

Characteristics of epilepsy and immunological markers in epileptic patients after influenza-associated encephalopathy

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Abstract

Objective: This study aimed to elucidate the electro-clinical characteristics of epilepsy and immunological markers in patients with epilepsy after influenza-associated encephalopathy/encephalitis (IAE). **Methods:** Eighteen patients with epilepsy after IAE (8 males, 10 females; mean age of onset 6.4±6.4 years) were studied. Antibodies to glutamate receptor (GluR) $\epsilon 2$ (NR2B) were examined by immunoblot and ELISA. Cytokines were measured by BioPlex. **Results:** Mean interval between IAE and epilepsy onset was 63.2 ± 95.0 days (mean ± SD). In 16 of 18 patients, complex partial seizures were observed. Most complex partial seizures were of short durations and showed few lateralizing signs. Interictal discharges were seen in the frontal area in 7 of 14 patients. Ictal EEG showed rapid propagation to bilateral hemispheres. Patients with higher cerebrospinal fluid levels of anti-GluR $\epsilon 2$ antibodies, higher cerebrospinal fluid levels of IL-1 β , soluble tumor necrosis factor receptor 1 and IFN- γ during chronic stage, had higher frequency of epileptic seizures.

Conclusion: This study indicates that the frontal lobes are susceptible to rapid epileptogenesis after IAE, and that epileptic partial seizures after IAE had characteristics resembling generalized seizures. Presence of anti-GluR $\epsilon 2$ antibodies and elevated IL-1 β , TNF α , and IFN- γ in cerebrospinal fluid may be associated with intractability of epileptic seizures.

INTRODUCTION

Sequelae affecting the central nervous system are common after influenza-associated encephalopathy / encephalitis (IAE). The death rate of acute disease is approximately 30%. Even among the surviving patients, approximately 25% have neurological impairment¹, and epilepsy occurs at a high frequency.² Rather than a direct effect of viral infection, TNF α and other inflammatory cytokines are reported to play an important role in the mechanism of IAE, and rapid progressive apoptosis of neuron is responsible for IAE.³ Therefore, the mechanism of epilepsy after IAE may differ from epilepsy after encephalitis with direct viral involvement of the cerebral parenchyma, as seen in herpes simplex virus (HSV)-1 encephalitis. The semiological characteristics, pathophysiology and seizure outcome of epilepsy after IAE remain unclear.

Glutamate receptor (GluR) is a receptor for glutamic acid, a neurotransmitter, and is

classified into ion channel types and metabotropic types.^{4,5} Ion channel type GluRs are classified pharmacologically into NMDA and non-NMDA types. NMDA type GluRs (NR) have a tetrameric structure of heterogeneous subunits, composed of the essential GluR $\zeta 1$ (NR1) subunits and GluR $\epsilon 1-4$ (NR2A-2D) or GluR $\chi 1-2$ (NR3A-3B) subunits. Antibodies to GluR $\epsilon 2$ (NR2B) have been detected in patients with various conditions such as Rasmussen syndrome and non-herpetic acute limbic encephalitis. Antibodies to NMDA type GluRs have been reported to cause internalization of NMDA type GluR complexes, resulting in dysfunction of various neurological pathways.⁶

Recent immunological research in epilepsy has revealed the contributions of cytokines to epileptogenesis and ictogenesis.⁷ Interleukin (IL)-1 and tumor necrosis factor (TNF α) are known to be proconvulsant factors. Here we studied the clinical features, ictal and interictal EEGs, MRI findings and outcome of epileptic seizures after IAE, and examined immunological markers

including anti-GluR ϵ 2 antibodies and cytokines in cerebrospinal fluid (CSF). Since TNF α is unstable, soluble tumor necrosis factor receptor 1 (sTNFR1), which is the receptor of TNF α and indicates the levels of TNF α was also measured in our study.

METHODS

Patient background

Between January 2000 and July 2009, 15 patients were treated in our hospital for epilepsy after IAE, and 8 patients had samples and clinical data sent to our center for the purpose of autoantibody testing. Of these 23 patients, those with only convulsions induced by fever and those with a follow-up period less than 3 months were excluded. Eventually, 18 patients (8 males, 10 females) were studied. The age (mean \pm SD) at the last clinical follow-up for epilepsy was 11 \pm 9 years, and the interval (mean \pm SD) from IAE to last follow-up was 5.4 \pm 6.3 years. The type of IAE was widespread encephalitis in 4 patients, localized encephalitis in one patient, acute necrotizing encephalopathy in one patient, Reye syndrome in one patient,

mild type encephalopathy in 2 patients, unknown in 8 patients.

Influenza virus infection was diagnosed by a positive rapid test for influenza antigen in 17 of 18 patients, and by a two-fold increase of serum antibodies to influenza virus in the remaining patient. The causative influenza virus was type A in 8 patients, type B in 2 patients, and unknown in the remaining 8 patients because the information was not provided by the referring doctors. Three patients received influenza vaccination for that season, 6 patients did not receive vaccination, and no information was available from the remaining 9 patients.

