Clinical manifestations – All 29 patients presented with fever at the onset of neurological symptoms, as well as throughout the acute phase. High-grade fever was observed in 23 patients (higher than 39°C), which was persistent in most cases. Intermittent fever concomitant with aggravation of seizures was also present.

The initial neurological manifestations were seizures in 20 patients, altered consciousness in seven patients, visual agnosia in one patient, and unidentified in one patient, whereas the manifestations in one patient could not be identified.

Seizures were constantly the most prominent and significant manifestation of AERRPS (Table 2). Partial seizure was invariable, and in the vast majority of cases, it was the predominant seizure type: Most commonly, these seizures took the form of eye deviation (69%) and hemifacial twitching (62%), with an occasional development to ipsilateral clonic seizure (48%). Autonomic manifestations such as apneic spell were not uncommon (28%). Seizures usually lasted 1–5 min (83%) and terminated spontaneously, but often occurred in clusters without recovery of consciousness during the interval periods. Within a week, they increased in frequency despite treatment and became full-blown, being periodically repeated every 5–10 min in 14 cases (48%).

Impairment of consciousness was also common. Other neurological symptoms included psychiatric and movement disorders, and memory impairment.

Table 2 Clinical features and laboratory findings

	No. of patients
Acute symptoms	
Seizure	
Simple partial	1
Complex partial	25
Secondary generalized	24
Generalized tonic–clonic	8
Tonic	8
Myoclonic	4
Impairment of consciousness	24
Psychiatric disorders	9
Movement disorders	12
Memory impairment	8
Laboratory findings	
Blood	
High ferritin	4/4 (221–2.370 mg/dl)
Positive anti-GluRε2 Ab	6/9
CSF	
Pleocytosis (>5/mm³)	19/29 (6–25/mm³)
High protein concentration (>45 mg/dl)	5/29 (46–85 mg/dl)
High neopterin	4/4 (246–1.154 nmol/ml)
High neuron specific enolase	2/6 (33–34 mg/dl)
Positive anti-GluRε2 Ab	5/9

Ab, antibody.

EEG findings – A total of 71 EEGs was studied (1–289 days of admission). During the first 14 days of neurological illness, pretreatment EEGs consisted principally of high-voltage slow background activity (7/9, 78%). At the later stage, all 29 patients developed interictal epileptiform discharges with a variety of spatial distribution. Multiple independent foci were observed in 15 patients (54%). Seven patients (24%) were found to have epileptic foci that migrated during the acute phase. Ictal discharges were recorded in 24 patients. They typically began with localized rhythmic activities consisting of spikes or sharp waves and progressively involved the adjacent areas, thus leading to secondary generalization. Ictal discharges disappeared spontaneously within a few minutes and then reappeared, being periodically repeated every 5–10 min.

Neuroimaging – Magnetic resonance imaging (MRI) was examined at least once in all patients. Those performed within 7 days after onset (14 cases) revealed mild brain edema in two patients but were otherwise normal. Subsequently, six patients showed hippocampal or amygdaloid hyperintensities on fluid-attenuated inversion recovery (FLAIR) without the evolution of epileptic foci at the corresponding area. Abnormal symmetrical T2 hyperintensity in the periventricular white matter and claustrum were found in four and two patients, respectively.

Laboratory examinations – The routine blood cell count and biochemistry, as well as blood levels of glucose, ammonia, and lactate were generally unremarkable. The data on inflammatory and autoimmune markers are summarized in Table 2. Plasma amino acid and urinary organic acid revealed no abnormalities. Extensive virological studies were also conducted. Herpes simplex virus was serologically negative or had remotely infected 27 patients who were examined. Serological studies for cytomegalovirus ($n = 16$), Epstein–Barr virus ($n = 20$), and human herpes virus 6 ($n = 11$) showed no serial elevation of antiviral titer. Viral cultures from CSF or throat swabs in 14 patients were all negative.

Treatment – Intravenous barbiturates were administered in 22 patients, of whom 13 showed complete, three excellent, and four good responses, while none were poor. Pentobarbital was most frequently used (15 patients), followed by thiopental (five) and thyamiral (four). The effective and maximal doses of pentobarbital were 4.22 ± 1.82 and 4.98 ± 2.06 mg/kg/h, respectively. The EEG backgrounds when seizure had been suppressed were high voltage slow wave in one, burst-suppres-

sion pattern in 14, and complete suppression in three. The duration of barbiturate infusion ranged from 4 to 312 days (52.3 ± 72.6 days).

Benzodiazepines, mainly midazolam, were administrated in 25 patients, of whom three showed complete, five good, and 17 poor effects. The maximal dose of midazolam was 0.47 ± 0.33 mg/kg/h. Diazepam was used in bolus injection successfully in five of 12 patients, which were only temporarily effective. The efficacy of intravenous lidocaine (1.5–6 mg/kg/h) and phenytoin (5–25 mg/kg/day) were limited (8% and 30%, respectively), transient, and incomplete.

Immunomodulatory treatments were challenged in some cases. Twelve patients were treated with corticosteroids mostly by intravenous methylprednisolone, of whom two were effective. Intravenous immunogloburin (IVIG) in 13 patients did not result to any improvement. One patient underwent plasma exchange, which was unsuccessful.

Chronic phase

Course and prognosis

Two of the 29 patients dropped out, and therefore, the remaining 27 patients received follow-up, with a mean period of 60.9 months (ranging from 8 to 194 months). All patients had residual epilepsy. As defined in the diagnostic criteria, all patients showed continuous evolution from encephalitis to residual epilepsy without a latent period. The types of seizures were essentially the same as those in the acute phase except for scarce secondary generalization. Most patients had residual cognitive impairment. Intelligence quotients (IQs), measured using the Wisconsin Intelligence Scale for Children-III (WISC-III), were less than 70 in 16 patients and below 20 in 10 patients. All patients who had the antibody against GluRε2 were found to have residual cognitive impairment. Other residual neurological deficits included memory impairment (15%), autistic tendency (22%), hyperkinetism (15%), learning disability (15%), personality change (15%), and emotional instability (22%). One patient suddenly died of unknown cause 9 years after onset. Serial MRI scanning revealed diffuse brain atrophy after a month or more. Hippocampal or amygdaloid signal abnormalities remained unchanged in four of six patients.

Discussion

The clinical entity of AERRPS arose in 1986, when Awaya et al. described five cases of 'peculiar onset post-encephalitic epilepsy' (9). In his investigation

into post-encephalitic epilepsy, he found a novel subtype of epilepsy characterized by refractory partial seizures persisting from the onset of encephalitis to the convalescent phase. Meanwhile, in 1989, Shiomi advocated a subgroup of encephalitis characterized by very frequent seizures that can be suppressed only by intravenous barbiturates. It should be noted that Awaya defined this illness as post-encephalitic 'epilepsy' and therefore, discussed mainly its epileptogenesis (4), while Shiomi classified it as a subtype of 'encephalitis' and put emphasis on the symptoms in the acute phase. These two clinical entities shared some characteristics: acute onset of illness, very frequent partial seizures, extremely refractory trait of seizures, inconspicuous switchover from encephalitis to subsequent epilepsy, and residual cognitive impairment. In 2001, we proposed the term AERRPS to integrate the characteristics of these entities (5). To date, more than 30 cases compatible to this condition have been accumulated in Japan (4).

