Determinants for Control of Status Epilepticus in Patients with Anti-N-Methyl-D-Aspartate Receptor Encephalitis

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Abstract

Background: Treatment guideline for status epilepticus (SE) specifically in patients with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is insufficient. This study aimed to clarify the determinants for the control of SE in adult patients with anti-NMDAR encephalitis.

Methods: Medical records of all patients with anti-NMDAR encephalitis hospitalized between Jan. 2010 and Sep. 2019 were analyzed for the time sequence of seizures and treatments, and antiepileptic drug (AED) regimens related to SE. The outcomes were control of SE and seizures, and the discharge score of modified Rankin Scale (mRS).

Results: All eight patients had seizures and seven (87.5%) suffered from SE which lasted for 3.6 ± 3.9 days. Five patients (71.4%) had SE earlier than using IT, whose SE was controlled by AEDs alone (n = 4) or combined with teratomas resection (n = 1). Another two patients suffered from SE after receiving IT, and one of them had SE only for 1 hour. Moreover, all SE patients received increased types and dosages of AEDs at SE end. A shorter duration of refractory SE was associated with its later occurrence after seizure onset ($p = 0.005$) and longer duration of AEDs use before SE ($p = 0.026$). All cases achieved seizure freedom after receiving AEDs and IT.

Conclusions: In these patients with anti-NMDAR encephalitis, all the SE which occurred before initiating IT was successfully controlled by AEDs alone or combined with teratoma resection, and later onset of refractory SE was associated with a shorter SE duration.

Keywords: anti-N-methyl-D-aspartate receptor encephalitis, seizure, status epilepticus, antiepileptic drugs, immunotherapy.

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune encephalitis that is caused by autoantibodies against the GluN1 subunit of NMDA receptors[(1)]. This disease can be treated by immunotherapy (IT) and resection of underlying teratomas[(1,2)], and early treatment is associated with better outcomes[(3)]. On the contrary, the disease can lead to death if untreated[(2,3)]. The disease was characterized by multistage presentations,

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including psychosis, memory deficit, seizure, personality change, unresponsiveness with catatonic features, as well as autonomic and respiratory instability[2-5]. Owing to the multistage manifestations and minimal encephalitis signs, it is difficult to make early diagnosis for this disease[1].

Seizure is presented in about 70% of patients with anti-NMDAR encephalitis[3], and these patients are also at the risk of status epilepticus (SE) which usually occurs early in the course of seizures and require admission in intensive care units[6,7]. A challenging issue of treatment for this disease is rapid control of seizure and status epilepticus[2,6]. However, there is contradictory evidence regarding the comparison of the efficacy of antiepileptic drugs (AEDs) and IT for control of seizures related to autoimmune encephalitis[8,9]. One study suggested that IT was more effective than AEDs for the control of seizures in patients with autoimmune encephalitis, by comparing AEDs and IT in the treatment durations before seizure free, and comparing which treatment was used while seizure freedom was achieved[8]. In another large case series study of autoimmune encephalitis-related epilepsy, seizures were controlled by AEDs alone in 22% of all patients and in 33% of the patients who achieved seizure freedom[9]. Furthermore, guidelines on how to choose AEDs for controlling of seizures and SE in patients with anti-NMDAR encephalitis are insufficient[8]. Hence, this study aimed to clarify the determinants for the control of SE in adult patients with anti-NMDAR encephalitis.