Soon after the onset of influenza, all patients subsequently developed encephalopathy/encephalitis. The age (mean \pm SD) at onset of IAE was 6.4 \pm 6.4 years, and 11 patients (61%) were aged 1-5 years at onset (Figure 1A). The first neurological symptom of IAE was febrile convulsive seizures in 50% of patients with onset age at 1-5 years, and impaired consciousness in 25% of patients with onset age at 6-15 years (Figure 1B). Behavioral abnormality was frequently the first neurological symptom in

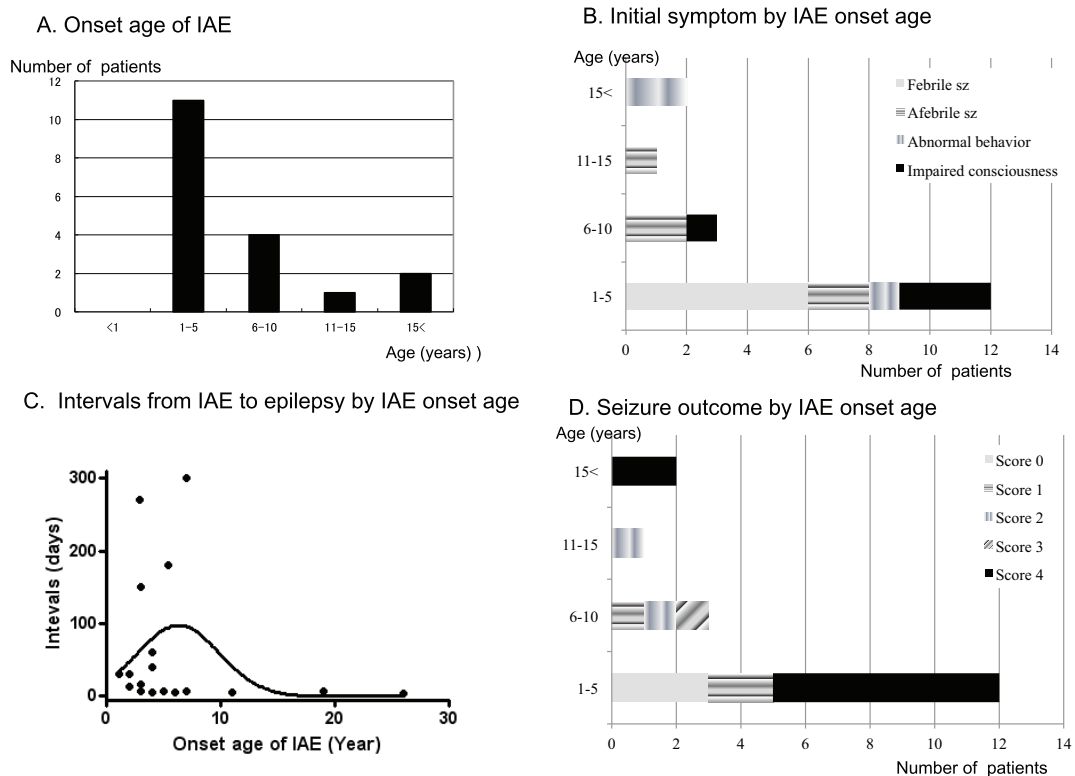


Figure 1. Clinical data of patients with epilepsy after influenza-associated encephalopathy (IAE). **A:** Onset age of IAE. **B:** Initial symptom of IAE according to IAE onset age. **C:** Intervals from IAE to epilepsy according to IAE onset age. **D:** Seizure outcome according to IAE onset age. Score 0 (daily seizures), 1 (weekly seizures), 2 (monthly seizures), 3 (yearly seizures), 4 (no seizures).

patients with onset age older than 11, which mimics the initial symptom of limbic encephalitis. Of 11 patients whose initial neurological symptom was convulsive seizure, 4 had status epilepticus. Motor development outcome demonstrated a bipolar trend, with three of 16 patients having severe quadriplegia, and 13 patients free from motor function impairment. The degree of cognitive outcome varied.

Electro-clinical evaluation of epileptic seizures

Ictal semiology of epileptic seizures was evaluated by reviewing medical records and video-EEG recordings (seven patients). Ictal EEGs were evaluated by reviewing video-EEG recordings in seven patients.

Outcome evaluation

Seizure outcome was classified into five categories, score 0 (daily seizures), 1 (weekly seizures), 2 (monthly seizures), 3 (yearly seizures) and 4 (no seizures).

Examination of antibodies to GluRε2 (NR2B)

Antibodies against the GluRε2 molecule were assayed as described previously, by immunoblot using whole molecule of GluRε2 (NR2B) protein as antigen (anti-GluRε2 antibody)⁸ and by ELISA using synthetic peptides of the N-terminal and C-terminal of GluRε2 as antigens (anti-GluRε2-NT2 antibody and anti-GluRε2-CT antibody, respectively).⁹ Control levels of anti-GluRε2 antibodies were obtained by measuring the antibody levels in the CSF of control patients without epilepsy or IAE (n = 9).

Measurements of cytokines, chemokines and growth factors

The following immunological markers were measured by the BioPlex system (BioRad): IL-1β, IL-1r, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin, basic fibroblast growth factor, granulocyte colony-stimulating factor (CSF), granulocyte macrophage CSF, interferon (IFN)-γ, interferon gamma-induced protein (IP)-10, monocyte chemotactic protein (MCP)-1, MIP-1α, MIP-1β, platelet-derived growth factor (PDGF)β, regulated upon activation, normal T cell expressed and secreted (RANTES), TNFα, and vascular endothelial growth factor (VEGF). Soluble TNFR1 was determined using an ELISA kit (Cosmo Bio

BMS03). Control levels of these markers were obtained by measuring the respective levels in the CSF of control patients without epilepsy or IAE (n = 9)

Statistical analyses

Statistical analyses were performed by Mann-Whitney test. Data are expressed as mean ± SD.