We report the first multicenter collaborative study on acute encephalitis with refractory, repetitive partial seizures (AERRPS) to clarify its clinical features. The definitive features became evident as a result of this study. Several clinical aspects that seem to be characteristics of AERRPS are vital for the diagnosis, and these are listed in the diagnostic criteria (Table 3). EEG findings in AERRPS, particularly ictal recordings, are of diagnostic significance. The repetitive EEG pattern of ictal discharges has been described (6). In

Table 3 Diagnostic criteria for AERRPS

Mandatory:
1. Acute onset of seizures or consciousness impairment, in the absence of underlying developmental delay or prior unprovoked seizures
2. Extraordinarily frequent and refractory partial seizures, referred to as 'refractory partial SE': The patients usually show partial seizures characterized by eye deviation and facial twitching which repeat within an interval of 30 minutes or less, and necessitate long-term anesthesia (2 weeks or more) with intravenous barbiturates or benzodiazepines to attain burst-suppression coma on EEG
3. Continuous switchover to refractory epilepsy without a latent period

Supportive findings:
1. Antecedent febrile illness, which occurs 2–10 days before the onset of neurological symptoms
2. Persistent fever during the acute phase of illness
3. CSF findings: mild pleocytosis or slight increase in protein (inflammatory markers such as IL-6 or neopterin may be upregulated) or both
4. EEG: slow background during the acute phase and multifocal spikes during the chronic phase (ictal EEG reveals variable foci of epileptiform discharges and frequent secondary generalization)
5. MRI: no specific abnormalities except for occasional T2/FLAIR hyperintense signal of mesial temporal lobe
6. Profound neurological sequelae: cognitive deterioration, psychiatric disorders, and memory impairment, as well as occasional motor disability

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.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical features.

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

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Acute Nonparaneoplastic Limbic Encephalitis in Childhood: A Case Series in Japan

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Limbic encephalitis not associated with malignancy was investigated in Japanese children, with particular focus on clinical features distinct from adult cases. Clinical, laboratory, and radiographic findings were studied in pediatric nonparaneoplastic limbic encephalitis, based on a literature review and questionnaire-based analyses. Analysis of 14 cases revealed the predominance of seizure occurrence, disturbance in consciousness, and frequent extralimbic signs. The majority manifested antecedent febrile illnesses, suggesting the involvement of infection-induced autoimmunity targeted to neuronal antigens. These clinical observations indicate a child-specific phenotype of limbic encephalitis. Further studies on its immunopathogenesis are needed to determine whether childhood limbic encephalitis is a distinct subcategory. © 2010 by Elsevier Inc. All rights reserved.

Introduction

Limbic encephalitis is characterized by a triad of signs, i.e., short term memory deficit, limbic seizures, and psychiatric signs, together with frequent mesial temporal hyperintensity evident on T$_2$-weighted magnetic resonance imaging [1]. Limbic encephalitis associated with malignancy is recognized as classic paraneoplastic limbic encephalitis [2]. A similar condition, termed the nonparaneoplastic form of limbic encephalitis, lacks tumor formation and occasionally affects young children. It has become an important clinical concern [3]. However, few patients with childhood onset limbic encephalitis have been reported, and this condition has not been investigated exten-

sively in a large cohort. We sought to clarify the clinical, laboratory, and neuroradiologic features of limbic encephalitis occurring in childhood.

Patients and methods

We performed an online retrieval of limbic encephalitis case reports from *Japana Centra Revuo Medicina*, a Japanese bibliographic database of medical journal articles, using the keywords "limbic encephalitis" and "child." Although the definition of limbic encephalitis varied widely between studies, we adopted the criteria proposed by Bataller et al., i.e., predominant limbic signs, including confusion, seizures, short term memory loss, or psychiatric signs, in association with one or more of the following: (1) neuroimaging evidence of temporal lobe involvement, (2) cerebrospinal fluid inflammatory abnormalities, or (3) detection of antibodies associated with limbic encephalitis [4]. Patients were excluded from the study under certain circumstances: (1) paraneoplastic limbic encephalitis and encephalitides caused by certain neurotropic viruses, (2) age of more than 15 years (because such patients are conventionally seen by adult neurologists in Japan and are not identified as childhood cases), and (3) immunocompromised backgrounds (limbic encephalitis was reported in immunocompromised hosts, caused by a reactivation of human herpesvirus-6).

Twenty cases of childhood onset limbic encephalitis were identified between 2003 and 2008. Two cases were paraneoplastic. Among 18 patients without malignancy, seven were described in case reports, and 11 in conference abstracts. We sent a questionnaire to the physicians treating the 11 patients described in conference abstracts. Questions involved antecedent infections, clinical signs (impaired consciousness, seizures, memory impairment, psychiatric signs, and higher brain dysfunction), laboratory findings (involving cerebrospinal fluid, electroencephalograms, magnetic resonance imaging, and single photon emission computed tomography), treatments (antiviral agents and immunomodulation), and prognoses. Five of the physicians responded. Fourteen patients (8 boys and 6 girls) were enrolled in the study, including one patient who was treated at our hospital.

Results

Clinical and laboratory features are indicated in Tables 1 and 2. Six patients (1, 2, 3, 6, 7, and 10) were reported previously [5–10]. The median age of patients was 10 years (range, 4-14 years).

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Table 1. Clinical features

Patient	Age	Sex	Antecedent Illness*	Fever	Presenting Sign
1	14	F	Respiratory infection (5)	ND	Irritability
2	12	F	Unknown febrile illness (5)	+	Somnolence; seizure
3	13	F	Unknown febrile illness	ND	Disorientation
4	6	F	Unknown febrile illness (0)	+	Disorientation; somnolence; oral automatism
5	4	M	Unknown febrile illness (4)	+	Aphasia; seizure
6	6	M	None	−	Seizure
7	8	M	Unknown febrile illness (9)	+	Seizure
8	12	M	Unknown febrile illness (2)	ND	Seizure
9	14	F	None	+	ND
10	8	M	Gastroenteritis (5)	+	Seizure; consciousness impairment
11	11	M	Respiratory infection	ND	Abnormal behavior; delirium; insomnia
12	10	M	Respiratory infection (6)	−	Seizure
13	9	F	Unknown febrile illness (7)	+	Seizure
14	9	M	Unknown febrile illness (7)	+	Seizure

* Number in parentheses represents latency period (days).

