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Status epilepticus in the elderly: Prognostic implications of rhythmic and periodic patterns in electroencephalography and hyperintensities on diffusion-weighted imaging

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ABSTRACT

Objective: To delineate the clinical characteristics and functional outcome of status epilepticus (SE) in elderly people, and elucidate prognostic implications of SE-associated rhythmic and periodic patterns (RPPs) in electroencephalography and hyperintensities on diffusion-weighted imaging.
Methods: We retrospectively investigated 107 consecutive patients with SE aged ≥ 65 years in a comprehensive community hospital. RPPs were classified using the 2012 American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology. Poor outcome was defined as an increase in modified Rankin Scale (mRS) score at discharge compared with that at baseline, including death.
Results: Median age of patients was 80.0 years. Median mRS score at baseline was 3. Thirty-four patients (31.8%) had a previous diagnosis of epilepsy. Cerebrovascular disease and dementia were major etiologies. Poor outcome occurred in 41 (38.3%). In electroencephalography, periodic discharges (PDs) were present in 21.0% (22/105), rhythmic delta activity (RDA) in 10.5% (11/105), and conventional seizure patterns in 9.5% (10/105). Diffusion-weighted hyperintensities associated with SE were observed in 28.0% (26/93). With univariate analysis, poor outcome was significantly associated with no previous diagnosis of epilepsy, etiology, refractory SE, specific electroencephalographic patterns (PDs and conventional seizure patterns, but not RDA), and diffusion-weighted hyperintensities. With multivariate logistic regression analysis, diffusion-weighted hyperintensities (OR 6.13 [95% CI 1.72–21.9]) and refractory SE (OR 5.36 [95% CI 1.28–22.4]) were independently associated with poor outcome.
Conclusions: SE often occurred as the first seizure in already disabled elderly people, further worsening their functional disabilities. Diffusion-weighted hyperintensities and refractory SE, but not RPPs in electroencephalography, were independent functional prognostic factors.

1. Introduction

Status epilepticus (SE) is a common neurological emergency with high morbidity and mortality, and associated with high economic burden [1]. Epidemiological studies have shown that both incidence of and mortality in SE are higher in elderly people [2–7]. Although the global population is rapidly aging, a thorough study on SE in this population, which assesses their functional outcome with an objective score rigorously, and analyzes sufficient electroencephalography (EEG) and magnetic resonance imaging (MRI) data, is lacking.

Abbreviations: ACNS, American Clinical Neurophysiology Society; ADC, apparent diffusion coefficient; cEEG, continuous electroencephalography; CSE, convulsive status epilepticus; DWI, diffusion-weighted imaging; EEG, electroencephalography; EMSE, Epidemiology-based Mortality score in SE; FLAIR, fluid-attenuated inversion recovery; GPDs, generalized periodic discharges; GRDA, generalized rhythmic delta activity; ILAE, International League Against Epilepsy; IQR, interquartile range; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NCSE, nonconvulsive status epilepticus; PDs, periodic discharges; RDA, rhythmic delta activity; RPPs, rhythmic and periodic patterns; SE, status epilepticus; STESS, Status Epilepticus Severity Score; SW, spike-and-wave.

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Rhythmic and periodic patterns (RPPs) in EEG are generally considered to represent ictal-interictal continuum in critically ill patients [8], and are observed in the ictal and peri-ictal phase of SE. The 2012 American Clinical Neurophysiology Society (ACNS)'s Standardized Critical Care EEG Terminology was proposed to describe RPPs in critically ill patients, to allow multicenter research projects and to facilitate communication among clinicians as well as researchers [9]. However, the clinical significance of classifying RPPs in SE by this new terminology has not been well elucidated.

Hyperintensities on diffusion-weighted MRI (DWI) are sometimes observed in specific regions of the brain (e.g., cerebral cortex, thalamus, hippocampus) in the ictal and peri-ictal phase of SE [10–12]. However, the pathophysiology of this abnormal signal is not precisely understood, and its clinical impact on the outcome of SE has not been investigated.

