptom of exacerbation. In the later disease stage, seizure reoccurrence was not necessarily associated with new lesion generation, indicative that she had developed epileptogenesis. The cumulative incidence for epilepsy 10 years after a diagnosis of multiple sclerosis is reported to be 1.9% [9,10]. Therefore, our patient's seizures of cerebral origin, the initial and main manifestations, do not support a diagnosis of MS. MELAS is reported to be associated with seizures and laminar cortical necrosis [11], but our patient is not likely to have suffered MELAS

because brain MRI showed white matter dominant involvement not cortical necrosis. Cerebral vasculitis, which is associated with collagen vascular diseases, Behchet's disease, sarcoidosis and isolated angiitis of the central nervous system, also could be ruled out as the clinical cause because repeated blood and CSF analysis results showed no traces of inflammation throughout the long, 21-year course of her disease. Confined hemispheric involvement also does not support such a diagnosis, although there is one report of a patient with vasculitis whose lesion was limited to the right cerebral hemisphere [12].

RE is a chronic inflammatory disease that usually begins in childhood and produces chronic encephalitis confined to one hemisphere which leads to disabling neurological deficits, cognitive decline and intractable seizures, including epilepsia partialis continua [1,7]. Cerebral hemispheric atrophy develops rapidly during the acute phase, defined as the stage with a rapid increase in seizure frequency of more than 10 simple partial motor seizures per day accompanied by the worsening of hemiparesis [5] over an average duration of 8 months [7]. Few RE patients suffer the condition in adolescence or adulthood [13–17]. Those who do experience adult-onset RE, however, often have a more protracted, milder clinical course [6,16]. Our patient had a fairly mild course with few disabilities: aphasia, right hemianopsia, mild right hemiplegia and partial seizures usually presenting as transient nausea attacks several times a month but causing no deficit in social functioning. Brain hemiatrophy development also was mild. Bien et al. [6] analyzed serial brain MRI findings, determined the HR and demonstrated that most damage in RE occurs during the first 8–12 months, 0.72 being the average value one year after onset. Our patient had slower brain deterioration and an HR of 0.78 at age 41, 14 years after onset. The ratio did not decrease over the next 7 years, indicative that her condition has been managed favorably. Such a relatively benign course may be associated with the nature of her adult-onset type RE variant, her favorable response to immunotherapy that included interferon β-1b, or both.

Another notable symptom of our patient is bilateral uveitis which occurred at age 46. Uveitis is a rare RE complication. Occlusion of the central retinal vein of the left eye, seen at age 44, may be associated with it. To our knowledge, only two reports have described three cases of RE with ipsilateral uveitis [20,21], and those were child-onset cases. In one report, uveitis preceded the emergence of RE [21]. The other two patients had acute uveitis during the early progressive stage [20]. Our patient's uveitis is peculiar because it is bilateral, although more prominent on the ipsilateral side and appeared at a later RE stage. Uveitis often is associated with inflammatory conditions such as Behchet's disease, sarcoidosis and with infectious diseases such as syphilis. Our patient's condition was not complicated by any of those diseases, nor was her uveitis confined to one side. Glutamate is a major excitatory neurotransmitter in the retina where GluRs are expressed [22]. Circulating serum anti-GluR antibodies may attack those receptors and cause bilateral uveitis.

As to RE treatment, immunosuppressive therapy that includes giving a high dose of steroid [17,23] or gammaglobulin [24] intravenously is reported to have a rapid, positive effect. Per oral administration of tacrolimus also may effectively prevent disease progression [25]. Intravenous administration of a high dose (500 mg) of methylprednisolone to our patient also produced a rapid, positive effect. Several immunosuppressants and interferon β-1b may persistently or chronically reduce exacerbation and stop RE progression. Use of these types of immunotherapy and high-dose gammaglobulin is reported to be effective in MS management. A common immunological mechanism that involves T cells [7,26] may operate in MS and RE. A similar pathophysiology therefore may have caused our patient's RE which had a similar positive response to immunotherapy.

We have reported the longitudinal clinical course of a patient with adult-onset RE who presented partial seizures, hemisphere-localized cerebral atrophy, left optic atrophy, bilateral uveitis and serum anti-GluR ε2 antibodies. Her symptoms were managed favorably by the use of immunotherapy and interferon β-1b. More published information about cases of adult-onset RE should help us gain a better understanding and management of RE.

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Brain & Development xxx (2009) xxx–xxx

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

www.elsevier.com/locate/braindev

Original article

Nationwide survey (incidence, clinical course, prognosis) of Rasmussen's encephalitis

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Received 19 September 2009; accepted 19 October 2009

Abstract

Purpose: Rasmussen's encephalitis (RE) is a progressive and catastrophic epileptic disorder caused by chronic localized encephalitis. We performed a nationwide survey of RE to assess the clinical picture, treatment effect, and prognosis of Japanese RE patients. *Subjects & methods:* The subjects were 27 patients (male:12; female:15) from 13 medical facilities. All of them satisfied the clinical and neuroimaging criteria for RE, including 14 pathologically proven cases. *Results:* They were divided into the childhood-onset rapidly progressive type (CORP, $n = 19$), and late-onset slowly progressive type (LOSP, $n = 8$). The mean age at epilepsy onset was 4 years and 4 months in CORP, and 16 years in LOSP. The mean period between the onset age of epilepsy and development of frequent seizures was 1 year and 4 months in the former, and 3 years and 4 months in the latter. The immunomodulatory treatment including high-dose steroid ($n = 14$) and high-dose intravenous immunoglobulin therapies (IVIgG, $n = 12$) achieved more than a 50% reduction in the seizure frequency in 5 (36%) and 4 (33%) patients, respectively. Eight and seven patients underwent focal cortical resection and functional hemispherectomy, leading to significant improvement in 5 of the 8 patients and excellent seizure control in all 7 patients, respectively. *Conclusion:* Although the high-dose steroid and IVIG therapies may have alleviated the exacerbation of seizures in those with RE, they could not halt the disease progression. Functional hemispherectomy is still the only curative therapy for RE, despite the fact that the early introduction of this procedure remains controversial.