METHODS

Patients

This retrospective observational research was conducted at National Taiwan University Hospital, which is one of the major tertiary referral centers in Taiwan. The Research Ethics Committee Office of National Taiwan University Hospital approved this study (permit number 201910028RINB). We enrolled all the patients with anti-NMDAR encephalitis who were hospitalized between Jan. 2010 and Sep. 2019. Since lack of a specific diagnostic code for anti-NMDAR encephalitis, a total of 916 patients with the diagnosis of "other cause of encephalitis", "encephalitis and encephalomyelitis, unspecified", "unspecified cause of encephalitis", or "other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus" based on the International Classification of Diseases 9th Revision (ICD-9) (before Dec. 31, 2015) and 10th Revision (ICD-10) (after Jan. 1, 2016) were retrieved. Subsequently, 418 pediatric patients aged younger than 20 years were excluded, since their different presentations[3], different pharmacokinetics[10,11], and different treatment decisions compared with adult patients[12]. Next, 487 patients were excluded due to not meeting with the following definition of anti-NMDAR encephalitis: presence of one or more of the six major groups of symptoms and presence of immunoglobulin G anti-glutamate ionotropic receptor NMDA type subunit 1 (anti-GluN1) antibodies in cerebrospinal fluid (CSF)[13]. Three patients diagnosed as anti-NMDAR encephalitis at other hospitals were also excluded due to lack of detailed medical records. Finally, eight patients were included in this study.

Among the eight patients with anti-NMDAR encephalitis, seven patients developed SE. In these patients with SE, two patients received immunotherapy (IT) before occurrence of SE (grouped as IT-SE), while five patients received IT after SE (grouped as SE-IT). The flow chart of recruiting patients in this study and the classification of the enrolled patients was shown in Fig. 1.

Medical information

We recorded the clinical manifestations focusing on seizure types[14,15] and time courses, examination results of CSF study, brain magnetic resonance imaging and electroencephalogram (EEG) of each patient. Convulsive SE was defined as ≥ 5 min of (1) continuous seizure or (2) two or more seizure events between which there was incomplete recovery of consciousness[14]. Nonconvulsive SE was identified according to EEG findings[16]. The regimens of IT and AEDs were also recorded. First-line IT included high-dose intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIg), and double filtration plasmapheresis (DFPP), whereas rituximab, cyclophosphamide, and azathioprine were categorized as second-line IT[3,8,12]. Non-anesthetic AEDs were classified according to mechanisms, focusing on the AED regimens 'before SE onset' and 'at SE end'. Resection for teratomas was also recorded.

To clarify the temporal relationship of treatments with disease course, we measured several time parameters

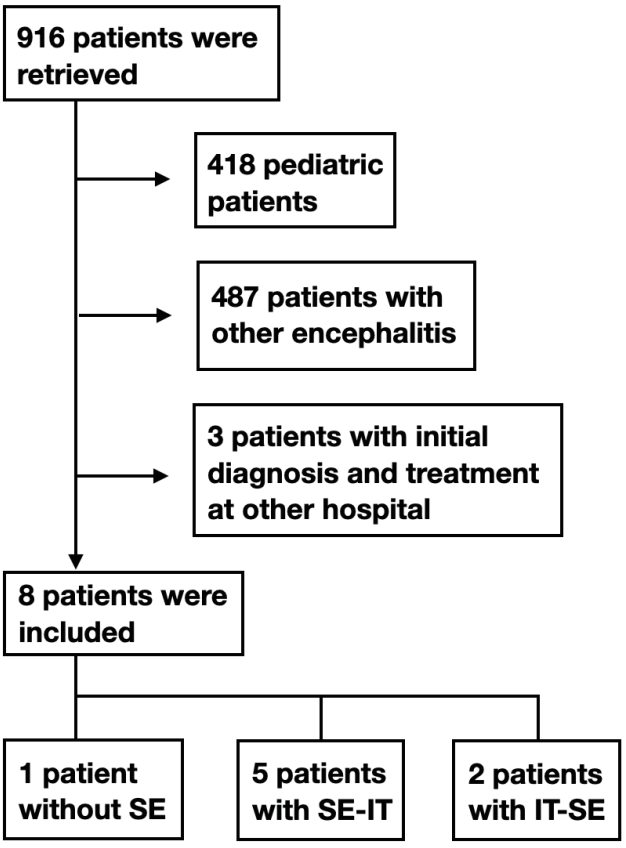

Fig. 1. Flow chart of recruiting patients in this study and the classification of the enrolled patients. Abbreviations: SE = status epilepticus; IT = immunotherapy; IT-SE = SE occurred after IT; SE-IT = SE occurred before IT

including onset-to-IT interval (from disease onset to initiating IT, indicating delay of treatment), seizure-to-AED or -IT interval (from seizure onset to initiating AED or IT), seizure-to-SE interval (from seizure onset to SE onset), AED- or IT-to-SE interval (interval from initiation of AED or IT to SE onset), SE duration, and seizure duration. The outcome measures were control of SE and seizure based on clinical observation and EEG, and modified Rankin Scale (mRS) score at discharge[18,19].