The aim of this study was to delineate clinical, EEG and DWI features of SE in elderly patients, and to elucidate its functional prognostic factors, especially the prognostic significance of RPPs and diffusion-weighted hyperintensities.

2. Methods

2.1. Study design and participants

We retrospectively searched the admission database of the neurology department of Kobe City Medical Center General Hospital, a comprehensive community hospital in Kobe, Japan from July 2011 through October 2014 for patients aged 65 years or older who were admitted for SE. Simple partial SE and postanoxic SE were excluded. All electric medical records and available EEGs of patients with possible SE were inspected to identify eligible patients. A standardized form was used to collect clinical data when reviewing medical records, EEGs and MRIs. The institutional review board of Kobe City Medical Center General Hospital approved this study (zn150412) and waived the need for written informed consent, because this retrospective, observational study involved no experimental intervention and no risk to patients.

2.2. Definition of SE and other variables

SE was defined as either >30 min of continuous seizure activity, or intermittent seizures without full recovery of consciousness between the consecutive seizures. We adopted this definition of SE to include only patients with definite SE, because it can be difficult to accurately estimate the duration of SE in a retrospective study. SE was labeled as refractory when a benzodiazepine and another antiepileptic drug could not discontinue the clinical or EEG seizure activity.

Seizure types of SE were classified electro-clinically, i.e., focal vs. generalized, and convulsive vs. nonconvulsive. Seizures were labeled as generalized when rhythmic jerking of the extremities was observed bilaterally, or when EEG revealed generalized seizure patterns; otherwise they were considered focal. Seizures were regarded as convulsive once apparent rhythmic jerking of the extremities (with the exception of subtle motor movements, such as rhythmic muscle twitches or tonic eye deviation) was observed during the course of SE. For the definition of nonconvulsive SE (NCSE), the working clinical criteria for NCSE in 2013 were used [13].

Etiologies of SE were classified by the International League Against Epilepsy (ILAE)'s guidelines for epidemiologic studies on epilepsy in 1993 [14], but the progressive symptomatic etiology was incorporated into the remote symptomatic etiology, resulting in three major categories: acute symptomatic, remote symptomatic, and cryptogenic. Acute symptomatic etiologies were further specifically defined by the ILAE's recommendation for a definition of acute symptomatic seizure in 2010 [15]. Patients with SE who had no etiological causes other than degenerative dementia (e.g., Alzheimer disease and dementia with Lewy bodies) were classified into dementia in the remote symptomatic etiology.

Patients' functional disability and mortality were assessed at baseline and at hospital discharge by modified Rankin Scale (mRS) [16]. The baseline mRS was evaluated by interviewing patients and/or their families during hospitalization. Poor outcome was defined as an increase in mRS score at discharge compared with that at baseline, including in-hospital death.

2.3. EEG recordings and data classification

Routine video EEG was performed for at least 20 min as soon as possible after admission, using the international 10–20 system with 21 electrodes (Neurofax EEG-1200; Nihon Kohden, Tokyo, Japan). Band pass filters were set at 0.5 and 120 Hz, and a notch filter was used as needed. All of the first EEG recordings after admission were reviewed at the time of the study by a board-certified neurophysiologist (R.M.) and a board-certified neurologist (H.Y.), who were blinded to clinical information other than that patients were admitted for SE. RPPs were defined as rhythmic or periodic discharges that were continuous or abundant (i.e., present for >50% of the recording period), and classified by the 2012 ACNS's Standardized Critical Care EEG Terminology [9], using "main term 1" (generalized [G], lateralized [L], bilateral independent [BI], multifocal [Mf]) and "main term 2" (periodic discharges [PDs], rhythmic delta activity [RDA], spike-and-wave [SW]). The following patterns without RPPs were designated as "conventional seizure patterns": generalized spike-wave discharges of 3 Hz or faster; and clearly evolving discharges of any type that reach a frequency > 4 Hz, whether focal or generalized. When judgment was not unanimous, consensus was achieved by discussion between two reviewers.

