Epilepsy Research 158 (2019) 106215

Contents lists available at ScienceDirect

Epilepsy Research

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

Prognostic significance of subsequent extra-temporal involvement in cryptogenic new onset refractory status epilepticus (NORSE) initially diagnosed with limbic encephalitis

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ARTICLE INFO

Keywords:
New-onset refractory status epilepticus
Limbic encephalitis
Claustrum
Pulvinar

ABSTRACT

Introduction: New-onset refractory status epilepticus (NORSE) is defined as refractory SE in patients without active epilepsy or relevant neurological disorder with no clear active causes. Diverse types and etiologies of NORSE are reported in various groups. Limbic encephalitis (LE) is reported as one of etiologies of NORSE. In this study, we investigated whether there were any intersections between NORSE and limbic encephalitis, as well as the presence of prognostic factors in intersection patients.

Methods: We retrospectively analyzed patients who met both the definition of NORSE and diagnostic criteria of LE at the initial presentation from our database. Clinical characteristics and blood test, cerebrospinal fluid, electroencephalography, and magnetic resonance imaging results were reviewed. Prognosis was recorded as ICU admission stay, total length of hospitalization, and modified Rankin Scale at discharge. In particular, we determined which factors were associated with patients' prognosis.

Results: Thirteen patients were selected. Nine of the 13 patients had myalgia and 8 patients had fever in the prodromal period. Twelve of the 13 patients had acute memory impairment or confusion before SE development. In addition, 46.2% of the patients showed leukopenia or thrombocytopenia. Median body temperature at hospital arrival was 37.6 °C. Nine patients showed generalized tonic-clonic SE. All patients were treated with immunotherapy and 11 of the 13 patients achieved burst suppression through induced coma therapy. Ten patients showed lesion extension on follow-up imaging. The most common extension site was the claustrum. Patients with more lesion extension showed poorer outcomes than those without lesion extension.

Conclusion: Subsequent extratemporal lesion extension was closely associated with poor prognosis in NORSE-LE patients. This study explores a new subtype of NORSE and suggests a possible common underlying pathomechanism between NORSE and LE.

1. Introduction

Status epilepticus (SE) is a common devastating neurologic emergency. New-onset refractory SE (NORSE) is defined as refractory SE in previously healthy individuals without a clear acute or active structural, toxic, or metabolic cause (Hirsch et al., 2018). Recently, researchers considered autoimmunity or autoantibodies as an etiologic mechanism of NORSE due to the responsiveness of NORSE patients to immunotherapy and approximately 40% of NORSE patients have autoantibodies present (Gaspard et al., 2015). Cryptogenic NORSE can be diagnosed after extensive investigation of onconeuronal autoantibodies and autoantibodies to the neuronal surface antigen (Iizuka et al., 2017).

Recent studies have shown various radiological findings in brain magnetic resonance imaging (MRI) in NORSE. Two studies have reported NORSE after febrile illness with claustrum involvement (Meletti et al., 2017, 2015). Other studies have reported multifocal bilateral involvement, including mesial temporal structures in cryptogenic NORSE patients (Khawaja et al., 2015). The largest NORSE cohort study to date has shown broad-spectrum MRI findings of NORSE, including involvement of the limbic area (Gaspard et al., 2015).

Limbic encephalitis (LE) is defined as an inflammation of limbic structures, particularly mesial temporal structures and clinically

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https://doi.org/10.1016/j.eplepsyres.2019.106215
Received 11 October 2018; Received in revised form 30 July 2019; Accepted 6 October 2019
Available online 12 October 2019
0920-1211/

presents as memory impairment, labile mood, psychotic feature, or seizure (Graus et al., 2016). Generally, LE is considered an autoimmune etiology and has been proposed as a cause of refractory SE (Kaplan and Probasco, 2017; Salter and Lane, 2014).

The involvement of limbic structures in NORSE cases and refractory SE cases of LE suggest an intersection between NORSE and LE. To date, limited data are available to support the possibility of an intersection between NORSE and LE. In addition, there is no definite radiologic prognostic factors to predict patients' functional outcome in NORSE. In this study, we aimed to describe patients who fulfilled the diagnostic criteria of LE and definition of NORSE and to propose the radiologic prognostic factors that might be relevant in patients with NORSE and LE.