Statistical analysis

The data were presented as mean ± standard deviation, and percentage or range were presented in parentheses. The comparisons of continuous variables between the two groups were analysed using the Mann-Whitney U test. Linear regression was used to analyze the variables associated with SE duration or discharge mRS score. P-value less than 0.05 was considered significant. These data were analysed by Numbers 6.2.1 for Mac (Apple Distribution International Ltd. Ireland).

RESULTS

In the eight patients with anti-NMDAR encephalitis, the mean age of onset was 31.3 ± 8.6 years, and this study predominantly comprised women (75%) (Table 1). All patients had epileptic seizures, seven (87.5%) developed SE, and six (75%) suffered from refractory SE. All patients received routine EEG exams or with additional 24-hour EEG monitoring, and extreme delta brush pattern was noted in 6 patients (75%).

The timelines of seizures and treatments in all patients are shown in Fig. 2. All patients received screening for tumors, and all teratomas (3 patients, 37.5%) were surgically resected on day 27.7 ± 5.1 after disease onset. All eight patients received IT, and one patient only receive second-line IT due to underlying systemic lupus erythematosus. Except one patient receiving reduced dose of IVMP due to concomitant pneumonia, the regimens of other IT followed the suggested guidelines[3].

Table 1. Demographic characteristics and clinical features of enrolled patients with anti-N-methyl-D-aspartate receptor encephalitis

No	Sex	Age	Symptoms	Seizure type	SE type	Tumor[b]	IT	Mechanical ventilation (day)[c]	Septic shock	Acute kidney injury	Liver injury	TPN use	Other auto-immune disease	Discharge mRS
1	M	20	Seizure[a], fever, agitation, movement disorder	Focal seizure, GTC, NCS	CSE	-	IVMP, IVIg, RTX	1	-	-	+	-	-	2
2	F	34	Headache[a], amnesia[a], agitation, seizure, movement disorder	GTC	CSE	OT, MT	IVMP, IVIg, RTX	-	-	-	-	-	-	2
3	F	34	Hallucination[a], dizziness[a], agitation, seizure, movement disorder	Focal seizure	CSE	-	IVIg	72	+	+	+	-	-	5
4	F	21	Confusion[a], impaired memory[a], agitation, seizure, movement disorder	GTC, NCS	NCSE	-	RTX, CP	-	-	-	+	-	SLE	3
5	M	38	Agitation[a], self-harma, confusion[a], hallucination, seizure, movement disorder	GTC, NCS	NCSE	-	IVMP, DFPP	-	-	-	-	-	-	3
6	F	24	Fever[a], hallucination, agitation, seizure, movement disorder	GTC	CSE	OT	IVMP, IVIg, DFPP, RTX	231	-	-	+	+	-	5
7	F	35	Acute confusion[a], seizure, hallucination, agitation, movement disorder	GTC	CSE	OT	IVMP, IVIg	-	-	-	+	-	-	3
8	F	44	Alexia[a], fever, seizure	NCS	-	-	IVMP, IVIg, AZA	-	-	-	-	-	-	1

[a] Initial presentations

[b] All patients underwent whole-body CT screening for tumours, and all tumours were surgically resected.

[c] Mechanical ventilation used for operation was excluded.