2.4. Neuroimaging assessment

All patients underwent brain computed tomography on admission. Brain MRI was performed as soon as possible after admission with a 1.5 or 3-T MRI system (Magnetom Avanto 1.5T and Skyra 3T, Siemens, Munich, Germany), excluding patients who had metallic implants or unstable general condition, or who were considered to have no need for it by treating physicians. Transverse DWI and fluid-attenuated inversion recovery (FLAIR) images were acquired. Scanning parameters are shown in Supplementary Table 1. All images were reviewed at the time of the study by a board-certified radiologist (H.U.) and a board-certified neurologist (H.Y.), independently, who were blinded to clinical information other than that patients were admitted for SE. Diffusion-weighted hyperintensities associated with SE were inspected visually, especially in the cerebral cortex, thalamus, hippocampus, cerebellum and splenium of the corpus callosum, regardless of apparent diffusion coefficient (ADC) values. When ADC was reduced, they were discriminated from acute ischemic stroke with their characteristic location, distribution and/or time course. When ADC was not reduced, they were discriminated from old lesions with their normal intensity on simultaneous FLAIR images or their disappearance at follow-up FLAIR images. When judgment was not unanimous, consensus was achieved by discussion between two reviewers.

2.5. Treatment

Convulsive SE (CSE) was treated basically according to the standardized protocol: diazepam (0.1–0.15 mg/kg intravenously, repeated if necessary) as the first-line drug; phenytoin/fosphenytoin (15 mg phenytoin equivalents/kg intravenously) as the second-line drug; and anesthetic drugs (propofol or midazolam, dosing titrated to cessation of electrographic seizures) as the third-line drug. Phenobarbital (10–15 mg/kg intravenously) could be used as the second- or the third-line drug when phenytoin/fosphenytoin was contraindicated or when treating physicians preferred it to anesthetic drugs. NCSE was mostly treated at the discretion of treating physicians, although the treatment protocol was basically the same as that for CSE.

2.6. Statistical analysis

All data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY). First, univariate analyses were conducted to identify variables significantly associated with poor outcome, using Pearson's chi-square and Fisher's exact tests as appropriate. Then, all variables statistically significant in univariate analyses were entered into a multivariate logistic regression model to identify independent predictors of poor outcome. All available data were included in univariate analyses. Patients with any missing data were excluded from subsequent multivariate analysis. Variables assessed as prognostic factors were compared between patients with and without missing data, using Pearson's chi-square and Fisher's exact tests as appropriate. Interrater agreement between two reviewers on EEG patterns and diffusion-weighted hyperintensities was evaluated by Cohen's kappa (κ) statistics. All statistical analyses were 2-tailed, and p values < 0.05 were considered statistically significant.

3. Results

We identified 107 consecutive elderly patients with SE (43 men and 64 women). The clinical characteristics of these patients are summarized in Table 1. The median age was 80.0 years. The median mRS score at baseline was 3. Only 34 patients (31.8%) had a previous diagnosis of epilepsy. In other words, SE was the first seizure for ~70% of patients. With regard to the seizure type of SE, 98 patients (91.6%) had CSE, and 9 patients (8.4%) had NCSE. In 15 patients, CSE developed into NCSE clinically or electroencephalographically, and these patients were classified into CSE. SE was refractory in 33 patients (30.8%). The median mRS score at discharge was 4. Forty-one patients (38.3%) had poor outcomes, including seven in-hospital deaths (6.5%). The breakdown of mRS scores at baseline and at discharge is shown in Fig. 1. The etiology of SE was as follows: acute symptomatic, 23 (21.5%); remote symptomatic, 66 (61.7%); cryptogenic, 18 (16.8%). Acute and remote cerebrovascular disease and dementia accounted for 63 patients (58.9%). Intravenous antiepileptic drugs actually used and their doses are shown in Supplementary Table 2.