Keywords: Rasmussen's encephalitis; Chronic localized encephalitis; Intractable epilepsy; Epilepsia partialis continua; Immunomodulatory therapy; Nationwide survey

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doi:10.1016/j.braindev.2009.10.004

1. Introduction

Rasmussen's encephalitis (RE) is characterized by intractable focal epilepsy and slowly progressive unilateral neurological deficits due to chronic localized encephalitis, primarily affecting children [1,2]. Although RE was fundamentally viewed as a clinico-pathological entity requiring pathological confirmation for a definite diagnosis, recent progress in neuroimaging techniques, excluding tumors or vascular abnormalities and visualization of slowly progressive unilateral cortical atrophy, now allows us to make a clinical diagnosis of RE with a relatively high accuracy [3–6]. The seizure and intellectual outcomes of this disorder are almost always poor, with few exceptions, often requiring radical epilepsy surgery, that is, functional hemispherectomy [7,8]. Attention has progressively been paid to immunomodulatory treatment, since evidence for the immune-mediated inflammatory process of this disorder has been accumulated since the 1990's [9–13]. Thus, recognition of this rare catastrophic disorder is important in order to predict poor responses to antiepileptic drugs, the appearance of epilepsia partialis continua (EPC) as well as progressive neurological deterioration, and to consider the early introduction of immunomodulatory treatment and surgical therapy. The various studies on RE have been conducted in North American as well as European countries, and exceptionally in Asian countries including Japan. However, there have been a few case reports of pathologically-proven RE from Japan, and the concept of RE is increasingly being recognized along with growing interest in epilepsy surgery in Japan [14–17]. Recently, we conducted a nationwide survey of RE to reveal the clinical picture, treatment effect, and prognosis of Japanese RE patients. We herein report the results of this first nationwide survey of RE in Japan.

2. Subjects and methods

We distributed a questionnaire, assessing whether physicians had ever encountered the cases fulfilling the criteria of RE, to 139 facilities all over Japan, including university hospitals, special epilepsy centers, and general as well as children's hospitals, where members of Japanese epilepsy and child neurology societies were practicing. The diagnostic criteria for RE proposed by Bien et al. [18] were employed in this survey. If we received a positive response, we then asked them to answer detailed questions with respect to the clinical pictures, neuroradiological findings, immunological examinations and their results, immunomodulatory as well as surgical treatment and the response, and neurological outcomes.

The responses to immunomodulatory and surgical treatments were evaluated primarily based on the seizure frequency and intensity before and after treatment. The effect of the treatment was defined as a more than 80% reduction in the seizure frequency or intensity as an excellent response, 50–80% reduction as a good response, less than 50% reduction as a poor response, more than 50% transient reduction as a transient response, and more than 50% increase in seizure frequency as aggravation at the latest follow-up. In addition, we objectively estimated progressive brain atrophy using the method described previously, assessing the volume of the affected hemisphere in relation to the unaffected one on the axial slice at the level including the Sylvian fissure by T1-weighted imaging (Hemispheric ratio: HR) [2]. The study protocol was approved by the ethical committee of Tokyo Women's Medical University. Informed consent was obtained from all parents or their caregivers.

Chi-square tests were used for comparisons between the two groups. $P < 0.05$ was considered to indicate a significant difference.

3. Results

We obtained responses from 62 of the 139 medical facilities, in which 13 including our hospital reported 27 patients (male:12; female:15) who fulfilled the criteria for RE. The diagnosis of RE was made clinically in 13 patients, and both clinically and pathologically in 14 patients. The clinical data of the 27 patients were shown in the Table 1. The details of 4 patients were also described elsewhere [14–17].

3.1. Clinical characteristics

The 27 patients were classified into 19 with the childhood-onset rapidly progressive type (CORP) and 8 patients with late-onset slowly progressive type (LOSP), based primarily on the interval between the onset age of epilepsy and that of frequent seizure recurrences (Table 2). They all showed normal development before the onset of epilepsy. Preceding infectious episodes within 6 months prior to the onset of epilepsy were confirmed in 8 cases (30%), including 2 with uveitis (Table 1). The ages at the onset of epilepsy ranged from 2 months to 9 years (mean: 4 years and 4 months) in those with CORP and from 6 years and 6 months to 28 years (mean: 16 years) in those with LOSP (Table 2). The initial epileptic seizures comprised focal motor seizures in 17 patients (3 with status epilepticus), complex partial seizures in 7, and generalized tonic–clonic seizures in 3. Epilepsia partialis continua (EPC) developed in 11 patients (58%) with CORP and 3 patients (38%) with LOSP. EPC involved the left side of the body in 9 patients (64%) and right side in 5 patients (36%). It started either from upper or lower extremity, and gradually affected both extremities (Table 1). The mean

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Table 1
Clinical data of 27 patients with Rasmussen's encephalitis.