Abbreviations:
CPS = Complex partial seizure
F = Female
GTCS = Generalized tonic-clonic seizure
M = Male
ND = Not described

Table 2. Laboratory and radiographic findings, treatments, and outcomes

Patient	Cerebrospinal Fluid	Electroencephalography	Magnetic Resonance Imaging	SPECT	Viral Study
1	CC 55; protein 10	Slowing	Normal	L frontal/temporal low	HSV-PCR(−); HSV antibody(−)
2	CC 2	Periodic epileptiform discharges	Bilateral hippocampus/ claustrum high	ND	HSV-PCR(−); HSV antibody(−)
3	CC 1; protein 24	Slowing	L temporal/parietal high	L temporal/parietal high	HSV(−)
4	CC 4; protein 11	Slowing	Normal	Temporal low	Negative viral isolation
5	CC 11; protein 21	Slowing	Normal	L temporal low	HSV-PCR(−); negative viral isolation
6	CC 19; protein 18	Slowing	Normal	L frontal/temporal low	HSV-PCR(−)
7	CC 13; protein 16	Slowing	Bilateral hippocampus/ claustrum high	ND	HSV-PCR(−); negative viral isolation
8	CC 4; protein 71	Spike/spike and wave	Bilateral hippocampus/ amygdala high	ND	HSV(−)
9	CC 48; protein 198	Slowing	Bilateral hippocampus/ insula high	Not tested	HSV-PCR(−)
10	CC 0; protein 45	Slowing; multifocal spikes	Bilateral claustrum high	ND	HSV-PCR(−); HSV antibody(−)
11	CC 17; protein 27	Slowing	R temporal high	R temporal high	HSV antibody(−); negative viral study
12	CC 2; protein 41	Slowing	Bilateral hippocampus/ amygdala high	Bilateral temporal low	HSV-PCR(−); negative viral isolation
13	CC 10; protein 41	Slowing; focal spike	Bilateral hippocampus/ claustrum high	Bilateral parietal/occipital low	HSV-PCR(−); negative viral isolation
14	CC 3; protein 55	Diffuse spikes and waves; slowing	Bilateral hippocampus high	Not tested	HSV-PCR(−); negative viral isolation

Abbreviations:
(−) = Negative
CC = White blood cell count/μL
FIQ = Full intelligence quotient
HSV = Herpes simplex virus
IVIg = Intravenous immunoglobulin
L = Left
ND = Not described
PCR = Polymerase chain reaction
R = Right
SPECT = Single photon emission computed tomography

Impairment of Consciousness	Seizures	Short Term Memory Loss	Psychiatric Signs	Other Signs
Disorientaion; stupor	–	+	Irritability; emotional lability	Agnosia; sleep disorder
Somnolence; coma	GTCS; eyelid twitch	Not evaluated	Irritability; emotional lability	Oral tendency; aberrant sexual behavior
Disorientaion	Epilepsia partialis continua	+	Hallucinations; perseveration	Spatial agnosia
Disorientaion; somnolence	GTCS	+	Emotional lability; hallucinations; abnormal behavior	Oral automatism; paratonic rigidity
Delirium	Partial seizure	+	Irritability; aggression; emotional lability; hallucination	Aphasia; hemiplegia; dystonia; sleep disorder
+	Hemiconvulsion	+	Irritability	Aphasia; myoclonus; stereotypy; sleep disorder; hemiplegia; dysarthria
+	GTCS	+	Emotional lability; personality change; aggression	Aphasia; dysesthesia; myoclonus; stereotypy; aberrant sexual behavior; dysarthria
Coma	GTCS; perioral twitch	+	Abnormal behavior	Aberrant sexual behavior
+	Partial seizure	Not evaluated	Irritability	Partial quadriplegia; bulbar palsy
Somnolence; disorientation	CPS; GTCS	+	Hallucination	Dysarthria
Disorientation	CPS	+	Abnormal behavior; irritability; aggression; emotional lability	Bulimia; aberrant sexual behavior; clumsiness; sleep disorder
+	+	+	Aggression; emotional lability	Aphasia; agnosia; hyperkinetism; aberrant sexual behavior
Somnolence	Partial seizure	+	Emotional lability; personality change	
+	+	+	Emotional lability; personality change	Sleep disorder; oral automatism

Acyclovir	Immunomodulation	Intellectual Outcomes	Residual Epilepsy	Other Neurologic Sequelae
+	–	Normal	–	Memory impairment; emotional lability
+	Dexamethazone	FIQ 93	+	ND
–	–	Normal	–	Sensory/auditory hypersensitivity
+	Dexamethazone	Normal	–	–
–	Methylprednisolone; IVIg	Normal	–	Impairment in visual perception
+	Methylprednisolone	Normal	+	ND
+	–	FIQ 99	–	Emotional lability
+	Methylprednisolone	Normal	+	ND
+	Methylprednisolone; IVIg; plasmapheresis	Severe mental retardation	–	Partial quadriplegia
+	Methylprednisolone	FIQ 107	+	ND
+	Methylprednisolone	Developmental quotient of 66	–	Amnesia
+	Methylprednisolone	FIQ 103	–	Aphasia; attention distractability
+	Methylprednisolone; IVIg	Mild mental retardation	–	Emotional lability; personality change; amnesia
+	–	FIQ 73	+	ND

Febrile illness, presumed to have an infectious cause, preceded the onset of neurologic signs by 0-9 days in 12 patients. Seizures (n = 10), impaired consciousness (n = 5), and psychiatric signs (n = 3) were the common initial signs. All patients exhibited impaired consciousness, which varied considerably in degree, from disorientation to coma. Psychiatric signs were also common, and included emotional lability (n = 7), irritability (n = 7), abnormal behavior (n = 4), hallucinations (n = 4), aggression (n = 4), and personality change (n = 2). Of the 15 patients with seizures, three manifested generalized seizures, six manifested partial seizures, and four manifested both. Seizure type was not described in three patients. Short-term memory loss was evident in 12 patients. Ten patients demonstrated all three signs of the limbic encephalitis triad. Higher brain dysfunctions, e.g., aphasia (n = 4) and agnosia (n = 3), were also observed. Other signs included movement disorders (n = 4), aberrant sexual behavior (n = 4), sleep disorders (n = 4), dysarthria (n = 2), oral tendency (n = 2), and stereotypy (n = 2).

Analysis of cerebrospinal fluid revealed mild to moderate pleocytosis in eight patients, and an elevated protein level in four. An electroencephalogram revealed slow background activity in 10 of 12 patients examined during the acute phase of their illness. Magnetic resonance imaging indicated signal abnormalities in hippocampal or amygdaloid formations (n = 9) and the claustrum (n = 4), whereas three patients exhibited normal results of magnetic resonance imaging. On single photon emission computed tomography, cerebral blood flow in the temporal lobe was decreased in four patients and increased in two. The anti-voltage-gated potassium channel antibody was negative in one patient. Other autoantibodies associated with limbic encephalitis were not examined. Herpes simplex virus, as tested by antibody measurement or polymerase chain reaction, was not evident in any patients.

Ten of 14 patients received immunomodulatory treatments, including corticosteroids, intravenous immunoglobulin, and plasmapheresis. The efficacy of these treatments was difficult to assess because spontaneous recovery probably occurs in limbic encephalitis. Prophylactic acyclovir was administered to 12 patients, and their overall prognosis was favorable. Ten patients demonstrated normal intellectual outcome after recovery, and only one manifested severe cognitive impairment. Other neurologic sequelae included residual epilepsy (n = 5), psychiatric disorders (n = 3), and memory impairment (n = 3).