Table 1
Clinical characteristics of status epilepticus in the elderly.

Characteristic	Value (n = 107)
Age, median (range), years	80.0 (66–98)
Male	43 (40.2)
mRS score[a] at baseline, median (IQR)	3.0 (2.0–4.0)
Living in nursing home	34 (31.8)
Duration of hospitalization, median (IQR), days	16.0 (8.0–28.0)
Previous diagnosis of epilepsy	34 (31.8)
Seizure type	
Focal convulsive	39 (36.4)
Focal nonconvulsive	7 (6.5)
Generalized convulsive	59 (55.1)
Generalized nonconvulsive	2 (1.9)
Refractory status epilepticus	33 (30.8)
Clinical refractory status epilepticus	18 (16.8)
Electrical refractory status epilepticus	15 (14.0)
mRS score[a] at discharge, median (IQR)	4.0 (3.0–4.0)
Poor outcome	41 (38.3)
Death	7 (6.5)
Etiology	
Acute symptomatic	23 (21.5)
Acute cerebrovascular disease	10
Drug withdrawal	4
CNS infection	2
Autoimmune encephalitis	2
Acute traumatic brain injury	2
Others[b]	3
Remote symptomatic	66 (61.7)
Remote cerebrovascular disease	38
Dementia	15
Remote traumatic brain injury	7
Brain tumor	4
Others[c]	2
Cryptogenic	18 (16.8)

Data are presented as number (percentage) of patients unless otherwise indicated.
CNS, central nervous system; IQR, interquartile range; mRS, modified Rankin Scale.
[a] Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.
[b] Hypertensive encephalopathy, 1; subdural hematoma, 1; hyperglycemia, 1.
[c] Post-encephalitis, 1; mental retardation, 1.

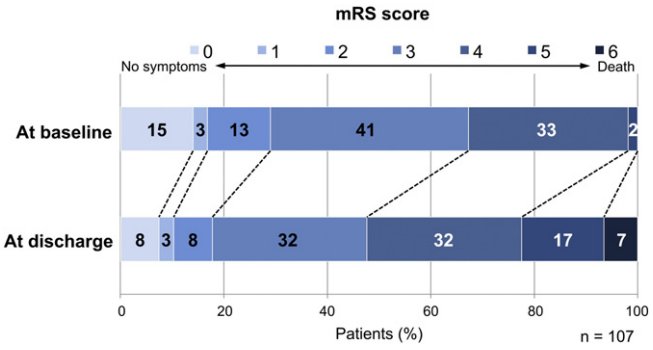

Fig. 1. Modified Rankin Scale (mRS) scores at baseline and at discharge in elderly people with status epilepticus.

3.1. EEG findings

EEG was performed in 105 patients with a median interval of one day after admission (interquartile range [IQR] 0–2 days). Lateralized periodic discharges (LPDs) were seen in 22 patients (21.0%); lateralized rhythmic delta activity (LRDA) in 8 (7.6%); generalized rhythmic delta activity (GRDA) in 3 (2.9%); and conventional seizure patterns in 10 (9.5%). Generalized periodic discharges [GPDs] and SW were not observed in this study population. Typical waveforms are shown in Supplementary Fig. 1. Interrater agreement between two reviewers was almost perfect (κ = 0.89, p < 0.001) on EEG patterns (i.e., LPDs, LRDA, GRDA, conventional seizure patterns, or none of these patterns).