Patient No.	Sex	Clinical features							Examinations					
		Type	Preceding infectious episodes	Age at epi. onset	Epilepsia partialis continua (EPC)	Period between epi. onset and the development of frequent seizures	Period between epi. onset and the development of hemiparesis	Neurological impairment	Glu-R antibodies	CSF finding	EEG findings (epileptic EEG foci)	Brain MRI finding	Intelligence test at first examination	Intelligence test at last examination
1	F	CORP	N	2 m	–	0 d	2 y	Left hemiplegia	CSF&S:+	WNL	Right hemisphere	Right hemispheric swelling	NP	DQ = 53
2	F	CORP	N	1 y 6 m	+	2 y 10 m	4 y 6 m	Right hemiplegia, retardation	NP	WNL	Left hemisphere	Progressive left atrophy	IQ = 84	IQ = 52
3	M	CORP	N	2 y	–	12 m	N	N	CSF&S:+	Increased lactate and pyruvate	Right F ~ T	T2 high spot of right T,O, and P regions	NP	FIQ = 72 VIQ = 87 PIQ = 61
4	F	CORP	2 y 5 m varicella 5 y ITP	2 y	–	3 y	6 y	Right hemiplegia	S:R2 – R3+	NP	Left hemisphere	Mild atrophy and T2 and FLAIR high signal of left area	NP	IQ = 29(9 y)
5	M	CORP	N	2 y 7 m	–	7 y	N	N	S:+	NP	Right F	No lesion	IQ = 85	FIQ = 82 VIQ = 80 PIQ = 87
6	F	CORP	Impetigo	3 y 6 m	+	1 y 6 m	4 y 6 m	Right hemiplegia	NP	WNL	Left hemisphere	Progressive left atrophy	IQ – 55	IQ – 47
7	M	CORP	Common cold and vomiting	3 y 7 m	+	3 m	N	N	CSF&S:+	WNL	Right F.C.P	FLAIR lesion of right F area	IQ = 95	IQ = 71
8	M	CORP	N	3 y 10 m	+	4 y	1 y 7 m	Left hemiplegia	S:+	NP	Right C.T	Atrophy of right F area	DQ = 73	IQ = 56
9	F	CORP	N	3 y 10 m	+	0 d	2 m	Right hemiplegia mental retardation		NP	Left hemisphere	Minimal progressive left atrophy	NP	TIQ = 40[VIQ = 51 PIQ = 46
10	M	CORP	Influenza	3 y11 m	+	1 y 5 m	1 y 6 m	Left hemiplegia	CSF&S:+	WNL	Right FP.F	FLAIR lesion of right F. Iright atrophy	IQ = 98	IQ = 94
11	M	CORP	N	5 y 0 m	–	12 m	N	Mental retardeation	S:+	WNL	Left O F C	Repetition of atrophy and swelling of left T ~ O area	NP	IQ – 53
12	F	CORP	N	5 y 3 m	+	11 m	1 y 5 m	Left hemiplegia	CSF&S:+	WNL	Right hemisphere	Progressive right atrophy, FLAIR high spots	TIQ = 85	TIQ = 89
13	M	CORP	N	5 y 4 m	+	1 m	7 y	Left hemiplegia	NP	Hyper NSE	Right F ~ FP	Progressive right atrophy	TIQ = 86	TIQ = 57
14	M	CORP	N	5 y 5 m	+	1 m	4 y	Left hemiplegia	NP	WNL	Right hemisphere	Mild progressive atrophy of right F area	TIQ = 77	TIQ = 66
15	M	CORP	N	5 y 10 m	–	8 m	4 y	Right hemiparesis	NP	Hyper NSE	Left F ~ C	Very minimal atrophy of left O area	TIQ = 73	NP
16	F	CORP	N	5 y 10 m	–	1 y 8 m	2 y 1 m	Right hemiplegia mental retardation	NP	Pleocytosis, Oligoclonal band(+)	Left C	Atrophy of left F, P,and T areas, LAIR high spots at insula	PIQ = 110	IQ 60
17	F	LOSP	Left uveitis	6 y 6 m	Only angle of month	7 y 5 m	5 y	Right hemiplegia	S:+	WNL	Left hemisphere	Progressive left atrophy	TIQ = 78	TIQ = 60
18	F	CORP	Influenzae	6 y 8 m	+	3 m	3 y	Left hemiplegia	CSF&S:+	WNL	Right T ~ O, P	Atrophy of right area	IQ = 105	NP
19	F	CORP	N	7 y 5 m	–	9 m	N	N	S:R2IgG(±). IgM(–) CSF:-	WNL	Left F.O low wave	Very minimal atrophy of left T area and caudate nucleus and DWI high signal of left T area	WISC-III (8 y 1 m) VIQ66, PEQ61, FIQ60	WISC-III (8 y 7 m) VIQ68, PIQ67, FIQ64
20	F	CORP	N	9 y 0 m	+	0 m	2 m	Left hemiplegia	IgG δ2(+) CSF&S: IgG ε2(–)	WNL	Right hemisphere	Atrophy of whole cortex, FLAIR high signal of right T ~ O area	VIQ = 103 PIQ = 51 TIQ = 76	VIQ = 76 PIQ = 57 TIQ = 99
21	F	LOSP	Left uveitis	11 y 6 m	–	9 m	N	Right hemiparesis mental retardation	NP	Oligoclonal band(+)	Left F ~ C	Mild atrophy of left F, T2 high signal of F and P areas	IQ = 87	IQ = 50
22	M	LOSP	N	12 y 2 m	–	1 y 10 m	1 y 1 m	Minimal right hemiparesis, mental retardation	NP	WNL	Left F	Repetition of appearance and disappearance of T2 high signal in left F area	TIQ = 67 VIQ = 62 PIQ = 79	NP
23	F	LOSP	Right uveitis	13 y 0 m	–	8 y 9 m	N	N	Glu R3:(–)	Increased protein, increased IgG	Right C.T	Minimal progressive atrophy of right FC area	IQ = 101	TIQ = 80
24	M	LOSP	Vaccination for Japanese encephalitis	15 y	+	6 m	N	N	S:+	WNL	Left F.Fz	T2 high signal of left F area	FIQ = 82 VIQ = 93 PIQ = 75	FIQ = 80 VIQ = 84 PIQ = 78
25	M	LOSP	N	18 y	+	5 y	10 y	Left hemiplegia	CSF:–	WNL	Right F-aT	T2 and FLAIR high signal of right C area, minimal atrophy of right area	IQ = 86	IQ = 103
26	F	LOSP	N	25 y	–	1y6m	N	N	S:+	NP	Bilateral F - c	No lesion	FIQ = 84 VIQ = 76 PIQ = 98	FIQ = 92 VIQ = 79 PIQ = 112
27	F	LOSP	N	28 y	–	1y	N	Aphasia	S:+	NP	Right F.Fz	FLAIR lesion of right F ~ P	FIQ = 64 VIQ – 62 PIQ = 75	PIQ = 74