Abbreviation: AZA = azathioprine; CP = cyclophosphamide; CSE = convulsive status epilepticus; DFPP = double filtration plasmapheresis; GTC = generalised tonic-clonic seizure; IT = immunotherapy; IVIg = intravenous immunoglobulins; IVMP = high dose intravenous methylprednisolone; mRS = modified Rankin Scale; MT = mediastinal teratoma; NCS = non-convulsive seizure; NCSE = non-convulsive status epilepticus; OT = ovarian teratoma; RTX = rituximab; SE = status epilepticus; SLE = systemic lupus erythematosus; TPN = Total parenteral nutrition

Table 2. Time factors regarding treatments and seizure courses in patients with anti-N-methyl-D-aspartate receptor encephalitis

No.	Onset-to-IT interval	Seizure-to-AED interval	Seizure-to-IT interval	Seizure-to-SE interval	AED-to-SE interval	IT-to-SE interval	SE duration	Seizure duration
1	31	5	31	41	36	10	0.04	46
2	31	0	14	0	0	-14	0.004	20
3	32	0	13	9	9	-1	2	25
4	15	3	6	13	10	15	8[a]	22
5	32	0	7	0	0	-4	3	37
6	28	0	21	2	2	-9	10	208
7	22	-19[b]	2	0	19	0	2	4
8	21	2	17	-	-	-	-	17

Unit: day(s).

[a] SE duration of this patient was determined according to routine electroencephalography exams; the data of other patients were determined based on continuous electroencephalography monitoring.

[b] Using valproate owing to clinical diagnosis of bipolar disorder

Abbreviations: AED = antiepileptic drugs; IT = immunotherapy; SE = status epilepticus; onset-to-IT interval = interval from disease onset to initiation of IT; seizure-to-AED interval = interval from seizure onset to initiation of AEDs; seizure-to-IT interval = interval from seizure onset to initiation of IT; seizure-to-SE interval = interval from seizure onset to SE onset; AED-to-SE interval = interval from initiation of AED to SE onset; IT-to-SE interval = interval from initiation of IT to SE onset; SE duration = duration from SE onset to SE end on EEG; seizure duration = duration from seizure onset to last seizure.

Table 3. Mechanisms and daily dosages of anticonvulsants used before SE onset and at SE end

	Anticonvulsants before SE onset						Anticonvulsants at SE end							
	SV2A	Multiple		Na+ channel		GABA	SV2A	Multiple		Na+ channel		Ca2+ channel	GABA	AMPA
No.	LVT	VPA	LCM	TPM	ZNS	CLZ	LVT	VPA	LCM	TPM	PHT	PGB	PHB	PER
1	3000	0	100	300	200	1	3000	0	600	300	0	0	0	4
2	0	0	0	0	0	0	1500	0	0	0	0	0	0	0
3	3000	0	0	0	0	0	3000	3000	0	0	1150a	0	0	0
4	3000	0	0	200	0	0	4500	0	0	200	450	0	0	0
5	0	500	0	0	0	0	2000	2400	0	0	950b	150	0	0
6	1500	0	0	0	0	0	4500	600	0	100	0	0	300	0
7	2500	0	100	0	0	0	2000	0	200	0	300	0	0	0

[a] Loading dose 1000 mg + maintenance dose 350 mg/day (one dose of 150 mg was given on that day)

[b] Loading dose 750 mg + maintenance dose 300 mg/day (two doses of 100 mg were given on that day)

Unit: mg/day

Abbreviations: AMPA = alpha-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CLZ = clonazepam; GABA = γ-aminobutyric acid; LCM = lacosamide; LVT = levetiracetam; Na+ channel = sodium channel; PER = perampanel; PGB = pregabalin; PHB = phenobarbital; PHT = phenytoin; SE = status epilepticus; SV2A = synaptic vesicle glycoprotein 2A; TPM = topiramate; VPA = valproate; ZNS = zonisamide