Discussion

Limbic encephalitis is characterized by a broad range of etiologies [1]. Table 3 lists the differential diagnoses of limbic encephalitis. Some neurotropic viruses, such as herpes simplex, preferentially infect the limbic system [11]. Human herpesvirus 6 is thought to be responsible for posttransplant acute limbic encephalitis, a serious complication after hematopoietic stem cell transplantation [12]. In addition,

Table 3. Differential diagnoses of limbic encephalitis in children and adolescents

Herpes simplex encephalitis [11]
Human herpesvirus-6 encephalitis
In immunocompromised hosts [12]
Associated with drug hypersensitivity syndrome [13]
Neuropsychiatric lupus [14]
Sjögren syndrome [15]
Hashimoto's encephalopathy [16]
Encephalitis lethargica [17]
Acute encephalitis with refractory, repetitive, partial seizures [18]

this virus is often reactivated in the cerebrospinal fluid of limbic encephalitis patients as a comorbidity of drug hypersensitivity syndrome [13]. Furthermore, neuropsychiatric lupus or other autoimmune diseases may mimic limbic encephalitis [14–18].

Autoimmune limbic encephalitis comprises another well established category, and most of these cases are indicated by autoantibodies (Table 4) [1,19–22]. This condition occurs in relation to senile cancer, and is associated with onconeuronal antibodies, including anti-Hu and anti-Ma antibodies [2,23–25]. These antibodies target intracellular antigens, whereas autoantibodies that are directed against cell surface antigens, including the voltage-gated potassium channel and N-methyl-D-aspartate receptor, are topics of interest [26,27]. Autoimmune limbic encephalitis commonly shares the classical triad of signs, whereas those cases caused by specific causative autoantibodies are characterized by unique signs. For example, anti-N-methyl-D-aspartate receptor antibody encephalitis often affects adolescents or young adults, and is associated with facial dyskinesia, hypertonia, autonomic instability, and hypoventilation [28]. Voltage-gated potassium channel autoimmunity is often accompanied by dysautonomia, peripheral neuropathy, or hypothermia [29,30].

Most cases of autoimmune limbic encephalitis in adulthood are associated with certain neoplasms, i.e., the disease manifests as a paraneoplastic syndrome. For example, anti-Hu or anti-voltage-gated potassium channel antibodies are associated with small cell lung carcinoma, whereas the anti-N-methyl-D-aspartate receptor antibody is associated with ovarian teratoma [19]. In children, however, these antibodies are often detected in patients devoid of neoplasms. In a recent study, only 25% of patients with anti-N-methyl-D-aspartate receptor encephalitis (age below 18 years) manifested a tumor [31].

Studies of large series of children with limbic encephalitis have not been conducted. The detailed clinical and laboratory features documented in the present study demonstrate a number of differences between childhood and adult limbic encephalitis. Rapidly developing seizures and impaired consciousness were the principle initial signs in children. This finding is in sharp contrast to limbic encephalitis in adulthood, which usually demonstrates a subacute onset of memory impairment or psychiatric signs. Furthermore, extralimbic signs, including dysarthria, higher

Table 4. Autoantibodies associated with limbic encephalitis

Antigen	Frequency in Children	Specific Features	Associated Cancers
Hu (ANNA-1) [2]	Infrequent	Neuropathy, ataxia, brainstem encephalitis, dysautonomia	SCLC
Ma, Ta [23]	Infrequent	Ataxia, brainstem encephalitis	Lung cancer, germ cell tumor
CV2/CRMP5 [24]	Infrequent	Ataxia, chorea, myasthenic syndrome, uveitis	SCLC, thymoma
Amphiphysin [25]	Infrequent	Neuropathy, myelopathy, stiff person syndrome	SCLC, breast cancer
Voltage-gated potassium channel [26,29,30]	Not uncommon	Hyponatremia, neuropathy, dysautonomia, hypothermia	SCLC, thymoma
NR1/NR2 subunits of N-methyl-D-aspartate receptor [27,28,31]	Frequent	Dyskinesia, autonomic instability, hypoventilation, catatonic-like state	Ovarian teratoma
Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [20]	Not reported	Concurrent systemic autoimmunity	Lung cancer, breast cancer, thymoma
Glutamic acid decarboxylase [21]	Unknown	Stiff person syndrome, ataxia	Uncommon
Gamma-aminobutyric acid receptor [22]	Unknown	Early or prominent seizures	SCLC

Abbreviation:
SCLC = Small lung cell cancer

brain dysfunction, aberrant sexual behavior, and oral tendency, are not usually evident in adult patients. Childhood limbic encephalitis was suggested to involve not only the limbic system, but also the basal ganglia, brainstem, and neocortex. Whether the wide variety of clinical phenotypes in childhood limbic encephalitis is dependent on age, or is attributable to an etiology distinct from adult cases, remains to be determined.

Antecedent febrile illness was common in children, suggesting that infection may exert considerable influence on the initiation of limbic encephalitis. Human herpesvirus-6 is unlikely to causes limbic encephalitis in previously healthy children, because this condition occurs almost exclusively in cases with an immunocompromised background, or in those receiving certain drugs, e.g., antiepileptic agents [12,13]. Herpes simplex virus infection was excluded in all patients. Furthermore, a majority exhibited negative virus isolation. These data indicate that direct viral invasion is unlikely to play a central role in childhood limbic encephalitis. A large part of adult limbic encephalitis is associated with neoplasms. In contrast, we discovered only two case reports of paraneoplastic limbic encephalitis in the last 5 years. In cases of anti-N-methyl-D-aspartate receptor encephalitis with ovarian teratoma, 72 of 84 patients manifested prodromal syndrome with hyperthermia [28]. This finding demonstrates that even in paraneoplastic limbic encephalitis, infection can trigger the onset of illness. Hence, antecedent infection may cause limbic encephalitis through a secondary autoimmune response.

This study was limited insofar as serum autoantibodies associated with limbic encephalitis were not investigated. Based on the diversity of clinical phenotypes, it is natural to assume that the pathomechanism of childhood limbic encephalitis is heterogeneous, possibly involving diverse causative antibodies. Therefore, thorough immunologic

investigation, including humoral and cellular immunity, will be necessary to elucidate age-related differences in limbic encephalitis.

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総　説

小児の自己免疫性神経疾患：脳炎を中心に

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要　旨

中枢神経系の自己免疫疾患には自己反応性 T 細胞が病態の中心となるもののほかに，自己抗体が関与する疾患群が存在する．これには自己免疫性辺縁系脳炎，抗 NMDA 受容体脳炎，難治頻回部分発作重積型急性脳炎，嗜眠性脳炎などが含まれ，比較的緩徐に発症するけいれん，精神症状，不随意運動，短期記憶障害，睡眠障害など臨床症状に共通点が見られる．辺縁系脳炎に関連する自己抗体としては，Hu 抗体などの古典的な抗神経抗体のほかに，各種のイオンチャネルや神経伝達物質受容体に対する抗体が知られている．グルタミン酸受容体に対する自己抗体は，認識されるエピトープにより異なるサブタイプがあり，疾患特異性や病原性に違いがある．中でも NMDA 型グルタミン酸受容体の NR1，NR2 サブユニット複合体を認識する抗体は不随意運動や中枢性呼吸障害などを引き起こし，若年女性では高率に卵巣奇形腫を合併する．難治頻回部分発作重積型急性脳炎は我が国で提唱された概念で，難治かつ頻回の部分発作を主徴とする特異な経過を示す．自己抗体の産生機序として，病原体抗原と自己抗原の分子相同性以外にも様々な機序が解明され，また神経細胞における抗原の局在（細胞表面か細胞外か）によっても自己抗体の病原性は異なると考えられる．これらの疾患はウイルス関連急性脳症と比べると頻度は低いが，診断・治療にしばしば難渋することから，小児科領域でも広く認知すべき疾患である．