2. Materials and methods

2.1. Patients

We retrospectively analyzed selected patients from January 2006 to December 2018 in an institutional neuro-ICU and EEG database who met the recently proposed diagnostic criteria for LE (Graus et al., 2016) and the definition of NORSE (Hirsch et al., 2018) at the initial presentation. Among selected patients, we excluded patients based on the following exclusion criteria: 1) patients having well-known autoantibodies and 2) absence of follow-up MRI between 10–20 days after first MRI at admission.

In all suspected LE patients, we recorded symptoms known to be associated with LE from families of patients using self-reported questionnaires and thorough history taking, which included documented fever, febrile or chilling sensation, headache, insomnia, hallucination, recent memory impairment, language problem, labile mood, aggression, and psychotic characteristics.

2.2. EEG and MRI acquisition

All patients underwent electroencephalography (EEG) either through continuous monitoring or repeated routine EEG. All EEG electrodes were placed according to the international 10–20 system. EEG data were reviewed and interpreted by an expert adult epileptologist (K.H.) and experienced adult epileptologist (J.Y.C.), according to the 2012 ACNS terminology (Hirsch et al., 2013). Electrographical seizures were defined by the Salzburg criteria (Beniczky et al., 2013). Any discrepancies were resolved following thorough review and discussion amongst investigators. All patients underwent brain MRI using 1.5 T or 3 T MRI at admission day. Initial MRIs included axial T1, axial T2, axial FLAIR, axial DWI, ADC, and T1 gadolinium enhancement images. Follow up MRIs were taken depending on patient's condition between 10–18 days after admission. Any high signal intensity lesions on FLAIR or T2 images were considered as newly developed lesion. Review of MRIs were performed by an experienced neuroradiologist (E.J.K.) without any of the patient's clinical information.

2.3. Laboratory evaluation

All patients were examined with routine blood and cerebrospinal fluid (CSF) tests during their initial examination. Blood tests and CSF tests were performed in addition to routine tests to identify various causes of SE, including autoimmune diseases and infectious causes. The tested panels of blood tests and CSF tests performed in all patients were as follows: rheumatoid factor, ANA, anti-dsDNA, ANCA, antiphospholipid Ab, thyroid antibody, IgG, and IgM for several viruses (including HSV, VZA, EBV, and CMV), viral PCR (HSV, VZV, and enterovirus), Jo-1, anti-Ro/La, C-reactive protein, erythrocyte sedimentation rate, electrophoresis, CSF oligoclonal band, serum ACE level, and CSF IgG index. All patients were tested for onconeuronal antibodies. Following 2012, the antibody test for neuronal surface antigen was performed. Additionally, all patients were assessed for malignancies with chest CT and abdominopelvic CT, with male patients also evaluated with testicular ultrasonography.

2.4. Statistical analysis

Statistical analysis was conducted using SPSS 18.0. Patients were divided two groups according to their mRS at discharge. Differences between the good outcome ($mRS \leq 2$) and poor outcome ($mRS > 2$) analyzed the χ^2 test, Fisher's exact test, or Mann Whitney U-test, as appropriate, for both continuous and categorical variables

3. Results

3.1. Patient selection and clinical features

Eighteen patients were selected from January 2006 to December 2018, who fulfilled both diagnostic criteria of LE and NORSE. Among the 18 patients, 5 were excluded as 3 patients were diagnosed with autoantibody induced autoimmune encephalitis (2 patients had anti-NMDA receptor encephalitis and 1 patient had anti-LGI1 encephalitis) and 2 patients did not undergo follow-up MRI between 10 and 18 days after initial MRI. Thereafter, 13 patients were finally selected. Table 1 summarizes the clinical characteristics, evaluation results, treatments, and outcomes of included patients.