Patient No.	High-dose steroid therapy	Treatment: Period between epi. onset and treatment (m)	Treatment: Treatment effect	Treatment: IVIG and other immunomodulatory agent	Treatment: Treatment effect	Surgical treatment	Treatment response	Pathological findings	Follow-up period	Age at last seizure	Outcome
1	NP	–	–	IVIG	Good	Right FH	Excellent	Chronic encephalitis	2 y 6 m	2 y 10 m	No seizure
2	ACTH	55	Transient improvement	NP	–	NP	–	–	3 y 7 m	7 y 9 m	Unknown
3	MP pulse Prednisolone	72	No improvement	NP	–	Focal resection	Difficult to judge	No specific finding	4 y 4 m	11 y 11 m	Frequent seizures pertisted
4	NP	–	–	NP	–	NP	–	–	7 y	9 y	Seizures persisted
5	NP	–	–	NP	–	Focal resection	Excellent	Chronic encephalitis	7 y	14 y 2 m	No seizure
6	MP pulse	29	No improvement	INF-α	Aggravation	NP	–	–	1 y 8 m	7 y 4 m	Died
7	NP	–	–	NP	–	Right FH	Excellent	Chronic encephalitis	3 y	4 y 10 m	No seizure
8	NP	–	–	IVIG	Transient improvement	Right FH	Excellent	Chronic encephalitis	1 y 2 m	9 y	No seizure
9	NP	–	–	NP	–	Focal resection	Excellent	Chronic encephalitis	6 y	24 y 7 m	Tonic seizure of right arm 1×/month
10	NP	–	–	NP	–	Right FH	Excellent	Chronic encephalitis	3 y	5 y 9 m	No seizure
11	Dexamethasone Prednisolone MP pulse	72	Transient improvement Excellent	IVIG CyA	No improvement Good No improvement	NP	–	–	11 y	17 y	Clustering on right side 1×/month
12	MP pulse	14	No improvement	NP	–	Right FH	Excellent	Chronic encephalitis	2 y 3 m	8 y 6 m	No seizure
13	MP pulse	61	Transient improvement	IVIG	No improvement	NP	–	–	8 y 6 m	14 y 3 m	EPC every day
14	MP pulse prednisolone	19	Aggravation	NP	–	Focal resection + MST	Excellent	No specific finding	13 y 8 m	19 y 8 m	EPC every day
15	NP	–	–	IVIG	Exellent	NP	–	–	6 y 5 m	13 y 3 m	Seizure only during sleep
16	NP	–	–	IVIG	Excellent	NP	–	–	4 y 11 m	10 y 9 m	Rare seizure persisted
17	NP	–	–	IVIG	No improvement	NP	–	–	9 y 6 m	22 y 1 m	Clustering of seizures 3-4×/month
18	Prednisolone	4	Excellent	IVIG tacrolimus	Good improvement	Right FH	Excellent	Chronic encephalitis	5 y	10 y	No seizure
19	MP pulse	9	Transient improvement	tacrolimus	Good	NP	–	–	15 m	9 y 2 m	Seizures 2×/month
20	MP pulse prednisolone	8	Good	IVIG	Transient improvement	Right FH	Excellent	Chronic encephalitis	1 y 2 m	10 y	no seizure
21	MP pulse	24	No improvement	IVIG	No improvement	NP	–	–	5 y 3 m	17 y 11 m	Died
22	Steroid	53	Excellent	IVIG ganciclovir	Transient improvement	Focal resection after brain biopsy	Excellent	Chronic encephalitis	9 y 8 m	21 y 10 m	GTCS 1×/month, atonic seizure 1×8/day
23	MP pulse	87	Aggravation	AZT	No improvement	Focal resection + MST (2 times)	Excellent	Chronic encephalitis	19 y 7 m	29 y 5 m	Mild seizures 1×/month
24	NP	–	–	NP	–	Focal resection	Difficult to judge	No specific finding	16 y	31 y	Seizures persisted
25	MP pulse prednisolone	96	Good	IVIG	No improvement	Brain biopsy	–	Chronic encephalitis	2 y	25 y 4 m	No seizure
26	NP	–	–	NP	–	Brain biopsy	–	Suggestion of chronic encephalitis	7 y	34 y	Right-sided seizures persisted
27.	NP	–	–	NP	–	Focal resection	Difficult to judge	Chronic encephalitis	12 y	40 y	Seizures persisted

Abbreviations: S, serum; WNL, within normal limit; NP, not performed; NSE, neuron-specific enolase; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; FIQ, full intelligence quotient; TIQ, total intelligence quotient; DQ, development quotient; MP, methyl prednisolone; IVIG, intravenous immunoglobulin; AZT, azathioprine; CyA, cyclosporine; FH, functional hemispherectomy.

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Table 2
Clinical characteristics of 27 patients.

	Childhood-onset rapidly progressive type (CORP)	Late-onset slowly progressive type (LOSP)
N (M:F)	19 (9:10)	8 (3:5)
Age at epilepsy onset (mean)	2 m~9 y (4 y 4 m)	6 y 6 m ~ 28 y (16 y)
Period between epilepsy onset and development of frequent seizures (mean)	0 d ~ 7 y (1 y 4 m)	6 m ~ 8 y 9 m (3 y 4 m)
Period between epilepsy onset and development of hemiplegia (mean)	2 m~7 y (3 y)	1 yl m ~ 10 y (5 y 4 m)
EPC	11	3
Hemiplegia	14	4
Surgical treatment	11	4
Hemispherectomy	7	0
Death	1	1

interval between the onset age of epilepsy and that of frequent seizure recurrences (daily seizures developed) were 1 year and 4 months in the former and 3 years and 4 months in the latter. The seizures affected the left side of the body in 14 patients (52%) and right side in the remaining 13 patients (48%). Fourteen of the 19 patients with CORP (74%) and 4 of the 8 patients with LOSP (50%) developed hemiplegia, either at the latest follow-up period or before epilepsy surgery. The average time from the onset age of epilepsy to the development of hemiplegia was 3 years and 5 years and 4 months, respectively. Thus, patients with CORP showed more frequent complications with EPC and hemiplegia than those with LOSP. Three patients with LOSP were accompanied by uveitis, ipsilateral to the involved hemisphere at 2 years before, at the period of, and at 6 years after epilepsy onset, respectively. One patient each with CORP and LOSP died of status epilepticus caused by infection at 7 years of age and of a sudden unknown cause at 17 years of age, respectively.

3.2. Immunological examinations

Serum or CSF autoantibodies against the *N*-methyl-D-aspartate glutamate receptor (NMDA-type GluR) ε2 subunit and its epitopes [11] were positive in 13 of the 18 patients (72%) and 6 of the 8 patients (67%), respectively (Table 1). CSF oligoclonal IgG banding was positive in one patient each. Serum cytokine levels were within the normal range in two patients with CORP, but were only measured during steroid therapy. CSF IL-6 was measured to be normal in one patient with LOSP.

3.3. Effect of immunomodulatory treatment

Immunomodulatory treatments including high-dose steroid therapy, high-dose intravenous immunoglobulin (IVIG) administration, and other immunomodulatory agents were tried in a total of 19 patients. They were initiated 4–96 months after the onset of epilepsy (Table 1). The high-dose steroid therapy in most cases was started with the intravenous administration of methyl-prednisolone (MP) for 3 consecutive days (MP pulse therapy) given twice or three times every other week, followed by oral prednisolone (1–2 mg/kg) over a period of a few to several months depending on the response. The high-dose IVIG therapy consisted largely of an initial administration of 200–400 mg/kg consecutively for 3 days, followed by the same single dose once a month for a few months depending on the response.

The high-dose steroid and high-dose IVIG therapies were tried in 14 and 12 patients, respectively. The duration of the one treatment course ranged from 1 to 4 months, depending on the response to treatment. The high-dose steroid therapy achieved more than a good response in 5 patients (36%), and transient response in 3 cases. The IVIG therapy achieved a more than good response in 4 cases (33%) and transient response in 3 cases (Fig. 1). The high-dose steroid and IVIG therapy appeared better in response for those with CORP and LOSP, respectively despite no statistical significance ($P > 0.05$). Azathioprine, INF-α, cyclosporine, and ganciclovir were tried in a few patients without appreciable effects. Three patients have now been placed on tacrolimus, but one of them recently underwent hemispherectomy because of neurological deterioration and continuous EPC, leading the patient to be confined to a wheelchair.