キーワード：抗神経抗体，辺縁系脳炎，抗 NMDA 受容体脳炎，
　　　　　　難治頻回部分発作重積型急性脳炎，嗜眠性脳炎

はじめに

中枢神経系は古くから「免疫学的特権部位」と呼ばれ，全身の免疫系から隔絶された特殊な器官であると考えられてきた．これは中枢神経系が血液脳関門という強固なバリアによって遮蔽され，かつその中にはリンパ球がほとんど存在しないという事実に基づいていた．しかし現在ではこのようなことは決してなく，中枢神経系は全身の免疫系によって常に監視され，両者は密接なクロストークにより相互に制御しあうことが明らかとなっている[1]．従って中枢神経系の自己抗原に対する免疫寛容が何らかの理由で破綻すれば，それらを標的とした自己免疫疾患が起こりうる．その代表例が，脳・脊髄の髄鞘タンパクを責任抗原とする多発性

硬化症である．中枢神経系に対する自己免疫反応に関する知見は，多発性硬化症とその動物モデルである実験的自己免疫性脳脊髄炎を用いた研究に負うところが大きい．いずれも自己反応性 CD4 陽性 T 細胞がその病態において主役をなす[2]．また Rasmussen 脳炎では CD8 陽性 T 細胞がアストロサイトを傷害することが証明されている[3]．これらの細胞性免疫による疾患に対し液性免疫が重要と考えられるものもあり，中枢神経系に存在する抗原を標的とした自己抗体が病態形成において中心的な役割を果たす．これらの自己抗体は，成人においては主に悪性腫瘍に随伴して産生されるが，小児ではウイルス・細菌等の感染によって誘発される場合が多い．

なお多発性硬化症では T 細胞だけでなく，抗体や自然免疫系の細胞（食細胞，樹状細胞など）も深く関与することが知られるようになっている．このように自己免疫疾患をはじめとする免疫学的異常を単一の免疫系の機能障害に帰するという考え方から，多彩な機能

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表1　自己抗体が関与する脳炎ならびに類縁疾患の神経症状

	自己免疫性辺縁系脳炎	抗 NMDA 受容体脳炎	嗜眠性脳炎	難治頻回部分発作重積型急性脳炎
けいれん	+	+		＋＋
精神症状	＋＋	＋＋	+	＋・
記憶障害	＋＋			+
不随意運動		＋＋	＋＋	
睡眠障害			＋＋	
高次脳機能障害	+		+	+
自律神経症状	+	＋＋		
その他		無反応，中枢性無呼吸	眼筋麻痺，視覚障害，無動無言症	

を持つ細胞集団が織りなす「ネットワーク」という視点から捉えるという考え方へのパラダイムシフトは，現代の免疫学における重要な流れである．

　ここでは中枢神経系の自己免疫疾患の中でも自己抗体が主に関与する脳炎を取り上げる．これまでに明らかにされてきた疾患についてその歴史的背景も含めて概説するとともに，自己抗体がどのように産生され，病態とどのように関連しているかについても，現在までに得られた知見を述べたい．なお「自己免疫性脳炎」という正式な学術用語はなく，従って厳格に定義づけることは困難であるが，ウイルスの直接浸潤による一次性脳炎，さらにはウイルスに対する過剰な非特異的炎症反応が推定されているサイトカイン・ストーム関連急性脳症などと区別する目的で,「中枢神経系の抗原に対する自己免疫反応に起因する脳炎」としてカテゴライズしたものである．

歴史的背景

　悪性腫瘍の患者で，腫瘍の原発巣とは無関係の臓器症状が出現する現象は古くから知られており，中でも中枢・末梢神経系の異常を呈するものは傍腫瘍神経症候群として既に20世紀半ばから報告されている[4]．後にこれらの患者の血清中に抗 Hu 抗体等の古典的な抗神経抗体が発見され，中枢神経系を標的とする自己抗体の存在がクローズアップされた．さらに近年は電位依存性カリウムチャネル（voltage-gated potassium channel，以下 VGKC)やグルタミン酸受容体に対する自己抗体が続々と発見され，この分野における知見は急速に増加している[5)6)]．これらの自己抗体の多くは悪性腫瘍を有する成人患者に見いだされるが，必ずしも腫瘍を伴わない場合もあることが明らかになり，特に小児ではその傾向が強い．傍腫瘍神経症候群は中枢・末梢神経系のあらゆる部位を傷害しうるが，その中で比較的頻度が高い病型は辺縁系脳炎と小脳変性症である[7]．従って辺縁系脳炎はいわば自己抗体による脳炎のプロトタイプと考えることができる．

グルタミン酸受容体に対する自己抗体

　自己免疫性の脳炎を引き起こす中枢神経系の抗原として最も研究が進んでいるのはグルタミン酸受容体である．イオンチャネル型グルタミン酸受容体は大きく alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid（AMPA）型，カイニン酸型，および N-methyl-D-aspartate（NMDA）型に分類され，さらにそれぞれサブタイプが存在する．1994 年に Rasmussen 脳炎の患者の血清中に AMPA 型受容体に対する抗体が存在することが報告され注目を浴びた[8]．この抗体は後に Rasmussen 脳炎の直接的な原因ではないことが証明されたが，興奮性神経伝達において中心的な役割を担うグルタミン酸受容体に対する自己抗体の発見は，その後この分野の研究に大きな影響を与えることになった．その後 Takahashi らは Rasmussen 脳炎で新たに NMDA 受容体に対する抗体を発見した[9]．NMDA 受容体は NR1 と NR2 の二つのサブユニットからなるヘテロダイマーだが，この抗体は NR2 サブユニットを認識する．自己免疫性辺縁系脳炎や各種の脳炎後てんかんなど様々な疾患でも陽性となることから，その疾患特異性については結論が出ていない．しかし NMDA 受容体は後シナプス電位を形成して記憶や学習に関与するとされ，また抗体陽性例では知能予後が不良であることから，この抗体が何らかの機序により NMDA 受容体を有する神経細胞の障害に関与すると考えられている[10]．この仮説は，神経精神ループスにおいて二本鎖 DNA に対する抗体が NMDA 受容体 NR2 サブユニットと交差性を示し，この抗体がマウスで実際に神経障害を起こすという事実と合致する．さらに 2007 年に Dalmau らは，卵巣奇形腫に伴い辺縁系症状や不随意運動などを呈する特異な脳炎の存在を報告し，患者血清中に NMDA 受容体の NR1, NR2 サブユニットの複合体を認識する抗体が存在することを明らかにした[6)11)]．