The median age was 45 years (interquartile range [IQR] = 33–50.5), with seven male and six female patients. The most common constitutional symptoms were myalgia and febrile sense/documented fever. Nine patients (69.2%) had myalgia and 8 patients (61.5%) had fever. Headaches were reported in five patients. The most common limbic symptom was memory impairment and confusion. Seven patients (53.8%) showed memory impairment or confusion. The median interval between onset of prodromal symptoms and SE was 5 days (IQR = 4–7). Median body temperature at arrival was 37.6 °C (IQR = 37–38.05). Median C-NORSE score according to previous report (Iizuka et al., 2017) was 5 (IQR = 4–5)

3.2. Results of blood and cerebrospinal fluid evaluation

At initial blood evaluation, eight patients (61.5%) showed elevated AST and ALT and six of the 8 elevated liver enzyme patients had elevated creatine kinase. Six patients (46.2%) patients showed thrombocytopenia, five of 6 thrombocytopenia patients had elevated AST/ALT and three of the 6 thrombocytopenia patients had leukopenia. One patient had only thrombocytopenia. Median C-reactive protein was 0.52 mg/dl (IQR = 0.19–1.12). Following CSF evaluation, median opening pressure was 165 mmH_2O (IQR = 122.5–205), median white blood cell counts were 2 (IQR = 1–21.5), median protein level in CSF was 42 mg/dl (IQR = 38.5–50.5), and median glucose level in CSF was 75 mg/dl (IQR = 68–100). All patients did not have any systemic rheumatologic disease or underlying malignancy after thorough investigation.

3.3. Electroencephalographic findings and treatment of patients

Nine patients were initially diagnosed with generalized convulsive SE. After the second-line AED treatment, five patients changed to subtle SE and three persistently showed generalized convulsions. The four remaining patients were initially diagnosed as having complex partial SE (CPSE). On EEG monitoring, all patients showed electrographical seizures from right or left temporal areas. The most common interictal period was generalized periodic discharge (53.8%), followed by bilateral independent lateralized periodic discharge (38.5%) and lateralized periodic discharge (7.7%). Eleven patients (84.6%) received induced coma therapy by using continuous anesthetics, such as midazolam, propofol, or pentobarbital. All 11 patients who received

Table 1
Summarized data of all of the selected patients.

Total case number, n			13
Male:Female			7:6
Age, mean (median, IQR)			45 (33, 49)
Prodromal symptoms	Constitutional symptoms	Fever, chilling, febrile sensation (n, %)	8 (61.5)
		Headache (n, %)	5 (38.5)
		Myalgia (n, %)	9 (69.2)
		URI Sx (n, %)	4 (30.8)
		Nausea/vomit (n, %)	3 (23.1)
	Symptoms suggest limbic system involvement	Drowsiness/somnolence (n, %)	3 (23.1)
		Memory impairment (n, %)	7 (53.8)
		Confusion (n, %)	7 (53.8)
		Language abnormality (n, %)	5 (38.5)
		Labile mood (n, %)	1 (7.7)
Interval between prodromal Sx and SE (median, IQR)			6 (4, 7)
Body temperature at arrival, ‘C (median, IQR)			37.6 (37, 38.05)
Blood test		WBC, counts/μl, (median, IQR)	4500 (3700-10245)
		Platelet, counts/μl, (median, IQR)	126 K (87.5K-165 K)
		AST, U/L (median, IQR)	63 (24-203)
		ALT, U/L (median, IQR)	56 (17.5-242.5)
		CRP, mg/dl (median, IQR)	0.52 (0.19-1.12)
		CK, U/L (median, IQR)	215 (93-1218.5)
CSF test		Pressure, mmH_2O (median, IQR)	165 (122.5-205)
		WBC, counts/μl, (median, IQR)	2 (1-21.5)
		Protein, mg/dl, (median, IQR)	42 (38.5-50.5)
		Glucose, mg/dl, (median, IQR)	75 (68-100)
Clinical presentation of SE	Initial	GCSE (n, %)	9 (69.2)
		CPSE (n, %)	4 (30.8)
	After 2nd Tx	GCSE (n, %)	3 (23.1)
		CPSE (n, %)	5 (38.5)
		SSE (n, %)	5 (38.5)
EEG finding		Seizure (n, %)	13 (100)
		GPD (n, %)	7 (53.8)
		Bi-PD (n, %)	5 (38.5)
		LPD (n, %)	1 (7.7)
Treatment	Anti-seizure	Median number of concomitant AED	3 (3, 4.5)
		Induced coma therapy (n, %)	11 (84.6)
		Burst suppression (n, %)	11 (84.6)
	Immunotherapy	Steroid/IvIgG (n, %)	13 (100)
		Plasma exchange (n, %)	6 (46.2)
		Rituximab (n, %)	2 (15.4)
C-NORSE score (median, IQR)			5 (4, 5)
Lesion on follow up MRI except bilateral mesial temporal regions		Claustrum (n, %)	10 (76.9)
		Pulvinar (n, %)	2 (15.4)
		Neocortex (n, %)	3 (23.1)
Outcome		Tracheostomy (n, %)	7 (53.8)
		ICU stay (median, IQR)	21 (15.5-69)
		Hospitalization (median, IQR)	46 (32.5-91)
		mRS at discharge (median, IQR)	3 (2-5)