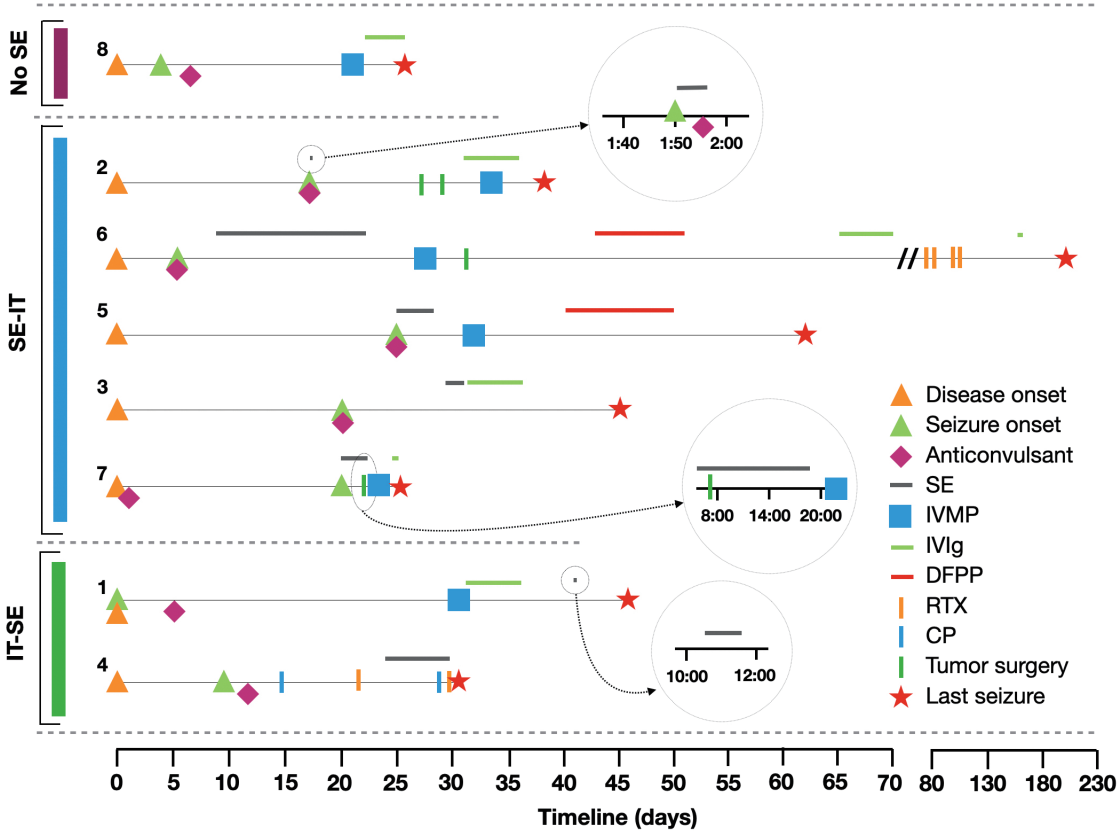

Fig. 2. Timelines of seizures and treatments in patients with anti-NMDA receptor encephalitis manifesting with epileptic seizures

The timelines of all patients were shown from disease onset to last seizure. Different colors on the left side indicated different disease courses: (1) No SE: no status epilepticus (purple) (2) SE-IT: SE onset before initiating IT (blue), (3) IT-SE: SE onset after initiating IT (green). The number on the left side indicated case number. AEDs were marked as the initiating day.

Abbreviations: AEDs = antiepileptic drugs; SE = status epilepticus; IT = immunotherapy; IT-SE = SE occurred after IT; SE-IT = SE occurred before IT; IVMP = high dose intravenous methylprednisolone; IVIg = intravenous immunoglobulins; DFPP = double filtration plasmapheresis; RTX = rituximab; CP = cyclophosphamide

SE control was achieved by AEDs before initiating IT in all patients of the SE-IT group (n = 5), and one of them also received tumor resection. In the IT-SE group (n = 2), one patient had completed the IT regimens before SE occurrence, whose SE started after reducing lacosamide and stopped immediately after reloading lacosamide. The other one patient in IT-SE group was administered the second cycle of IT with the same regimen during SE. All patients with SE received increased dosages and types of AEDs at SE end.