3.4. Neuroimaging characteristics

MRI demonstrated progressive atrophy of the left hemisphere in 11 patients and of the right hemisphere in 14, although 2 pathologically-proven RE patients showed no apparent hemispheric MRI lesions. SPECT and PET studies all supported the lateralization of the MRI and EEG findings. The evolutionary changes in the HR were evaluated in 9 patients (CORP: 6 cases;

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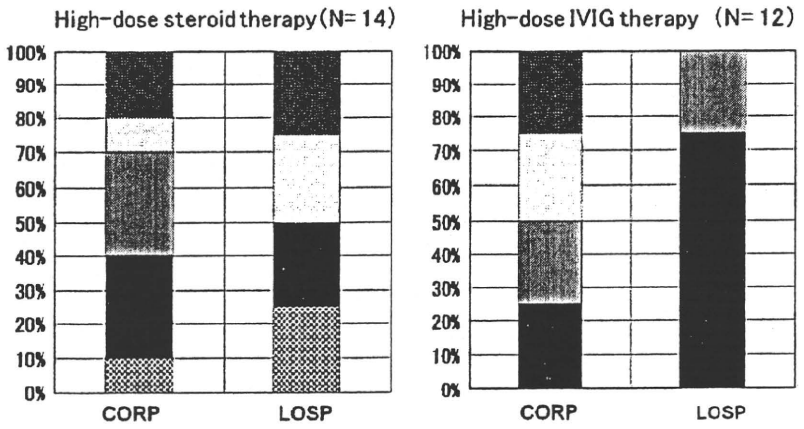

Fig. 1. Effectiveness of immunomodulatory therapy. Excellent, good, no improvement: more than 80% reduction, 50% to 80% reduction, and less than 50% reduction of the seizures, respectively. Transient improvement: more than 50% transient reduction of the seizures. Excellent ■, good response □, transient response ▨, poor response ■, aggravation ▩.

LOSP: 3 cases). The HR changes in the former showed a more rapid decline from the first examination than that in the latter, indicating a more rapidly progressive shrinking of the affected hemisphere in the former (Fig. 2).

3.5. Response to epilepsy surgery

Focal resection with or without multiple subpial transection and functional hemispherectomy was undertaken in 8 and 7 patients, respectively. The former procedure achieved a more than good response in 5 (63%) patients, although none of them became seizure-free. All 7 patients undergoing functional hemispherectomy have remained seizure-free.

4. Discussion

This study is the first Japanese nationwide cohort study involving 27 patients with RE. There have been a large number of investigations regarding various aspects of RE, all of which involved Caucasian patients. The clinical pictures, as well as progressive nature of the disorder in our patients recruited based on the proposed RE criteria, are consistent with those from previous studies. We can subclassify them into those with a childhood-onset rapidly progressive clinical course (CORP) compatible with classical RE, and those with a late-onset slowly progressive clinical course (LOSP) compatible with adult type RE [1,2,18,19]. The average time between the onset age of epilepsy and that of frequent seizure recurrence, and the mean period between the onset age of epilepsy and development of hemiplegia in our series were also similar to those of previous reports.

Bien et al. measured the hemispheric ratio (HR), in which the axial cross-section of the affected hemisphere is expressed in relation to the unaffected one, and quantitatively showed the progressive destruction of the affected hemisphere over time [2]. This method applied to 9 of our patients demonstrated the difference in the HR between those with CORP and those with LOSP, and seemed to be useful for the evaluation of treatment.

Regarding the pathogenesis of RE, since Rogers et al. [9] identified the autoantibody against the ionotropic glutamate receptor GluR3 in the serum of RE patients, the autoimmune process underlying RE has received growing attention. Subsequently, autoantibodies against GluRε2, munc-18, and glial cells have been demonstrated in the serum of RE patients [10,11,13]. We also found GluRε2 antibody in the serum or CSF of roughly 2/3 of our patients at either the onset of epilepsy or in the middle of the clinical course [20]. However, the specificity of these autoantibodies as a primary etiology remains unclear because they were also found in other noninflammatory focal epilepsies or nonspecific encephalitis. Recently, interest is growing toward cell-mediated rather than humoral immunity, with the speculation that cytotoxic T cells destroy neurons through the release of granzyme-B, leading to the progressive destruction of the hemisphere [12,20]. Thus, the notion of a previous infection or vaccination prior to the onset of RE triggering the autoimmune process of the disorder has been challenged, although we could identify these episodes in only one third of our series [21]. However, among them, there were 3 patients with LOSP experiencing uveitis ipsilateral to the affected hemisphere, either long after or before the onset of epilepsy. Uveitis is caused mostly either by viral infections or an autoimmune process in those with systemic autoimmune disorders. Together with previous case reports, the combination of uveitis and RE is not a coincidental event but indicates the same autoimmune process involving both the uveal tract and ipsilateral hemisphere with other sys-

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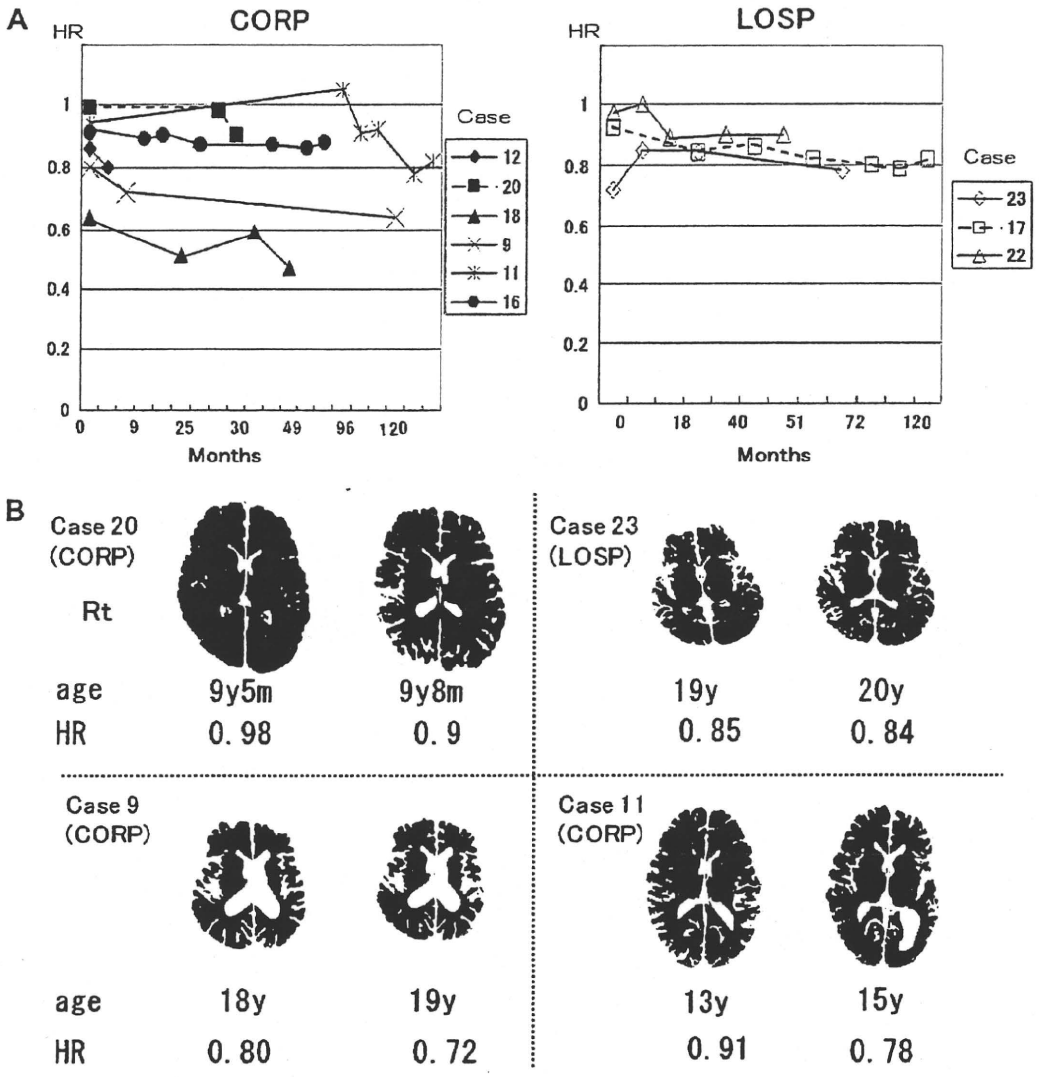