Abbreviations: URI = upper respiratory tract infection, Sx = symptoms, SE = status epilepticus, WBC = white blood cell, AST = aspartate transaminase, ALT = alanine transaminase, CRP = C-reactive protein, CK = Creatine Kinase, CSF = cerebrospinal fluid, GCSE = generalized convulsive status epilepticus, CPSE = complex partial status epilepticus, SSE = subtle status epilepticus, EEG = electroencephalography, GPD = generalized periodic discharge, Bi-PD = bilateral independent lateralized periodic discharge, LPD = lateralized periodic discharge, AED = antiepileptic drug, IvIgG = intravenous immunoglobulin G, C-NORSE = cryptogenic new onset refractory status epilepticus, MRI = magnetic resonance image, ICU = intensive care unit, mRS = modified Rankin scale.

coma therapy achieved burst suppression patterns on their EEG. All 13 patients were treated with simultaneous or sequential intravenous prednisolone and immunoglobulin as first-line immunotherapy. Six patients (46.2%) were treated with plasmapheresis and two patients were treated with rituximab as second-line immunotherapy. All patients were treated with multiple anti-epileptic medications. The median number of AEDs was 3 (IQR = 3–4.5).

3.4. Magnetic resonance imaging findings

All patients showed bilateral mesial temporal high signal intensity at their first MRI. Intriguingly, 10 of the 13 patients (76.9%) showed bilateral claustrum involvement at their subsequent follow up MRI. Among the 10 claustrum-involved patients, 3 showed neocortex involvement and 2 showed bilateral pulvinar involvement. Based on these imaging findings at follow-up MRI, patients were classified as follows: 1) patients who only showed bilateral mesial temporal involvement; 2) patients who showed bilateral mesial temporal and claustrum involvement; and 3) patients who showed bilateral mesial temporal, claustrum, and neocortex/pulvinar involvement. Fig. 1 shows MRI findings of each type of classification according to involvement pattern.

3.5. Outcomes according to imaging findings

Different clinical outcome/prognosis were noted according to each of the three types. Of the three groups, group 3 had the highest proportion of patients who received tracheostomy, the longest ICU stay, hospital stay and highest mRS. Table 2 summarizes the clinical outcomes according to the three groups. We compared variables between patients with good outcome (mRS ≤ 2) and poor outcome (mRS > 2), follow up MRI finding was the only significant variable between two groups. Table 3 summarizes the comparison of variables between two groups.