表2 自己免疫性脳炎とウイルス関連急性脳症の比較

	自己免疫性脳炎	ウイルス関連急性脳症
先行感染から発症までの期間	数日～2週間	0～2日
発症様式	比較的緩徐な発症	急性発症
意識障害	軽度	高度，急速に進行
けいれん	部分けいれん	全般性けいれん重積
その他の神経症状	精神症状，短期記憶障害，不随意運動，睡眠障害	回復期に時に不随意運動
髄液所見	細胞数軽度増加	細胞数正常
脳波所見	局在性異常	全般性高振幅徐波
MRI 所見	局在性信号異常（大脳辺縁系・基底核）	び漫性異常（脳浮腫，拡散能低下）
予後	知能障害，てんかん，精神症状，高次脳機能障害	四肢麻痺，高度知能障害

自己抗体が関与する脳炎：各論

　自己抗体が関与する脳炎にはいくつかの病型が含まれるが，臨床症状には共通点が見られる（表1）．このことは各病型間にオーバーラップがありうることを示唆しており，これがしばしば診断を困難にする要因となる．従って自己免疫性脳炎を診断する際には類似疾患を注意深く鑑別する必要がある．またウイルス関連急性脳症と比較することでこれらの疾患の特徴を明確にすることができる（表2）．

1）自己免疫性辺縁系脳炎

　古典的な傍腫瘍神経症候群では精神症状や記憶障害など大脳辺縁系，とりわけ海馬・扁桃体などの側頭葉内側の構造に由来する症状を呈することが多く，これらの症例に対して辺縁系脳炎 limbic encephalitis という語が用いられるようになった[4]．自己免疫性辺縁系脳炎の明確な定義は定まっていないが，精神症状・けいれん・記憶障害の三徴に加えて，画像上大脳辺縁系の異常を認め，さらにヘルペス脳炎など既知の原因を除外したものを指すのが一般的である[12]．しばしば用いられる Gultekin らによる傍腫瘍性辺縁系脳炎の診断基準には，主要三徴に加えて腫瘍の証明，神経画像または脳波上の辺縁系の異常が含まれている[13]．先行感染は必ずしも認められず，初発症状は精神症状や記憶障害が多いため，成人では精神疾患や痴呆性疾患を疑われることも少なくない．けいれんは側頭葉内側に由来する複雑部分発作が多い．意識障害はあっても軽度の場合が多く，高度の意識障害が主症状の場合は他の疾患を考えるべきである．なお，我が国で小児の辺縁系脳炎として報告された症例は，成人例と比較してけいれんと意識障害が顕著な例が多い[14]．

　辺縁系脳炎という概念は国際的に統一されておらず，我が国では感染性脳炎も含めた幅広い概念として定義づけられている．この結果，ウイルス関連急性脳症の中で行動異常を呈する例がしばしば誤って辺縁系脳炎と診断されていることに懸念が広がっている．一方で欧米では自己抗体から自己免疫性辺縁系脳炎を分類するという考え方が主流である．辺縁系脳炎と関連する古典的な抗神経抗体は抗 Hu 抗体，抗 Ma2 抗体，抗 CV2/CRMP5 抗体，抗 amphiphysin 抗体などを含むが，ほとんどの例は悪性腫瘍を持つ成人患者に限られる[13]．しかし近年確立した概念である VGKC 抗体陽性辺縁系脳炎は小児例もしばしば報告されている[5][15]．これらは辺縁系脳炎の中核症状に加え低ナトリウム血症を合併することが多く，また自律神経症状や低体温なども認めうる．中枢神経症状以外にもミオトニー，末梢神経障害等を合併する場合があり，Morvan 症候群として知られている[16]．神経画像所見は典型的な辺縁系の異常を示す場合が多く，免疫調整療法に対する反応性は良好とされる．最近，この病型における責任抗原は実は VGKC ではなく leucine-rich, glioma-inactivated 1（LGI1）という分子であるという説が出されている[17]．

　この他にも，辺縁系脳炎に関連する自己抗体として，抗 AMPA 型グルタミン酸受容体[18]，抗 Glutamic acid decarboxylase（GAD）抗体[19]，抗 Gamma-aminobutyric acid（GABA）-B 受容体抗体[20]などが明らかになっている．膠原病に辺縁系脳炎を合併する場合があり，全身性ループスエリテマトーデス（SLE），Sjögren 症候群に合併した例が報告されている[21][22]．橋本病に合併する脳症は意識障害・精神症状・けいれんなどを呈するが，辺縁系脳炎の病像を呈することもある．血清中にαエノラーゼの N 末端領域に対する抗体（抗 NAE 抗体）が見いだされ，診断に有用な疾患特異的マーカーである[23]．また抗てんかん薬をはじめとする薬剤による hypersensitivity syndrome において，皮疹の出現からやや遅れて辺縁系脳炎を発症する例がある．皮疹の

2～3週間後にヒトヘルペスウイルス6型（HHV-6）DNA が血中に検出され，その後抗体価の上昇を伴う場合が多いことから，HHV-6 の再活性化が関与すると考えられている[24]．幹細胞移植などに伴う免疫抑制状態の小児で，HHV-6 の再活性化による辺縁系脳炎が知られているが[25]，これについては感染性脳炎に分類されるためここでは割愛する．

2）抗 NMDA 受容体脳炎[26]

抗 NMDA 受容体脳炎は卵巣奇形腫を持つ若年女性に多く見られ，先に述べた血清中の NR1, NR2 ヘテロダイマーを認識する抗体が原因と考えられている[6]．この抗体は単独の NR1, NR2 サブユニットには強い親和性を有さず，ヘテロダイマーの三次構造を認識する．

抗 NMDA 受容体脳炎は若年女性に多く，4割は18歳未満の小児に発症する．臨床的には，発熱が前駆症状としてみられた後に，大部分が不安，興奮，異常行動，せん妄等の精神症状で発症する．短期記憶障害，けいれんも見られ，時にけいれんは難治化する．このような状況（精神病期）が1～3週間程度続いた後に，無反応期と呼ばれる状態に移行する．この時期には反応性が低下し，開眼しているが自発運動や発語は乏しく，受動的な姿勢を保持するカタレプシーが認められることも多い．同時に顔面，特に口周囲のジスキネジア（強制的笑い，咀嚼様運動，開閉口の反復，瞬目など），常同的・反復的な異常運動，自律神経症状（心拍数・血圧の著しい変動など）がしばしば認められ，中枢性無呼吸のため人工呼吸管理を要することも少なくない．このような状況が数週間から長い場合は一年以上にわたって持続する．しかしその後不随意運動の軽減とともに意識レベルは徐々に回復し，急性期を乗り切ることができれば最終的には多くの例が社会復帰可能なレベルにまで回復する．経過中に再発を認める例がある．

髄液では急性期に細胞数や蛋白が軽度上昇する．MRI では辺縁系に異常信号を認めることはむしろ少なく，大脳皮質や基底核の散在性 T2 延長病変や髄膜の増強効果も認めうる．腫瘍の検索は本疾患の診断に極めて重要であり，女性例では大部分で卵巣奇形腫が発見される．急性期に画像上奇形腫を確認できず後になって顕在化する場合もあることから，画像検査を繰り返し行う必要がある．奇形腫は神経系組織を含み，NMDA 受容体の発現が見られる[27]．