RESULTS

Clinical features of epilepsy

The mean interval from IAE to onset of epilepsy was 63.2 ± 95.0 days (Table 1). Epilepsy occurred within one month after IAE in two-thirds of all patients, but some patients with onset of IAE around 5 years of age had longer intervals of more than 100 days (Figure 1C).

The epileptic seizure type at the last follow-up could be studied in 17 of 18 patients, while the data of one patient was not available. The seizure type was complex partial seizure (CPS) alone in 9 patients, CPS plus secondary generalized tonic-clonic seizure (sGTC) in 5, CPS plus simple partial seizure (SPS) in 2, and sGTC alone in one.

Epilepsy was classified as symptomatic localization-related epilepsy in all 17 patients with confirmed seizure types.

Interictal EEG

Interictal discharges could be studied in 14 patients. Discharges in bilateral frontal lobes were observed in 3 patients, discharges in unilateral frontal lobe in 2 patients, and bilateral independent frontal spikes in 2 patients (Table 1). In 2 patients who had no interictal discharge, seizures were controlled for several years after IAE.

Semiology of epileptic seizures

Of 2 patients with SPS, one manifested nausea, and the other inability to sustain thoughts. No patients had “postural seizures”; i.e., supplementary motor seizures, focal motor seizures or other typical seizures of frontal lobe origin, although interictal discharges were frequent in frontal regions. In seizures documented by video-EEG recordings, lateralizing signs were not observed in the very initial stage, but 4 of 7 patients became to show lateralizing signs after initial stage in the recorded seizures (Table 1).

Table 1: Clinical characteristics of the study patients

Pt	Sex	Type of IAE	Onset of epilepsy		Classification		Video-EEG recordings		Antibodies to GluRε2 (CSF)			Seizure outcome			
			Age (yr)	Latency from IAE (days)	Seizure	Epilepsy	Interictal EEG	Ictal EEG	Ictal semiology	IgG (IB)	IgM (IB)	NT2 (ELISA)	CT (ELISA)	Age	Score
1	M	ANE	2.9	270	sGTC	unknown	bilateral frontal sharp, bilateral diffuse spike	ND	ND	ND	ND	ND	ND	9	4
2	F	unknown	2	30	CPS	SPE	multifocal spikes & multifocal sharp waves	Fig. 3A: small spikes in bilateral frontal→diffuse attenuation→low voltage rhythmic waves in F3F4Fz	slight extension of shoulders and body trunk→antelexion of head and trunk→elevation of upper limb forward	ND	ND	ND	ND	4	0
3	F	unknown	3	7	unknown	unknown	unknown	ND	ND	ND	ND	ND	ND	4	4
4	F	unknown	7	7	CPS	SPE	unknown	ND	ND	-	-	ND	ND	7	2
5	F	WE	11	6	CPS, sGTC	SPE	bilateral frontal spike with slow	Fig. 3B: sharp wave in F3→diffuse attenuation→low voltage rhythmic waves in bil frontal regions	open eyes→extension of right upper extremities, twitching right mouth corner→right version of eyes and right limb hypermovement	ND	ND	ND	ND	25	2
6	F	WE	4	6	SPS, CPS	SPE	multifocal spikes & multifocal sharp waves	ND	ND	-	-	0.34	0.378	4	4
7	M	unknown	4	60	CPS	SPE	bilateral frontal dominant spikes	Fig. 3C: slow waves predominantly in bilateral frontal regions→diffuse attenuation	vibration of bilateral upper limbs in sleep	+	-	0.624	0.619	15	0
8	F	unknown	5.4	180	CPS	SPE	multifocal spikes with slow waves	Fig. 3D: sharp waves in Fp1Fp2→diffuse attenuation	head pulled back→dropout	+	-	0.136	0.168	7	0
9	F	unknown	6	5	CPS	SPE	left frontal spikes	ND	ND	-	-	0.156	0.298	10	3
10	M	unknown	1.1	30	CPS, sGTC	SPE	left temporal spikes (T3T5 spike)	slow waves in the F3FP1→slow waves in left hemisphere	motionless→right rotation of head, tonic convulsion of right upper limb	-	-	0.28	0.372	8	4
11	M	Reye syd.	3	150	CPS	SPE	right frontal sharp waves	ND	ND	ND	ND	ND	ND	28	4
12	M	mild	2.1	14	CPS, sGTC	SPE	unknown	ND	ND	+	+	0.237	0.237	2.5	1
13	M	LE	26	4	CPS, SPS	SPE	no ictal discharge	ND	ND	ND	ND	ND	ND	32	4
14	M	mild	3	16	CPS sGTC	SPE	no ictal discharge	ND	ND	ND	ND	ND	ND	6	4
15	M	WE	5	7	CPS	SPE	bilateral independent frontal spikes	Sp2 rhythmic waves at onset	loss of consciousness→tonic convulsion of right upper limb	+	+	0.345	0.302	13	1
16	F	unknown	7	300	CPS, sGTC	SPE	bilateral independent frontal spike with slow waves	Continuous Sp-W or slow waves in left frontal region	loss of consciousness→right version of eyes	+	-	0.554	0.563	7	1
17	F	WE	19	7	CPS	SPE	unknown	ND	ND	ND	ND	ND	ND	19	4
18	F	mild	4	40	CPS	SPE	T5	ND	ND	ND	ND	ND	ND	10	4

ANE; acute necrotizing encephalopathy; WE, widespread encephalitis; LE, localized encephalitis; SPS, simple partial seizure; CPS, complex partial seizure; sGTC, secondarily generalized tonic-clonic seizure; ND, not done; CSF, cerebrospinal fluid; Sp-W, spike with slow; Age, years old; Latency, latency from IAE to epilepsy onset (days); score, score of epileptic seizure in Table 1; IB, immunoblot assay; SP, sphenoidal electrode.