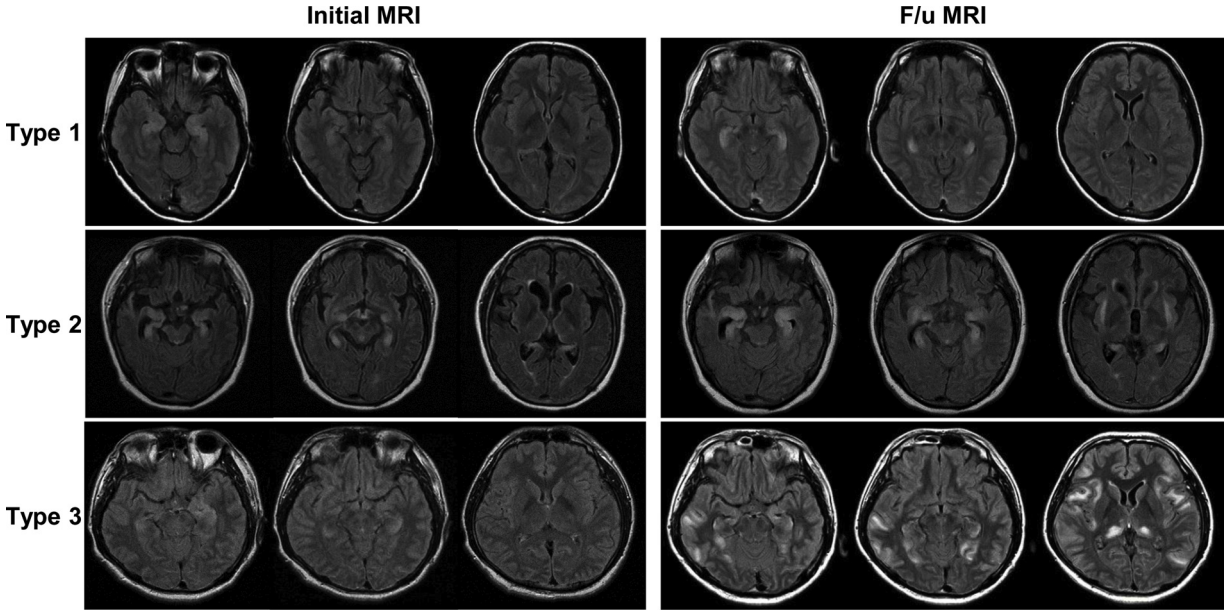

Fig. 1. Representative images of patient grouping according to lesion involvement at follow up magnetic resonance image. Type 1 group showed no lesion extension. Type 2 showed lesion extension only in claustrum. Type 3 showed diffuse lesion extension including claustrum with or without pulvinar involvement.

Table 2
Clinical outcomes according to follow up imaging type.

	Type 1 (n = 3)	Type 2 (n = 7)	Type 3 (n = 3)
Tracheostomy %, (n)	33.3 (1)	57.1 (4)	66.6 (2)
ICU stay, day, median (IQR)	17 (15-17)	21 (7-57)	102 (16-102)
Hospital stay,day, median (IQR)	46 (29-46)	41 (36-80)	102 (16-102)
mRS, median (IQR)	2 (2-2)	3 (2-3)	6 (6-6)

Abbreviations: ICU = intensive care unit, mRS = modified Rankin scale.

4. Discussion

This study described the clinical, electrographical, serological and radiological features of patients who fulfilled with both criteria of NORSE and LE. Half of NORSE-LE patients showed thrombocytopenia, or leukopenia at their initial evaluation. Notably, almost all patients showed lesion progression from mesial temporal area to extratemporal structures. The claustrum was the most common extratemporal involvement site, and extratemporal involvement was associated with poor prognosis.

4.1. Appropriateness of NORSE-LE diagnosis

According to recently proposed diagnostic criteria, definite LE could be diagnosed, if the following criteria are met; 1) Subacute onset of memory deficits, seizures or psychiatric symptoms suggesting involvement of the limbic system. 2) Bilateral highly restricted medial temporal lobes abnormality on fluid-attenuated inversion recovery MRI. 3) CSF pleocytosis or EEG with epileptic or slow-wave activity involving the temporal lobes. 4) Exclusion of alternative causes. Although we cannot completely rule out the possibility that bilateral temporal abnormalities were caused by prolonged seizure and the possibility of seizure related CSF pleocytosis, all of the initial features of included patients complied with the definite LE criteria. Until now, there is no criteria for when to take MRI in LE patients. There is also no standard for follow up MRI in LE patients. Therefore, we think this study may provide a suggestion for taking MRI in LE patients.

Recent consensus definition of febrile infection-related epilepsy syndrome (FIRES) is considered as a subcategory of NORSE (Gaspard et al., 2018). NORSE-LE patients in this study do not seem to be a significant difference if they are regarded as FIRES. In previous studies, however, ninety-six percent of patients with FIRES had preceding fever (Kramer et al., 2011) but only one third of patients with NORSE had preceding fever (Gaspard et al., 2015). Therefore, strictly applying rule of preceding fever, we think included patients in this study are closer to NORSE than FIRES.

LE has been considered one of the causes of SE (Gaspard, 2016; Kaplan et al., 2012). However, few studies have directly addressed the relationship between LE and NORSE (Hainsworth et al., 2014; Kaplan and Probasco, 2017). Almost of the articles on LE and SE focused on causative antibodies. In this paper, however, we focused on patients who met both cryptogenic NORSE and LE. This is the first report on the imaging prognostic factor of patients who meet both cryptogenic NORSE and antibody negative LE, we ever known, and the novelty in this article is due here. However, because of the small number of patients and the possibility of undiagnosable autoantibody, we think that a more thorough larger cohort-based approach is needed for clearly defining NORSE-LE entity.