All seizure patients received AEDs and IT, and achieved control of seizure and SE. Seizure duration was 47.4 ± 66.1 days (4–208 days), and SE duration was 2.8 ± 3.7 days (6 min–10 days) (Table 2). No difference was observed in seizure durations between patients with and without teratomas. The seizure-to-AEDs interval was shorter than the seizure-to-IT interval (-1.1 ± 7.5 days vs. 13.9 ± 9.3 days, respectively, p = 0.002).

Just before SE onset, five (71.4%) of the SE patients received levetiracetam (Table 3). At SE end, six patients (85.7%) received sodium channel blockers and levetiracetam, and three of them (42.9%) received a

Table 4. Regression analysis summary predicting the duration of refractory status epilepticus and functional outcome

	1/(SE duration)			Discharge mRS score		
	β	R^2	P-value	β	R^2	P-value
Onset-to-IT interval	0.464	0.100	0.542	0.056[a]	0.064[a]	0.545[a]
Seizure-to-AED interval	0.439	0.142	0.462	-0.023[a]	0.015[a]	0.773[a]
Seizure-to-IT interval	0.731	0.624	0.062	-0.018[a]	0.014[a]	0.780[a]
Seizure-to-SE interval	0.604	0.884	0.005	-0.037	0.182	0.399
AED-to-SE interval	0.659	0.751	0.026	-0.014	0.019	0.795
IT-to-SE interval	0.498	0.196	0.379	-0.025	0.039	0.708

[a] These data were analyzed in all patients with seizure (n = 8), while other data were analyzed in all patients with refractory SE (n = 6).
Abbreviations: SE = status epilepticus; mRS = modified Rankin Scale; AED = antiepileptic drug; IT = immunotherapy; onset-to-IT interval = interval from disease onset to initiation of IT; seizure-to-AED interval = interval from seizure onset to initiation of AED; seizure-to-IT interval = interval from seizure onset to initiation of IT; seizure-to-SE interval = interval from seizure onset to SE onset; AED-to-SE interval = interval from initiation of AED to SE onset; IT-to-SE interval = interval from initiation of IT to SE onset

combination of sodium channel blockers, levetiracetam and valproate. The SE duration in patients receiving combined valproate and phenytoin at SE end was 2.5 ± 0.7 days (n = 2), and SE was dramatically controlled within 1 day after initiation of phenytoin in both cases. On the contrary, the SE duration was 4.0 ± 4.7 days in those not receiving the combination (n = 5).

For patients with refractory SE, SE duration was reciprocally associated with seizure-to-SE interval and AED-to-SE interval (p = 0.005 and 0.026, respectively) (Table 4). There was no association between SE duration, seizure duration, mRS score and other time parameters.

DISCUSSION

A challenging issue of treatment for anti-NMDAR encephalitis is efficient control of seizure and SE. However, evidence on how to choose AEDs for this disease is insufficient, and it is unclear about which factor determines the control of SE and seizure related to this disease. Here, we showed that AEDs were used much earlier than IT after seizure onset in these patients. All the SE that occurred before initiating IT was successfully controlled by AEDs alone or combined with surgical removal of teratoma. The seizures of all the cases were controlled by combining AEDs and IT, and with tumor resection in the cases having teratomas. Of note, the duration of refractory SE was reciprocally associated with seizure-to-SE interval and AEDs duration before SE. At SE end, patients received increased dosages and types of AEDs, specifically sodium channel blockers and valproate.