Ictal EEG

The time lag (mean \pm SD) from the start of ictal discharge to appearance of clinical seizure symptoms was 1.90 ± 1.36 seconds. The mean duration of ictal event was 80.1 ± 73 seconds. In 4 (Patient. 2, 5, 7 and 8) of 7 patients evaluated for ictal EEG, initial epileptic discharges appeared simultaneously in 4 or more leads of the frontal regions (Table 1). The frontal dominant ictal discharges were followed by diffuse or focal attenuation of electrical activity bilaterally, with or without fast activities for usually several seconds (Figures 2A-D). In 2 other patients (Pts. 10, 16), initial ictal discharges appeared in the left frontal region. In the remaining patient (Patient 15), initial ictal discharges were recorded as rhythmic waves in right sphenoidal electrode. Multifocal epileptic foci were not found on ictal EEG in any of the patients, although multifocal or bilateral and diffuse interictal discharges were observed in almost all patients.

MRI

In the chronic stage of epilepsy, atrophic MRI lesions were observed in 5 of 18 patients, and high intensity lesions on FLAIR MRI were found in 2 of 18 patients. The lesions were frontal lobe dominant in 3 of the 7 patients (atrophy in one, and high intensity lesion in 2).

There was no correlation between characteristics of MRI and clinical manifestation of IAE.

Epileptic seizure outcomes

At the last follow-up, epileptic seizures persisted in 8 of 18 patients, and patients with younger onset of IAE tended to have frequent seizures (Figure 1D). Patients with onset age up to 5 years had bipolarized seizure outcome: almost half (7 of 12) of these patients were seizure-free, while the other half had high seizure frequencies at weekly or daily levels.

Nine patients received prophylactic antiepileptic drugs after IAE, but their epileptic seizure outcome was not different from that of patients not treated prophylactically. Antiepileptic drugs succeeded to control seizures in 9 patients: carbamazepine was effective in 4 patients, and valproic acid in 5 patients.

Seizure outcome and immune markers in CSF

In the chronic stage after IAE, CSF study was performed in 9 patients at 46 ± 53 months (mean \pm SD) after onset of IAE. Of 9 patients,

5 were positive for anti-GluR ϵ 2 IgG antibodies (immunoblot), and 2 were positive for anti-GluR ϵ 2 IgM antibodies (immunoblot). Seizure frequency (score of epileptic seizures) was not related to the presence of anti-GluR ϵ 2 IgM antibodies in CSF ($p = 0.13$), but was significantly higher in patients with anti-GluR ϵ 2 IgG antibodies in CSF ($p = 0.02$) (Figure 3A, B). Seizure frequency was not related to the presence of IgM or IgG antibodies to GluR ϵ 2 in serum (Figure 3C, D). Measurements of CSF levels of anti-GluR ϵ 2-NT2 and -CT antibodies in CSF showed that patients with higher levels of antibodies to GluR ϵ 2 appeared to have poorer seizure outcome (Figure 4A, B). Exceptionally, Patient 8 had antibody levels of control subjects, but this patient had daily seizures (score 0) (Table 1).

Study of cytokines in CSF showed that seizure outcome appeared to be poorer in patients with higher levels of IL-1 β , IFN γ and sTNFR1 in CSF (Figure 4C-E). Other cytokines, chemokines or growth factors examined by BioPlex were not related to seizure outcome (data not shown). Although Patient 8 who had daily seizures had low anti-GluR ϵ 2 antibodies at control levels, she had extremely high levels of IL-1 β (2.22 pg/ml), IFN γ (81.52 pg/ml), and sTNFR1 (1.16 ng/ml). Patient 7 who also had daily seizures had high levels of anti-GluR ϵ 2 antibodies and low sTNFR1 at control level. Patient 16 with weekly seizure had medium levels of antibodies to GluR ϵ 2, and low IL-1 β , IFN γ and sTNFR1 at control levels. Patient 15 with weekly seizure had higher levels of antibodies to GluR ϵ 2-NT2, and low cytokines and sTNFR1 at control levels. Patient 12 with weekly seizure had low anti-GluR ϵ 2 antibodies and cytokines at control levels.

DISCUSSION

Epileptic seizures in patients with epilepsy after encephalitis/ encephalopathy (EAE) are often intractable. Among 383 pediatric patients admitted between 1993 and 1994 to our epilepsy center for the treatment of intractable epilepsy, the most frequent causal disease was EAE (10.4%).¹⁰ In 67 consecutive patients with EAE in our center, the major causal microbe was influenza virus (21%), followed by HSV (10%).¹⁰ Therefore, understanding of the clinical characteristics and pathophysiology of epilepsy after IAE is important to improve outcome of the disease.