Fig. 2. Serial changes in the hemispheric ratio (HR). (A) Serial HR changes depicted as a sequential line graph for each RE type. (B) Typical examples of HR. Case letters correspond to those of Fig. 2A.

temic autoimmune disorders [14,22]. There must be various factors contributing to the onset of RE, in which the mutation of *SCN1A* causing severe myoclonic epilepsy in infants or generalized epilepsy with febrile seizure plus may be a candidate [17].

Thus, various immunomodulatory treatments have been attempted in patients with RE based on the autoimmune hypothesis. Promising results of high-dose intravenous immunoglobulin (IVIG) treatment have recently been demonstrated in patients with adult-onset RE [23,24]. Leach et al. demonstrated sustained improvement in patients following the long-term usage of high-dose IVIG, despite resistance to steroid treatment in these patients [23]. High-dose steroid treatment has been attempted more frequently than IVIG therapy, with inconsistent results [25–27]. In our results, the high-dose steroid and IVIG therapies brought a better than good response in approximately one third of cases, respectively. The high-dose steroid therapy was more effective for those with LOSP than the IVIG therapy, while the latter therapy appeared to be more beneficial in those with CORP than the former therapy. However, these two therapies could not fully control the seizures nor halt the neurological deterioration, even in responding cases. Tacrolimus has been shown to have a beneficial effect on reducing the progression of hemiatrophy, but does not improve the seizure outcome [28]. In our series, there were 3 patients taking tacrolimus, although one of them finally underwent hemispherectomy due to neurological deterioration and daily EPC up to the level of becoming unable to walk. The effect of tacrolimus will remain undetermined until long-term follow-up data

Please cite this article in press as: Muto A et al. Nationwide survey (incidence, clinical course, prognosis) of Rasmussen's encephalitis. Brain Dev (2009), doi:10.1016/j.braindev.2009.10.004

from a larger number of patients are provided. The effect of immunomodulatory therapy for RE remains equivocal in part due to a limited number of case trials, the differences in treatment regimens, and the slowly progressing and relapsing-remitting clinical course of this disorder itself, hampering a precise assessment of efficacy [1]. In the meantime, these immunomodulatory treatments should be initiated cautiously and stopped when no meaningful improvement is recognized.

Regarding surgical treatment, functional hemispherectomy has been shown to be the final and best option for condition, although this procedure is only possible when hemiplegia has stabilized [7]. In addition, this procedure should be cautiously considered when RE affects the dominant hemisphere. In our series, the hemispherectomy was performed on only non-dominant right hemisphere in all 7 patients. If dominant left hemisphere is affected, we have to wait for this radical procedure until the language center transfer to the non-dominant hemisphere, which can be ascertained by Wada test or fMRI study [29]. Although early hemispherectomy is recommended to reduce the involvement of the unaffected hemisphere by some, a consensus regarding when to introduce hemispherectomy has not been determined globally [8,30]. The hemispheric ratio may become one of the objective markers to introduce hemispherectomy.

In this study, we were able to identify a significant number of patients with RE in Japan, who showed a similar clinical course as well as neuroimaging findings with those reported from Western countries, and have received appropriate immunomodulatory as well as surgical treatment.

Disclosure of conflict of interest

We have no conflicts of interest.

Acknowledgement

This study was supported by the Japan Epilepsy Research Foundation. We confirm that we have read the Journal's position regarding issues pertaining to ethical publication, and affirm that this report is consistent with those guidelines.

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Please cite this article in press as: Muto A et al. Nationwide survey (incidence, clinical course, prognosis) of Rasmussen's encephalitis. Brain Dev (2009), doi:10.1016/j.braindev.2009.10.004

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Please cite this article in press as: Muto A et al. Nationwide survey (incidence, clinical course, prognosis) of Rasmussen's encephalitis. Brain Dev (2009), doi:10.1016/j.braindev.2009.10.004

Microbiol Immunol 2010; **54**: 471–474
doi:10.1111/j.1348-0421.2010.00234.x

NOTE

Detection of DNA of six human herpesviruses in the cerebrospinal fluid of immunocompetent non-herpetic acute limbic encephalitis patients

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ABSTRACT

In order to determine whether six other human herpesviruses, aside from herpes simplex virus, are associated with non-herpetic acute limbic encephalitis in immunocompetent individuals, real-time PCR was used to detect the DNA of herpesviruses in CSF collected from 61 patients with this form of encephalitis. Five of the human herpesviruses tested were not detected in any of the 61 CSF samples. EBV DNA was detected in one CSF sample. The EBV DNA-positive patient was a 36-year-old woman who presented with fever, headache, mild somnolence, and the typical neuroimaging findings.

Key words limbic encephalitis, real-time PCR, EBV.