4.2. Relevance of abnormal blood test results

About half of NORSE-LE patients showed thrombocytopenia or leukopenia. These findings in febrile patients might be considered as the results of a part of systemic inflammatory responses such as atypical bacterial infections, viral infections, or autoimmune phenomena. In the case of FIRES, some triggering factors such as viral infections provoke the inflammatory reaction, which leads to SE generation and persistence (Nabbout et al., 2011; van Baalen et al., 2017). The combination of blood tests findings in NORSE-LE patients and the hypothetical mechanism of FIRES suggest that NORSE-LE in this study was also caused by a similar mechanism. In addition, the detailed immunological pathomechanisms may be different between patients with thrombocytopenia or leukopenia and patients without that findings. This part may need comparison in larger cohort studies in the future.

4.3. Comparison to recently reported NORSE cohorts

There are considerable similarities between the NORSE-LE patients and individuals with NORSE with claustrum involvement. As one-third

Table 3
Comparison between good outcome and poor outcome groups.

Variables		Good outcome, (mRS ≤ 2, n = 6)	Poor outcome, (mRS > 2, n = 7)	*p value*
Age		45.0 ± 9.9	40.6 ± 9.1	*0.628*
Male		3 (50%)	4 (57.1%)	*0.797*
Body temperature, ‘C		37.6 ± 0.6	37.7 ± 1.0	*0.945*
Blood	WBC, counts/μl,	6500 ± 7277	8798 ± 6802	*0.234*
	Platelet, counts/μl,	124 K ± 43 K	173 K ± 139 K	*0.836*
	AST, U/L	128 ± 148	106 ± 93	*0.775*
	ALT, U/	95 ± 117	166 ± 192	*0.475*
	CRP, mg/dl	0.38 ± 0.25	2.32 ± 3.72	*0.174*
	CK, U/L	231.7 ± 290.6	1295.1 ± 1555.1	*0.153*
CSF	Pressure, mmH_2O	180.0 ± 45.3	162.4 ± 49.5	*0.475*
	WBC, counts/μl,	2 ± 1.9	17.1 ± 16.9	*0.145*
	Protein, mg/dl,	39 ± 7.3	48.9 ± 11.3	*0.101*
	Glucose, mg/dl,	81.5 ± 31.0	88.6 ± 22.7	*0.316*
SE presentation	Initial GCSE	3 (50%)	6 (85.7%)	*0.164*
	GCSE after 2nd Tx.	0	3	*0.084*
EEG finding	EEG Seizure	6	7	–
	GPD	3 (50%)	4 (57.1%)	*0.797*
	Bi-PD	2 (33.3%)	3 (42.9%)	*0.725*
Treatment	Coma therapy	4 (66.6%)	7 (100%)	*0.097*
	Plasmapheresis	2 (33.3%)	4 (57.1%)	*0.391*
	Rituximab	2 (33.3%)	0	*0.097*
MRI type	Type 1	3	0	*0.047*
	Type 2	3	4	
	Type 3	0	3	

Abbreviations: SE = status epilepticus, WBC = white blood cell, AST = aspartate transaminase, ALT = alanine transaminase, CRP = C-reactive protein, CK = Creatine Kinase, CSF = cerebrospinal fluid, GCSE = generalized convulsive status epilepticus, CPSE = complex partial status epilepticus, SSE = subtle status epilepticus, EEG = electroencephalography, GPD = generalized periodic discharge, Bi-PD = bilateral independent lateralized periodic discharge, LPD = lateralized periodic discharge, AED = antiepileptic drug, IvIgG = intravenous immunoglobulin G, C-NORSE = cryptogenic new onset refractory status epilepticus, MRI = magnetic resonance image, ICU = intensive care unit, mRS = modified Rankin scale.

of NORSE patients with claustrum involvement showed medial temporal involvement and one patient was reported to have pulvinar involvement (Meletti et al., 2017), there is a possibility of overlap between these NORSE-LE and NORSE with claustrum involvement patients. However, scarce data were available about the prognostic significance of claustrum or pulvinar involvement in previous reports (Meletti et al., 2017, 2015). More cases are needed to generalize the prognostic significance of claustrum or pulvinar involvement in NORSE.