The mean Interval from IAE to epilepsy onset was 63.2 days, and all patients had onset of epilepsy within one year after IAE. On the other

Figure 2A

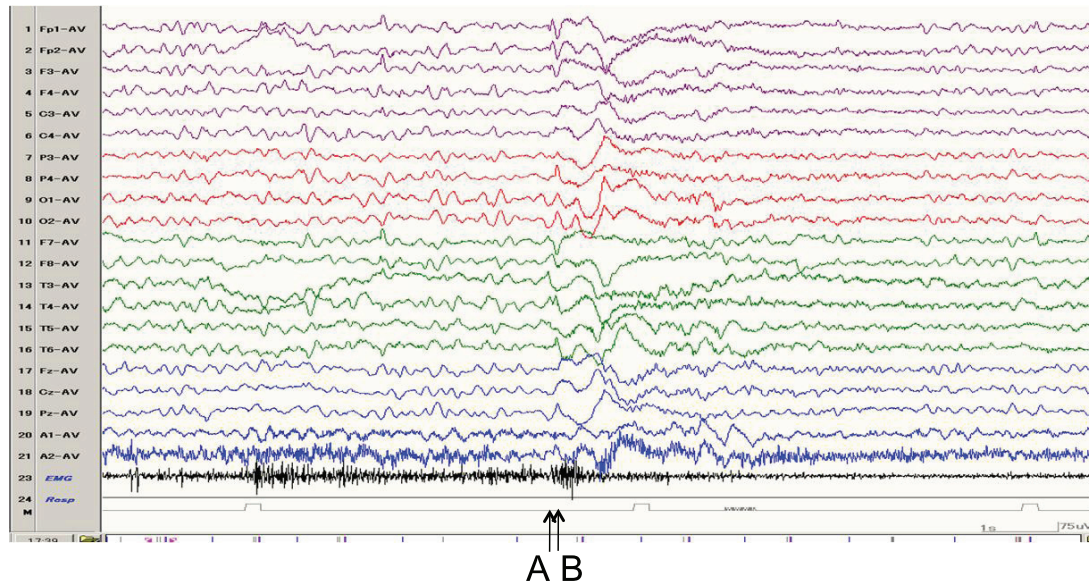
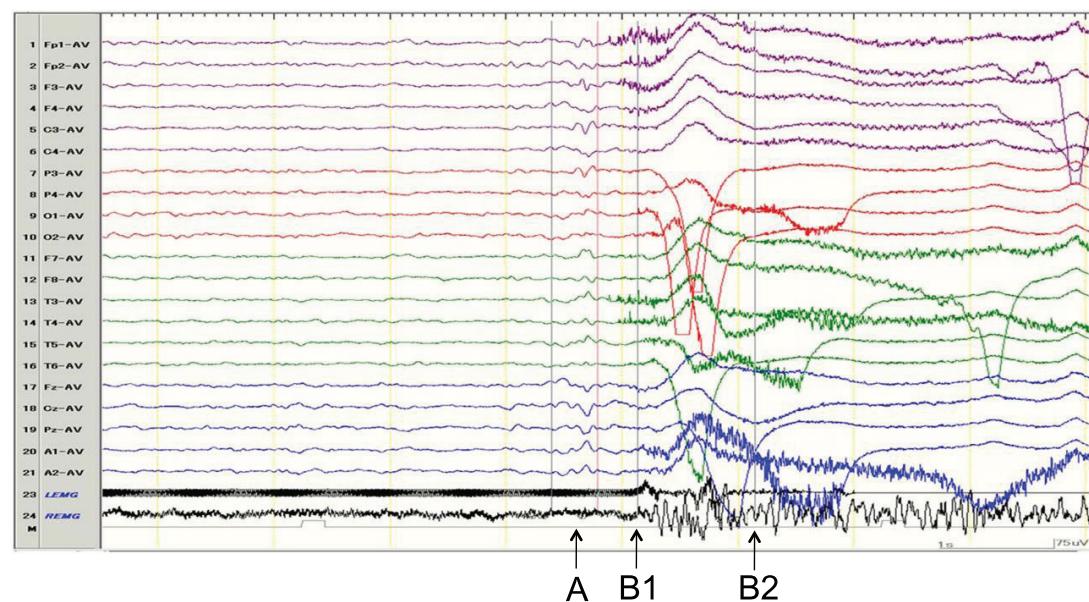