治療として免疫調整療法は一過性に有効な場合があるものの，単独では効果が不十分である．基本的に腫瘍の摘除が最も有効であり，免疫調整療法との併用が効果的とされている．一方で何ら治療を行わなくても自然回復する例があり，腫瘍の残存にもかかわらず抗体が陰性化した症例もある．しかし本疾患は急性期に

は重篤化し生命を脅かすことから，可及的速やかに腫瘍の摘除を目指すべきと考えられる．

小児の抗 NMDA 受容体脳炎は成人と比較していくつかの特徴がある．腫瘍非合併例が相対的に多く，また男児の割合が多い．症状としてはけいれん，言語障害，不随意運動を呈する例が多く，反対に自律神経症状や中枢性無呼吸を呈する例は少ない[28]．

奇形腫組織が NMDA 受容体を発現していることから，これが全身の免疫系により認識され抗体が産生されることで発症すると考えるのが自然であるが，先行感染を認める例が多いことや，抗体が自然消失する例が存在することは，腫瘍の存在以外に抗体の産生を修飾する因子が関与することを示唆している．

3）嗜眠性脳炎（Encephalitis lethargica）

嗜眠性脳炎は，先行する咽頭炎などの感染症に続いて睡眠障害・基底核症状(特にパーキンソニズム)・精神症状の三徴を呈するもので，1910 年代に流行したパンデミック・インフルエンザ(いわゆるスペインかぜ)に伴って多発したことで有名である[29]．現在では嗜眠性脳炎は小児を中心にインフルエンザとは無関係に散発的に発生している[30]．咽頭炎などの先行感染に引き続いて亜急性に発症することが多い．睡眠障害は過眠を示すことが多いが反対に不眠となる場合もある．開眼しているのに外的刺激に対して無反応となり，意識障害と見誤られる場合がある．基底核症状としてはパーキンソニズムが有名であるが，ジストニア・舞踏運動など様々な運動障害も出現し，これらが前景に立つ症例を dyskinetic type と呼ぶ場合がある．Immune mediated chorea encephalopathy syndrome という名称もこれとほぼ同義と考えてよい[31]．この他には精神症状に加えて眼筋麻痺，視覚障害，無動無言症，中枢性呼吸障害などがしばしば認められる．画像所見は目立った異常を呈さないことが多い．免疫調整療法は一部で有効だが，効果の発現には時間がかかることがある．ドーパミン神経系に影響を与える薬剤に対して極めて感受性が高く，これらの使用により症状の急激な増悪を来しうるので注意が必要である．

最近 dyskinetic type の嗜眠性脳炎の患者血清で抗 NMDA 受容体（NR1, NR2 サブユニット複合体）抗体が陽性を示す例が相次いで報告されており，臨床的にも抗 NMDA 受容体脳炎と症状の共通性が認められる．よって両者は連続したスペクトラムを形成することが示唆され，抗 NMDA 受容体脳炎という疾患概念が臨床的に多様性を示す可能性が出てきた[32]．

糸見，Okumura らは3～7日程度の比較的緩徐な経過で進行する意識障害，けいれん，行動異常を主徴とする亜急性脳症を報告した[33][34]．急性期には画像上の異常は乏しいが，回復期には軽度の脳萎縮と前頭葉優位

の血流低下を示し, ほとんどの症例で知能障害を残す. 亜急性脳症と嗜眠性脳炎との関係は明らかでないが, 臨床経過に類似点があることから両者が一部オーバーラップする可能性は否定できない.

4) 難治頻回部分発作重積型急性脳炎（Acute encephalitis with refractory, repetitive partial seizures, AERRPS）[35][36]

難治頻回部分発作重積型急性脳炎（AERRPS）は1986年に粟屋・福山により「特異な脳炎・脳症後てんかん」として提唱された疾患概念である[37]. 通常の脳炎・脳症後てんかんは一般に数か月～数年の潜伏期間を経て発症するが, 脳炎・脳症の急性期から極めて難治な部分発作が持続し, 潜伏期間を持たずに難治てんかんに移行する症例が存在することを彼らは指摘した. 後に塩見らも類似の病態を「頻回の痙攣を伴う脳炎」として報告している. 両者は共通点が多くほぼ同一の疾患概念と考えられ, 国際的な認知度を高める目的で AERRPS という英語名が提唱された[37]. なお, この疾患の原因は解明されておらず自己免疫性脳炎であるかどうかも不明であるが, 辺縁系脳炎や嗜眠性脳炎との類似性から免疫学的機序の関与が疑われるので, ここに含めることとした.

本症は1歳未満の乳児にはまれで, 学童期にピークがある. 先行感染から数日程度の潜伏期間を経て, 多くの場合けいれんまたは意識障害で発症する. けいれんは次第に頻度を増し, 5～15分間隔で周期的に出現するようになる. 発作型は例外なく部分発作あるいは二次性全般化発作で, 眼球偏位, 顔面間代, 片側四肢の間代などが多い. けいれんは極めて難治であることが特徴で, 通常の抗てんかん薬やベンゾジアゼピン系薬剤では十分抑制されないため, ピーク時にはバルビタール系薬剤の大量持続点滴が必要となる. けいれんは数週間～数か月かけて徐々に軽快するが, 潜伏期間を経ることなく難治てんかんに移行する. 急性期には大部分の例で持続性の発熱と意識障害を認め, 回復期に様々な不随意運動が出現することがある. 後遺症として知的障害, 精神症状, 高次脳機能障害などが高率に出現する. 重症例では痙性四肢麻痺など重度の神経学的後遺症を残し, 予後は一般に不良である.

髄液で軽度の細胞数増加, タンパク上昇, 血清フェリチンやネオプテリンの異常高値が見られる場合がある. 脳波では病初期は高振幅徐波が主体であるが, 発症後1～2週間以内に周期性てんかん放電に似た律動的異常波に出現する[35]. 発作時脳波の捕捉には amplitude-integrated EEG が有用である[38]. MRI では海馬・扁桃体や島皮質に T2延長病変を認めることがある. 本疾患に特異的な自己抗体は知られていない.

治療は急性期にはバルビタール系薬剤の大量投与を中心とした抗けいれん療法が中心となる. 静注薬からの離脱に際して非経静脈的フェノバルビタール大量療法が有効で, 急性期以降はゾニサミド, 臭化カリウムの有効例がある. 免疫調整療法の効果については十分検討されていない.

AERRPS に類似した疾患概念は我が国のみならず世界中で報告されているが, それぞれ異なる名称が用いられ統一されていない[39][40].

5) その他の自己免疫性脳炎類縁疾患

A群溶血性連鎖球菌感染症の合併症として古くから Sydenham 舞踏病が知られているほか, チック障害・トゥレット障害・強迫性障害を主徴とする pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) が注目を浴びている[41]. 不随意運動のメカニズムとして A群溶血性連鎖球菌の N-acetyl-beta-D-glucosamine に対する抗体が産生され, この抗体が基底核神経細胞に発現されている lysoganglioside と交差性を示すことが原因と考えられている[42].