In this study, it is not possible to completely exclude autoantibodies against neuronal surface antigens; although there are few differences, NORSE-LE patients appear that there are many aspects similar to the previously reported cryptogenic NORSE (Iizuka et al., 2017). Unlike previously reported C-NORSE, most patients in this study presented with symptoms suggesting an involvement of the limbic system with memory impairment and related symptoms. The median C-NORSE score was 5 (IQR = 4–5) in the present study, with previous studies reporting a median C-NORSE score of 6 in C-NORSE patients and 0 in anti-NMDA receptor antibody encephalitis (Iizuka et al., 2017). These differences suggest the subcategory may exist within cryptogenic NORSE. The differences in presented symptoms presumably were caused by differences in the involved lesions in previous reports and in this study.

4.4. Lesion extension in follow-up MRI and its relevance

Prolonged seizures can change MRI signals (Chatzikonstantinou et al., 2011; Mendes and Sampaio, 2016). At onset or in the early period of seizures, there are vasogenic edemas around the ictal onset zone because of hyperperfusion due to the seizure-induced hypermetabolic state. Apart from SE-induced vasogenic edema, during and after abnormally prolonged continuing seizure, cytotoxic edema appeared due to failure for compensation from the seizure-induced hypermetabolic state. In the present study, the claustrum was the most common site of lesion propagation, followed by the neocortex and pulvinar. This may be due to the continuing epileptic seizure, which is not detected by scalp EEG, and the accompanying excessive energy demand, resulting in MRI signal changes to structures that are closely related to the mesial temporal structure. In particular, in the case of the claustrum, there are various reports of a close relationship between the claustrum and limbic system. Furthermore, there are reports of a close connection between mesial temporal structures and the claustrum during electrical stimulation or limbic seizure (Dillingham et al., 2017; Markowitsch et al., 1984; Wada and Kudo, 1997; Wilhite et al., 1986). In a recent DTI study in humans, an anatomical direct link to the mesial temporal limbic structure and the claustrum has also been reported (Milardi et al., 2015). Therefore, there is a solid interconnection between the claustrum and limbic structures with respect to changes in MRI signals through seizure propagation. Similar to the claustrum, the pulvinar is also known to be closely related to the temporal limbic seizure (Rosenberg et al., 2006). A previous study has reported about 7.5% of SE patients having a pulvinar lesion in MRI within 24 h after onset (Ohe et al., 2014). One autopsy study showed neuronal loss and gliosis in SE-related pulvinar lesions and suggested excessive metabolic demand as a cause (Hernandez-Lain et al., 2013). The function of posterior gray matter of the thalamus and pulvinar is known to mediate respiration regulation, and the pulvinar has been associated with sudden unexpected death in epilepsy patients (Wandschneider et al., 2015). Therefore, pulvinar damage might contribute to the death of the two pulvinar-involvement patients.

In summary, electrical seizures undetectable by scalp EEG might change the MRI signals of structures that are closely associated with mesial temporal structures. In addition, extra-temporal involvement was found to be associated with poor prognosis.

4.5. Limitations

This study has limitations. First, there was the possibility of autoimmune encephalitis against neuronal surface antigen in our patients. Because autoantibody assay to neuronal surface antigen was available

at 2012 in Korea, six patients couldn't evaluate autoantibody assay. However, clinical features, imaging findings and C-NORSE score in our patients showed distinction from anti-NMDA encephalitis. Second, this is a retrospective and descriptive study conducted at an acute tertiary referral hospital. Therefore, it is possible that patients with more severe symptoms were included. Finally, the sample size was relatively small, because we strictly selected patients fulfilled both LE criteria and NORSE definition. Therefore, multicenter and larger cohort study should be necessary for generalization of our findings.

5. Conclusion

Subsequent extratemporal involvement is thought to be important for prognosis in NORSE-LE patients. Therefore, follow up MR imagings in NORSE-LE patients can help to determine further treatment strategy. Our study explores a new subtype of NORSE and suggests a possible common underlying pathomechanism between NORSE and LE. A larger cohort study is needed to validate our findings.

Declaration of Competing Interest

None.

Acknowledgements

This research was supported by the National Research Foundation (NRF) funded by the Korean government (MSIT) (NRF-2018M3A9E8023853, NRF-2018R1C1B6006145 and NRF-2019R1A5A2026045).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.106215.

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