This study revealed that AEDs were initiated much earlier than IT after seizure onset. This is reasonable because the decision of IT treatment was based on the diagnosis or suspicion of autoimmune encephalitis, while seizure especially after the second episode directly led to the prescription of AEDs. Previous studies have compared the efficacy of these two treatments for epilepsy related to autoimmune encephalitis with different conclusions[8,9], but a study specifically for SE in anti-NMDAR encephalitis has not been conducted. This present study showed that all patients in SE-IT group achieved control of SE by AEDs alone or combined with teratoma resection before initiating IT, and SE was controlled within 1 day after loading phenytoin in two of them. Although it was possible that AEDs alone or combined with teratoma resection controlled the SE in these cases, this result may also mean that there was no recurrence of SE after IT treatment. In addition to SE, many patients in this study also experienced a long period of seizures. Previous studies showed that more patients achieved seizure freedom after IT treatment (53%) compared with AEDs alone (14%)[8]. The seizures of all cases in the present study were controlled by combining both treatments, and there was no difference in seizure duration between IT-SE and SE-IT groups. Besides, the extremely short duration

of SE that occurred after IT in a case of IT-SE group might indicate the potential influence of IT for the control of a later-onset SE. However, another case in the IT-SE group received only second-line IT treatments which had slower onset of effect than first-line IT treatments, precluding the comparison of the two cases about IT effect on a later-onset SE. More cases of SE that occurs after IT with same treatments will be required to confirm this finding.

Prolonged SE is a poor prognostic factor for autoimmune encephalitis[23]. The present study revealed that seizure-to-SE interval and AEDs duration before SE were both reciprocally associated with the duration of refractory SE in patients with anti-NMDAR encephalitis. This phenomenon has not been reported previously in anti-NMDAR encephalitis or autoimmune encephalitis. Patients with earlier-onset SE were less likely to receive IT or adequate AEDs, and probably had higher autoimmune activities or more severe encephalitis, than patients with later-onset SE, which might contribute to a more prolonged SE.

In this study, SE occurred even under the treatment of levetiracetam, partly due to lower doses in some cases. At SE end, most patients received sodium channel blockers and levetiracetam, and around half of them received a combination of sodium channel blockers, valproate and levetiracetam. The SE of two patients in SE-IT group had a dramatic response to phenytoin loading, and the SE of another patient in IT-SE group occurred after reducing lacosamide and was controlled immediately after reloading lacosamide. These findings were in concordance with previous report that sodium channel blockers are effective for autoimmune encephalitis-related epilepsy[9].

Extreme delta brush pattern on EEG was noted in 6 cases (75%), which was higher than the reported 30% in patients with anti-NMDAR encephalitis[25]. The presence of this EEG pattern was associated with more prolonged hospitalization and prolonged continuous EEG monitoring[25]. In that study, 78% of the enrolled cases had seizures, and relatively higher percentage of patients had seizures in those with extreme delta brush pattern than those without it (85% vs 50%)[25]. However, the percentage of this EEG pattern in seizure patients was not reported. Besides, a case report of anti-NMDAR encephalitis showed extreme delta brush pattern evolving into SE on continuous EEG monitoring, indicating that this EEG pattern might belong to the spectrum of the ictal-interictal continuum[25]. Another case report demonstrated that this EEG pattern was accompanied with intractable convulsions, and hyperexcitable cortex was simultaneously revealed by somatosensory evoked potential examination[25]. Thus, extreme delta brush was associated with seizure activities, in line with our observation that all the patients with this EEG pattern also had SE. Besides, only one of the 6 cases were receiving benzodiazepine infusion while extreme delta brush pattern was recognized, precluding the possibility of benzodiazepine-induced mimicking waveforms in the other 5 cases. The high proportion of patients with extreme delta brush pattern might because all the enrolled cases had seizures and most of them had SE.

Our study had several limitations. The sample size was small because anti-NMDAR encephalitis is a rare disease especially in adults. Second, the high proportions of patients with seizures and SE in this study compared with other report indicated higher disease severity in the recruited population[3], and other patients with milder presentations might be underdiagnosed. Third, 24-hr EEG monitoring was conducted in 7 patients (87.5%), so non-convulsive seizures might be underestimated in the patient not receiving EEG monitoring.

In conclusion, this study showed that SE in patients with anti-NMDAR encephalitis that occurred before using IT could be successfully controlled by AEDs alone without recurrence. Later occurrence of refractory SE was associated with a shorter SE duration. Appropriate treatment to postpone or prevent SE might be a direction of management in these patients.

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