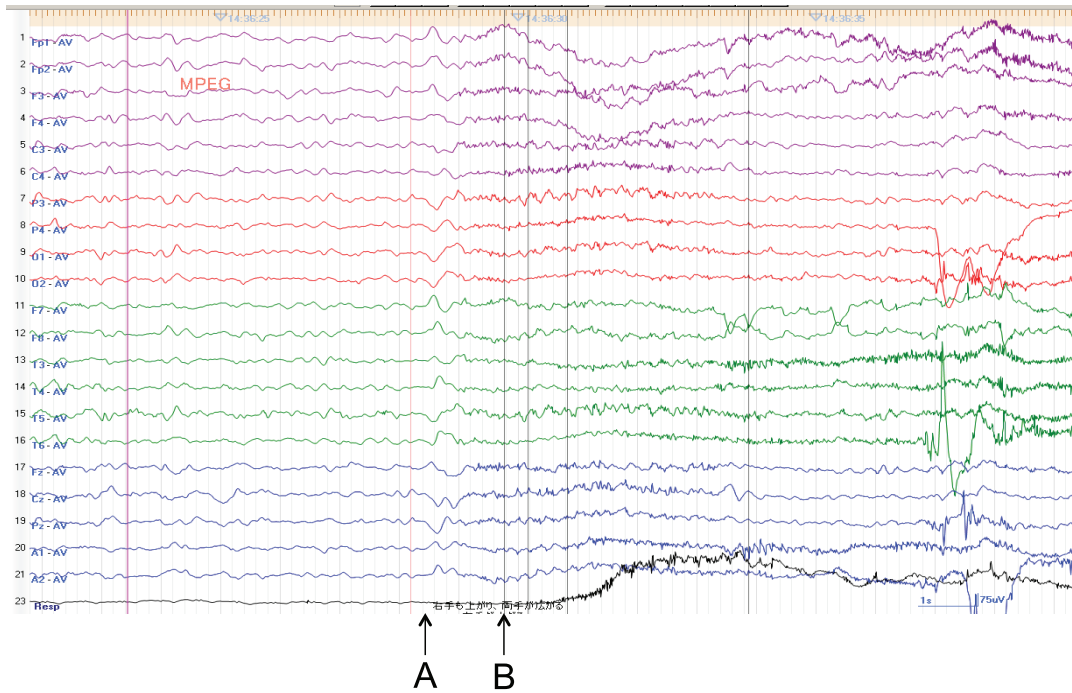
Figure 2. Ictal EEG recordings of patients with epilepsy after influenza-associated encephalopathy (IAE).
A: Ictal-EEG of Patient 2 (female) recorded at 2 years of age. This patient developed IAE on the first day of Influenza infection and epilepsy 30 days later. Almost immediately after ictal EEG onset (A), seizure appeared as slight extension of shoulders and body trunk (B) followed by anterior flexion of head and body trunk, and tonic contraction of upper limbs forward.

Figure 2B



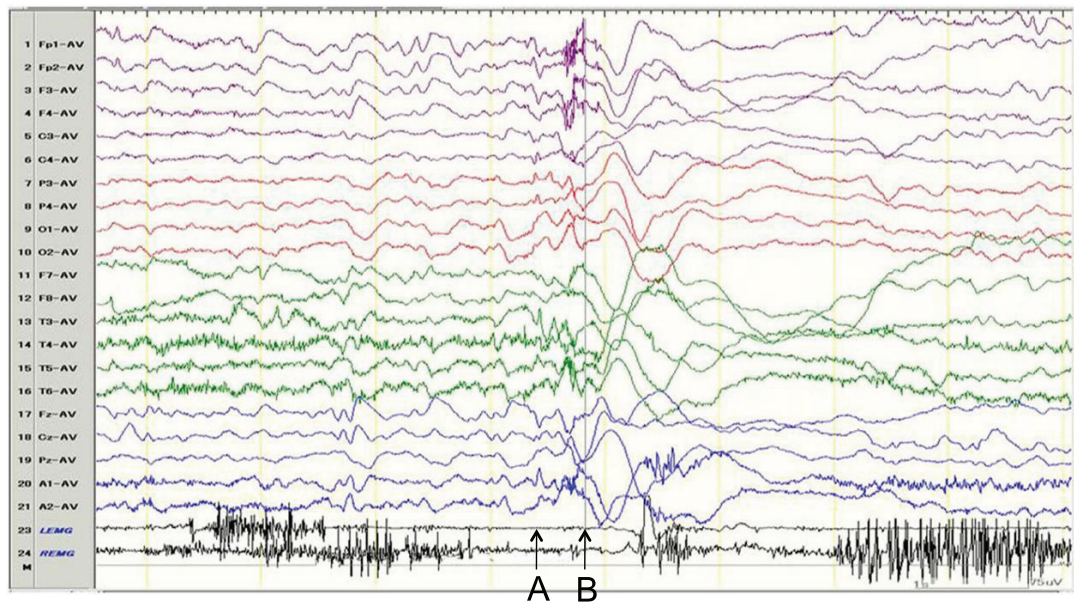
B: Ictal-EEG of Patient 5 (female) recorded at 11 years of age. This patient developed IAE on the 5th day of influenza A infection, and afebrile seizure on the 6th day. Soon after ictal EEG onset (A), seizure appeared as eye-opening (B1) followed by extension of right upper extremity (B2), twitching of right mouth corner, and abduction and hyperactive motor movement of right upper limb.

Figure 2C



C: Ictal-EEG of Patient 7 (male) recorded at 4 years of age. The patient developed IAE two days after influenza A infection, followed by afebrile seizure 60 days after the influenza infection. Soon after ictal EEG onset (A), seizure appeared as synchronous vibratory movement of bilateral upper limbs in sleep (B).

Figure 2D



D: Ictal-EEG of Patient 8 (female) recorded at 5 years of age. The patient developed IAE on the first day of influenza A infection, and subsequently developed epilepsy at 180 days after IAE. Soon after ictal EEG onset (A), seizure appeared as tilting of the head backward (B), followed by falling forward.