Limbic encephalitis was initially described as a syndrome based on clinical and neuropathological criteria. This disease is characterized by the subacute onset of temporal lobe seizures, short-term memory loss, confusion, psychiatric symptoms, and typical neuroimaging findings localized in the hippocampal regions. Although it has been suggested that onconeural antibodies are involved in the pathogenesis of limbic encephalitis, the disease mechanism remains unclear (1, 2). As HSV-1 and 2 are the most common human herpesviruses, and are associated with encephalitis, CSF samples of limbic encephalitis patients are initially screened for the DNA of these two viruses using PCR. Cases of limbic encephalitis that are not linked to HSV infection (non-herpetic acute limbic encephalitis patients) could be caused by various types of agents, including the six other human herpesviruses.

Recently, it has been suggested that HHV-6 is an important pathogen in post-transplant acute limbic encephalitis (3–5). Moreover, HHV-6 DNA has been detected in CSF collected from four immunocompetent adult encephalitis patients (6). In order to determine whether the six other human herpesviruses, aside from HSV-1 and 2, are associated with non-herpetic limbic encephalitis in immunocompetent individuals, we attempted to detect the DNA of these viruses by real-time PCR analysis of CSF samples collected from affected patients.

In this study 61 CSF samples collected from patients suspected to have non-herpetic acute limbic encephalitis were examined, the samples having been sent to the Department of Pediatrics, Fujita Health University School of Medicine and the Department of Research, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder. This study was approved by the review boards of the two institutes. These 61 patients (average age: 36.9 ± 22.9 years, 27 male and 34 female patients) were diagnosed with acute limbic encephalitis based on subacute onset of short term memory loss, behavior change, seizures, and involvement of the temporal lobes as determined by EEG, and/or imaging studies. Herpes simplex encephalitis was ruled out in all 61 patients by a PCR screen

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Received 1 February 2010; revised 27 April 2010; accepted 4 May 2010

List of Abbreviations: CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; MRI, magnetic resonance imaging.

for HSV viral DNA in CSF performed by commercial laboratories. Relevant information was obtained from forms that were completed by the referring neurologists. The detailed clinical course of the patient who was ultimately diagnosed with EBV encephalitis was retrospectively determined by review of the medical record.

DNA was extracted from 200 μl of CSF using a QIAamp Blood Kit (Qiagen, Chatsworth, CA, USA). After DNA extraction, DNA was eluted in 50 μl of elution buffer and stored at −20°C. Ten μl of DNA was used for real-time PCR analysis. Real-time PCR was performed to determine DNA copy numbers for varicella-zoster virus (7), EBV (8), cytomegalovirus, HHV-6, HHV-7 (9), and HHV-8 (10). PCR reactions were performed using the TaqMan PCR Kit (PE Applied Biosystems, Foster City, CA, USA). For each viral DNA assessment, standard curves were constructed using the C_T values obtained from serial dilution of plasmid DNA containing the target sequences (10 to 10^6 gene copies/tube). C_T values for each sample were plotted on a standard curve and Sequence Detector v1.6 software (PE Applied Biosystems) used to automatically calculate the sample DNA copy numbers. Detection limits of the all real-time PCR were 10 gene copies/reaction (250 gene copies/ml). Each sample was tested in duplicate, and the mean was used to determine the sample copy number.

None of the CSF samples contained varicella zoster virus, cytomegalovirus, HHV-6, HHV-7, or HHV-8 DNA. EBV DNA was detected in only one of the 61 CSF samples, with a copy number of 1184 copies/ml. The clinical course of the patient who had high concentrations of EBV DNA in her CSF is shown in Figure 1. This 36-year-old female patient presented to her family doctor with fever and severe headache, and was transferred to the university hospital because of mild somnolence. Although physical examination at the time of hospital admission (day 5 of the illness) revealed fever, mild somnolence, and a stiff neck, there were no signs or symptoms suggestive of infectious mononucleosis such as lymphadenopathy, hepatosplenomegaly or tonsillitis. The patient had mild pleocytosis and increased CSF protein concentrations. However, she did not have an increased number of atypical lymphocytes or hepatic impairment at the time of admission. A subsequent PCR analysis performed by a commercial laboratory did not detect HSV DNA in the CSF. Serological testing for EBV infection was not performed. The patient was suspected to have meningo-encephalitis and treated with acyclovir and antibiotics. Despite this treatment, her neurological symptoms persisted for 6 days after hospital admission. Moreover, short-term memory loss appeared on day 9 of the illness. Therefore, on day 11 of the illness, a spinal tap and MRI were performed to clarify the patient's diagnosis. Pleocytosis with mildly elevated CSF protein concentrations were again observed. A brain MRI revealed high signal intensities on fluid-attenuated inversion recovery and diffusion-weighted images of the bilateral hippocampus. Based on the imaging results and

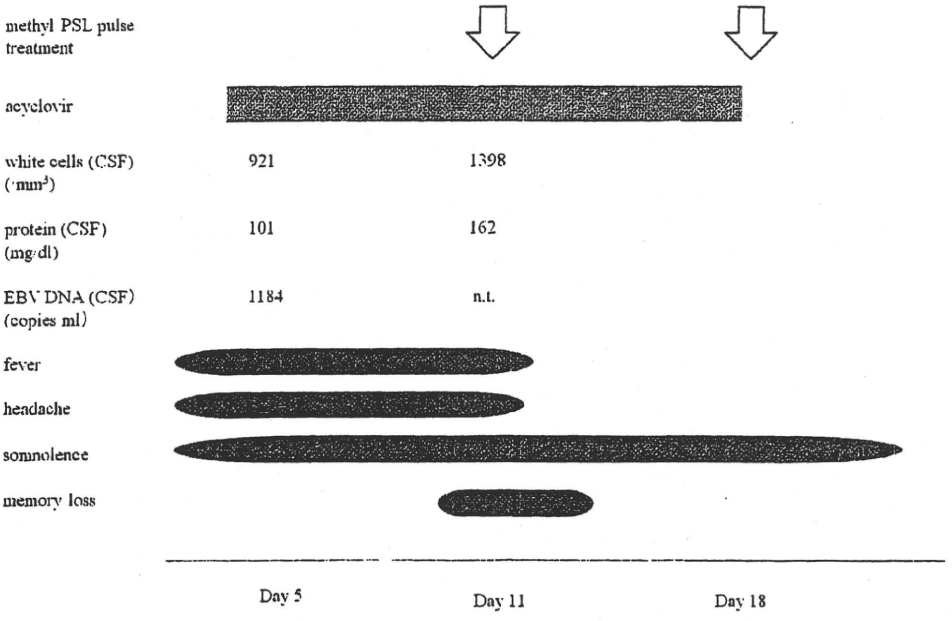

Fig. 1. Clinical course of the patient with positive EBV DNA in CSF. Onset of the symptoms was defined as the day 1 of the illness. PSL, prednisolone; n.t., not tested.

her clinical symptoms, she was finally diagnosed with non-herpetic limbic encephalitis and treated with methyl-prednisolone pulse therapy (1 g/day for 3 days). Immediately after starting steroid treatment, her fever and headache disappeared, and her short-term memory loss subsequently improved. However, because her mild somnolence persisted, a second cycle of methyl-prednisolone pulse therapy (1 g/day for 3 days) was commenced on day 18 of the illness. After this treatment, the patient recovered completely without any neurological sequelae.