自己抗体と免疫性神経疾患

1) 自己抗体の産生機序

神経疾患に限らず, 自己免疫疾患では様々な自己抗体が産生され, これらの中には高い疾患特異性から診断に重要なマーカーとして確立しているものも多い. しかしこれらの産生機序については十分に明らかにされたとは言いがたい. Guillain-Barre 症候群の一型である急性運動性軸索型ニューロパチーで高率に陽性となる抗ガングリオシド抗体は, *Campylobacter jejuni* が持つ糖脂質と交差性を示し, 感染により産生された抗体が末梢神経軸索表面に存在するガングリオシドを認識するために発症することが証明されている[43]. このような分子相同性と呼ばれるメカニズムは自己抗体が産生される機序として古くから重視されてきたが, 全ての自己抗体が分子相同性に基づいて産生されるわけではない. 重症筋無力症では抗アセチルコリンレセプター抗体がしばしば陽性となるが, 重症筋無力症では免疫反応に負の制御をもたらす制御性 T 細胞の質的・量的異常があり, この結果胸腺を中心に自己反応性 T 細胞の異常な増殖が起こり, 胸腺の腫大や自己抗体の産生をもたらすという考え方がある[44]. 全身性ループスエリテマトーデス (SLE) や皮膚筋炎などの膠原病においては, 抗核抗体, 抗 DNA 抗体, Jo-1 抗体など様々な自己抗体が血清中に検出されるが, これらの疾患の発症には I 型インターフェロンの過剰産生が重要な役割を果たすことが明らかになっている[45].

このように自己抗体の産生機序が多様であるという

事実は，自己免疫性脳炎にも当てはめて考える必要がある．抗 NMDA 受容体脳炎の場合は卵巣奇形腫が NMDA 受容体を発現していることが証明されており，この場合は免疫細胞による抗原の直接的な認識が抗体産生を引き起こすことは明らかである．しかし SLE や Sjögren 症候群に辺縁系脳炎が合併するという事実から，一部は I 型インターフェロンの過剰状態が関与している可能性もある．

　2）自己抗体の病原性

　もう一つ注意すべきなのは，自己抗体が必ずしも病原性を持つとは限らないという点である．神経細胞に対する抗体を例に挙げると，一般に細胞表面の抗原に対する自己抗体は直接的な病原性を有するとされている．具体的には神経細胞表面のチャネルや受容体に対する抗体であり，抗 VGKC 抗体，抗 NMDA 受容体抗体などがこれにあたる．これに対して，細胞内の抗原に対する自己抗体の場合は，抗体自身の病原性は乏しいと考えられている．これには辺縁系脳炎に関連する古典的な抗神経抗体が含まれる．抗 Hu 抗体による傍腫瘍性神経症候群においては T 細胞を介する免疫反応が中心と考えられているが，これには異論もある[7]．

　自己免疫性神経疾患の中で抗体だけが単独で疾患を引き起こすことはむしろ稀と考えられている．動物モデルでは，抗体の投与のみでは軽度の病理学的変化を再現することはできても多くの場合症状を呈することはなく，発症には抗原特異的 T 細胞の援助が必要である．一方で EAE などのモデルにおいて標的抗原に対する抗体の同時投与は重症化をもたらす場合が多く，細胞性免疫が中心の自己免疫疾患においても自己抗体が疾患促進的に働くことは十分考えられる．

　抗体が細胞表面の抗原に結合するだけでは細胞は必ずしも死に至らず，補体の作用や，さらには抗体や補体に対するレセプターを持つ免疫細胞の作用が加わってはじめて有効に細胞を傷害できる．しかし自己抗体の作用機序はこのような細胞傷害作用だけとは限らない．例えばチャネルや受容体に対する抗体がこれらの表面分子を介するシグナルを抑制することで細胞の機能に影響を与える場合がある．反対に受容体に対する抗体のアゴニスト作用が病態を引き起こすことも考えられる．抗 VGKC 抗体や抗 NMDA 受容体抗体などでは，詳細は依然不明であるもののこのような抗体による機能的傷害が重要と推測されており，これらの抗体により引き起こされる自己免疫性脳炎において標的器官の損傷が比較的軽度であり臨床的にも回復が見られやすいことと関係しているかもしれない．

　細胞内の抗原に対する抗体が果たす役割についてはさらに謎の部分が多い．これらの抗体が産生される機序として，細胞の壊死により細胞内の抗原が細胞外に

放出される結果，免疫細胞がこれらを認識して抗体産生を導くという考え方がある．そうであるとすれば，これらの抗体は病原性を持たない bystander であり，むしろ細胞死による過剰な免疫反応が惹起されるのを抑制する働きを持っているのかもしれない．このことは治療という観点からも重要で，自己抗体を除去するだけでは不十分である可能性を示している．傍腫瘍性神経症候群の場合，細胞表面の抗原に対する抗体が関与する群では免疫調整療法に対する反応性が比較的よい（抗 NMDA 受容体脳炎は例外）が，細胞内抗原に対する抗体の場合は効果を期待しがたいとされている．

未解決の問題と今後の展望

　自己免疫性脳炎に関する知見の多くは症例を中心とした臨床研究に基づいており，分子レベルでの病態解明は進んでいないのが現状と言える．最大の理由は，傍腫瘍神経症候群を含めた疾患の動物モデルが作製されていない点である．また Hu 抗体などの古典的な抗神経抗体についてはその抗原が未だ明らかにされておらず，実際に抗神経抗体の同定は今でも脳組織を用いた免疫組織化学に頼らざるをえない．従って様々なタイプの自己免疫性脳炎において自己抗体とその責任抗原を明らかにし，臨床像との相関を明らかにしていかなければならない．さらには自己抗体産生のメカニズムについても，サイトカインやインターフェロン等の液性因子や制御性 T 細胞等の免疫細胞の動態を含めて検討する必要がある．その際に，SLE など研究が進んでいる疾患をモデルとすることが病態解明への重要な糸口になると推定される．

　治療についても検討の余地が数多くある．傍腫瘍神経症候群に対する腫瘍の摘除を除けば自己免疫性脳炎に対する根本的治療は存在せず，また副腎皮質ステロイドや免疫グロブリン療法などの免疫調整療法も真に効率的な治療であるかどうかは未だ不明である．自己抗体の排除を目的とした血液浄化療法の効果が必ずしも思わしくないことからもわかるように，単に抗体のみに目を向けるだけでは解決は期待できない．今後は各々の病態に基づき，モノクローナル抗体なども含めた特異性の高い治療法の開発が望まれる．

　抗体が関与する自己免疫性脳炎は特に小児科領域においては，サイトカイン・ストーム関連急性脳症や痙攣重積型脳症などと比べて認知度が低く，正確に診断されていないケースも多数あると推定される．個々の疾患の頻度は高くないが，診療の場では上記の急性疾患以上に臨床医を悩ませているというのが実情であろう．しかし臨床所見を正確に記載し，血清や髄液の免疫学的解析を行うことにより，症例を一つ一つ積み重

ねていくことが病態解明への第一歩であることは言う
までもない．本稿をきっかけとして自己免疫性脳炎に
対する認識が少しでも広まり，臨床と基礎研究の有機
的なつながりが生まれることを期待したい．

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