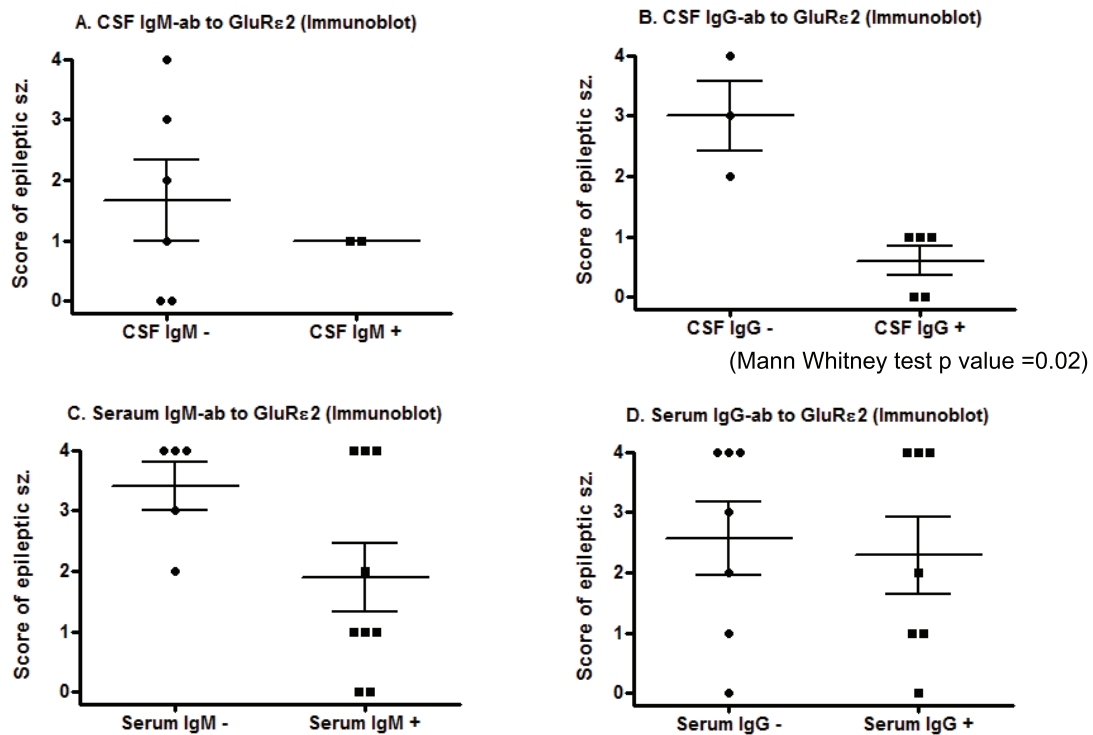


Figure 3. Seizure outcome and antibodies to GluR ϵ 2 detected by immunoblot CSF IgM, IgM antibodies to GluR ϵ 2 in CSF; CSF IgG, IgG antibodies to GluR ϵ 2 in CSF; Serum IgM, IgM antibodies to GluR ϵ 2 in serum; serum IgG, IgG antibodies to GluR ϵ 2 in serum.

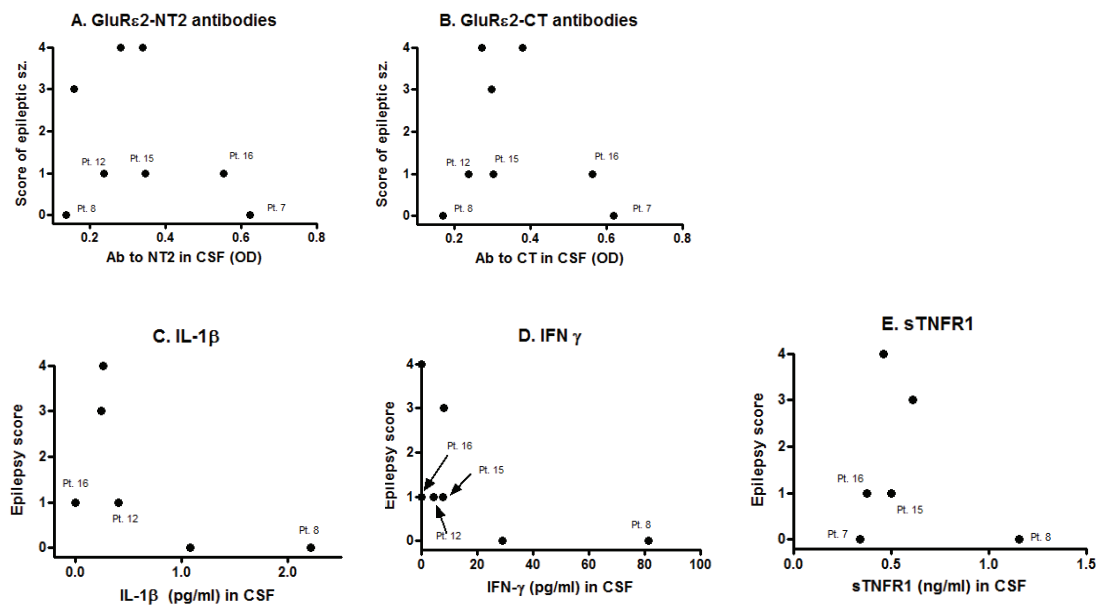


Figure 4. Relationship between seizure outcome and levels of anti-GluR ϵ 2 antibodies (ELISA) and cytokines in CSF. **A:** Antibodies to GluR ϵ 2-NT2 in CSF. Antibody level is expressed as optical density (OD) of ELISA. The OD (mean \pm SD) in CSF of control patients (n = 9) was 0.162 \pm 0.055. **B:** Antibodies to GluR ϵ 2-CT in CSF. Mean OD in CSF of control patients (n = 9) was 0.189 \pm 0.061. **C:** IL1 β in CSF. Mean level in control patients (n = 9) was 0.6 \pm 0.7 pg/ml. **D:** IFN γ in CSF. Mean level in control patients (n = 9) was 24.0 \pm 53.4 pg/ml. **E:** sTNFR1 in CSF. Mean level in control patients (n = 9) was 0.488 \pm 0.095 ng/ml.

hand, the mean interval from EAE to epilepsy onset in 67 patients was 6.4 months (0 month to 7 years and 3 months).¹¹ This finding suggests that epileptogenesis might take a shorter time after IAE comparing with EAE by microbes other than influenza.¹² Acute encephalitis with refractory, repetitive partial seizures (AERRPS) is known to show continuous evolution from encephalitis to residual epilepsy without a latent period.^{13,14} Epilepsy after IAE and AERRPS may share common factors such as immunological factors that contribute to early establishment of epileptogenesis.