As HSV infections are commonly associated with encephalitis, PCR detection of viral DNA in CSF is a popular method for diagnosing encephalitis. In general, patients who are suspected to have encephalitis, including limbic encephalitis, undergo an examination to determine whether the diagnosis is herpes simplex encephalitis. Non-herpetic acute limbic encephalitis case, which has been determined to be HSV-negative by PCR analysis of the CSF, could be caused by any of the six other human herpesviruses. In order to investigate this possibility we used real-time PCR methods, which have been suggested to be valuable tools for diagnosing encephalitis (11–14), to measure the viral DNA load in CSF samples. The reliability of the previously established real-time PCR methods is high, and the sensitivities of these methods (10 gene copies/reaction) were considered to be sufficient for detection of small amounts of viral DNA in CSF. None of the CSF samples collected from non-herpetic acute limbic encephalitis patients contained DNA from the six herpesviruses, except for one patient who was EBV DNA-positive. Although HHV-6 is thought to be a causative agent for post-transplant acute limbic encephalitis (3–5), none of the CSF samples in this study contained HHV-6 DNA. Although *in vitro* examinations were not performed to evaluate the patients' immunity, their medical records indicated that all of them appeared to be immunocompetent. Therefore, although there were a limited number of samples in this study, these results suggest that HHV-6 is not the main causative agent for non-herpetic acute limbic encephalitis in immunocompetent individuals. However, a limitation of this study is that only one CSF sample from each patient was tested. It is well known that repeat examination of CSF samples is useful to determine whether or not causative agents are present in the CSF. Large number of samples should be analyzed to further elucidate this question in a future study.

Only one CSF sample contained EBV DNA, and this was at 1184 copies/ml. As the patient did not show typical clinical features of infectious mononucleosis, serological examination for EBV infection was not performed. It has been suggested that the quantities of EBV DNA in the CSF vary according to the central nervous system manifestations observed in immunocompromised patients (13). In that study, in comparison with immunocompromised patients, relatively few copies of EBV DNA (500, 8000, and 77 000 copies/ml) were detected in CSF obtained from three immunocompetent patients with EBV-associated encephalitis. Krumbholz *et al.* have also reported that similar amounts of copies of EBV DNA (2100 and 5300 copies/ml) were detected in CSF obtained from two patients with EBV-associated encephalitis (15). Thus, the number of copies of EBV DNA detected in the CSF of our case is consistent with previous studies. Although serological analysis would have been necessary for a conclusive diagnosis in this patient, we believe that EBV might have been involved in the pathogenesis of her limbic encephalitis.

EBV can cause various types of central nervous system manifestations, such as encephalitis, meningitis, cerebellitis, transverse myelitis, and neuropathy (16, 17). It has been demonstrated that EBV infections of the central nervous system can occur without manifestations of infectious mononucleosis (16). However, only two limbic encephalitis cases with EBV infection have been previously reported (by Norwegian neurologists), and one of these cases did not exhibit the typical clinical features that are associated with infectious mononucleosis (18). Therefore, in order to diagnose EBV related non-herpetic acute limbic encephalitis, CSF should be examined for EBV DNA by using real-time PCR even when the patient does not exhibit typical clinical symptoms of infectious mononucleosis.

ACKNOWLEDGMENTS

The authors thank Mrs. Akiko Yoshikawa and Mrs. Akemi Miki for their technical support. This work was supported in part by a grant from the Ministry of Health, Labor and Welfare of Japan (H20-Kokoro-021).

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INTERNAL MEDICINE

□ CASE REPORT □

Expression of Various Glutamate Receptors Including *N*-Methyl-D-Aspartate Receptor (NMDAR) in an Ovarian Teratoma Removed from a Young Woman with Anti-NMDAR Encephalitis

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Abstract

A 21-year-old woman developed psychiatric symptoms, progressive unresponsiveness, generalized seizures, severe dyskinesia, marked fluctuation of blood pressure, and hypersalivation after a flu-like episode. Anti-glutamate receptor (GluR)ε2 and anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies were positive in both her serum and CSF. After she recovered five months later she underwent surgery to remove a right ovarian teratoma. Immunohistochemical examinations of her teratoma disclosed abundant expression of various GluRs including NR2B subunit of NMDAR, GluR1, and GluR2/3. These immunoreactivities of GluRs were seen not only in small areas of neural tissue identified as anti-glial fibrillary acidic protein (GFAP)-immunoreactive areas but also in other large areas of undifferentiated neuroepithelial tissue without GFAP immunoreactivity. Our findings strongly support the recent idea that neural elements in ovarian teratoma play an important role in the production of antibodies to NMDARs in anti-NMDAR encephalitis. Additionally, the study of control ovaries clearly showed NR2B-related immunoreactivity in the cytoplasm of oocytes, indicating that the normal ovary itself has expression of NMDARs. This finding might provide a clue to understand the pathogenesis of this disease in female patients without ovarian teratoma.

Key words: limbic encephalitis, paraneoplastic syndrome, ovarian teratoma, glutamate receptor, *N*-methyl-D-aspartate receptor (NMDAR)

(Inter Med 49: 2167-2173, 2010)
(DOI: 10.2169/internalmedicine.49.4069)

Introduction

A unique limbic encephalitis that predominantly affects young females and exhibits various manifestations including initial psychiatric symptoms, and subsequent central hypoventilation, intractable seizures, dysautonomia and prominent orofacial dyskinesia has been noted (1-3). Recently a causative relationship between such encephalitis and ovarian teratoma has been proposed (4-6) and in patients with this disorder a new anti-neural antibody for the NR1/NR2 heteromers of *N*-methyl-D-aspartate receptor (NMDAR) (NMDAR complex composed of NR1+NR2A or NR2B) has been identified as a disease-specific hallmark (2). This disease is, therefore, called anti-NMDAR encephalitis.

Ionotropic glutamate receptors (GluRs) are subdivided into three major subtypes: *N*-methyl-D-aspartate (NMDA)-type, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type and kainate (KA)-type (7). NMDA-type GluRs (NMDARs) have heterotetramer complex structures composed of NMDAR subunits (8). NMDAR subunits have the two nomenclatures from rats and mice, and NR1, NR2

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Received for publication June 11, 2010; Accepted for publication June 30, 2010
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