We found that epileptic seizure outcome is poorer in patients positive for anti-GluR ϵ 2 IgG antibodies (immunoblot) in CSF, and that CSF levels of anti-GluR ϵ 2-NT2 and anti-GluR ϵ 2-CT antibodies are negatively associated with seizure outcome. We also found that seizure outcome was apparently poorer in patients with higher CSF levels of the inflammatory cytokines IL-1 β , sTNFR1, and IFN γ . In 2 patients with daily epileptic seizures, one (Patient 8) had increased levels of cytokines only, and another (Patient 7) had increased levels of both cytokines and anti-GluR ϵ 2 antibodies. In 3 patients with weekly epileptic seizures, 2 (Patients 15 and 16) had increased anti-GluR ϵ 2 antibodies levels only, and one (Patient 12) had normal levels of antibodies and cytokines in CSF. These data suggest that antibodies to GluR ϵ 2, IL-1 β , IFN γ , and TNF α in CSF may be associated with the intractable seizures, in an additive manner. Because patients with daily seizure frequently had increased levels of proinflammatory cytokines, these cytokines (IL-1 β , IFN- γ , TNF α) in CSF may have stronger impact on seizure frequency than anti-GluR ϵ 2 antibodies. Cytokines in brain flow into subarachnoid space, and are diluted by CSF produced in choroid plexus to significant degree. Although the increased levels of cytokines were slight in epileptic patients after IAE, the actual increased cytokine levels in brain was assumed to be dozens of times of those in CSF.

IL-1 β secretion is prolific in perivascular astrocytes and is thought to destroy tight junctions, induce production of NO or matrix metalloproteinases (MMPs) in vascular endothelial cells and increase permeability of the blood-brain barrier, resulting in elevated albumin concentration in the central nervous system.¹⁵ Increased albumin level in the central nervous system leads consequently to neuronal excitability.¹⁶ IL-1 β activates the NR2A/NR2B subunits in N-methyl-D-aspartate (NMDA) type GluR

complex, thereby contributing to glutamic acid-induced neurodegeneration.¹⁷ IL-1 β is known to inhibit glutamic acid uptake by glia and enhance glutamic acid release from glia mediated by TNF α production, leading to elevated glutamic acid concentration in the synaptic gaps and ultimately to neuronal excitation.^{15,18} These findings suggest that IL-1 β may contribute to neuronal excitation by multiple mechanisms, probably also in epilepsy after IAE.

This study revealed that sTNFR1 in CSF may be associated with seizure frequency in epileptic patients after IAE. SolubleTNFR1 level in CSF has been reported to affect pediatric neurological prognosis in acute encephalitis/encephalopathy.¹⁹ TNF α is the ligand of sTNFR1, and dose-dependently regulates the seizure threshold. A certain concentration range of TNF α is thought to enhance susceptibility to acute seizure.²⁰⁻²² High concentrations of TNF α have been shown to increase excitotoxic death of neurons by increasing synaptic AMPA receptors and decreasing GABA receptors²³, and cause spasms in TNF α transgenic mice.²⁴ Based on these findings, it is possible that TNF α gradually increases neuronal excitability and contributes to epileptogenesis in patients after IAE.

This study suggested that INF γ in CSF might impact seizure frequency in epileptic patients after IAE. INF- γ predicts poor prognosis in HSV encephalitis²⁵, and appears in early stages of Rasmussen syndrome.²⁶ INF- γ may support production of TNF α in microglia or act on tight junctions. These findings suggest that INF γ may contribute to the production of TNF α , resulting in neuronal excitabilities.

Several functions of antibodies to NMDA-type GluR have been reported. Antibodies to NMDA-type GluR complex cause internalization of NMDA-type GluR complex resulting in dysfunction of various neurological pathways.⁶ Antibodies to ds-DNA, which cross-react with GluR ϵ 2, induce apoptosis of neurons, resulting in memory dysfunction and behavioral changes.²⁷⁻²⁹ The diverse functions of anti-GluR antibodies may contribute to cognitive impairment and behavioral changes in epileptic patients after IAE. Probable association of seizure outcome and the levels of antibodies to GluR and inflammatory cytokines may suggest that immunological injury by antibodies and inflammatory cytokines is causally related with pathogenesis of epilepsy after IAE. There was a study that active neuro-inflammation and marked cellular injury occur in pediatric epilepsy and may play a common pathogenic role

or consequences in childhood epilepsy of diverse etiologies.³⁰

In conclusion, we report the clinical characteristics and prognostic factors of epilepsy after IAE in 18 patients. Anti-GluR ϵ 2 antibodies and proinflammatory cytokines including IL-1 β , TNF α , and INF γ in CSF may impact seizure outcome in an additive manner.

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DISCLOSURE

Conflicts of interest: None

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