3.2. Diffusion-weighted MRI findings

Brain MRI was performed in 93 patients with a median interval of zero days after admission (IQR 0–1 day). Abnormal hyperintensities on DWI associated with SE were observed in 26 patients (28.0%): cerebral cortex, 19; hippocampus, 10; thalamus, 9; cerebellum, 1 (Table 2). Typical findings are shown in Supplementary Fig. 2. More than one region was involved in 10 patients. In 25 patients, diffusion-weighted hyperintensities were unilateral. The cerebellar hyperintensity was also unilateral, but contralateral to those of the cerebral cortex, hippocampus and thalamus. Only one patient had bilateral thalamic lesions. Hyperintensities in the splenium of the corpus callosum were not observed in this study population. Interrater agreement between two reviewers on diffusion-weighted hyperintensities was almost perfect in thalamus (κ = 0.88, p < 0.001), and substantial in cerebral cortex

Table 2
Diffusion-weighted MRI findings in elderly people with status epilepticus.

Variable	Value (n = 93)
Presence of abnormal hyperintensities	26 (28.0)
in cerebral cortex alone	10
in hippocampus alone	5
in thalamus alone	1
in cerebral cortex and thalamus	5
in cerebral cortex and hippocampus	2
in hippocampus and thalamus	1
in cerebral cortex, hippocampus and thalamus	1
in cerebral cortex, hippocampus, thalamus and cerebellum	1

Data are presented as number (percentage) of patients.
MRI, magnetic resonance imaging.

(κ = 0.76, p < 0.001), hippocampus (κ = 0.73, p < 0.001), and cerebellum (κ = 0.66, p < 0.001).

3.3. Prognostic factors of status epilepticus in elderly people

With univariate analysis, poor outcome was significantly associated with no previous diagnosis of epilepsy (p = 0.003), etiology (acute symptomatic [p = 0.003] and remote symptomatic [p = 0.02] compared with cryptogenic), refractory SE (p < 0.001), specific EEG patterns (LPDs [p < 0.001] and conventional seizure patterns [p = 0.001]), and abnormal hyperintensities on DWI (p < 0.001) (Table 3). Including all these factors significant with univariate analysis into multivariate logistic regression analysis, only abnormal hyperintensities on DWI (odds ratio 6.13 [95% CI 1.72–21.9], p = 0.005) and refractory SE (odds ratio 5.36 [95% CI 1.28–22.4], p = 0.02) were revealed to be independent prognostic factors for poor outcome (Table 4). There were no statistically significant differences in variables assessed as prognostic factors between patients with and without missing data (Supplementary Table 3).

4. Discussion

In the present study, SE often occurred as the first seizure in already disabled elderly people, and further worsened their functional disabilities. Acute and remote cerebrovascular disease and dementia were major etiologies. RPPs were observed in 30% of patients, and diffusion-weighted hyperintensities associated with SE in 30%. Classifying RPPs by the 2012 ACNS's Standardized Critical Care EEG Terminology [9], PDs were associated with poor outcome in univariate analysis, while RDA was not. However, after adjusting for a previous diagnosis of epilepsy, etiology, and EEG patterns, only the presence of hyperintensities on DWI and refractory SE were independent functional prognostic factors.

Table 3
Univariate analysis of prognostic factors of status epilepticus in the elderly.

Variable	Poor outcome[a]	OR (95% CI)	p value
Age			
≥ 80	23/55 (41.8)	1.36 (0.62–2.97)	0.44
≤ 79	18/52 (34.6)	1.00	
Sex			
Female	22/64 (34.4)	0.66 (0.30–1.46)	0.31
Male	19/43 (44.2)	1.00	
mRS score at baseline			
≥ 3 (dependent)	26/76 (34.2)	0.56 (0.24–1.30)	0.17
≤ 2 (independent)	15/31 (48.4)	1.00	
Previous diagnosis of epilepsy			
Yes	6/34 (17.6)	0.23 (0.09–0.63)	**0.003**
No	35/73 (47.9)	1.00	
Etiology			
Acute symptomatic	13/23 (56.5)	10.4 (1.93–56.1)	**0.003**
Remote symptomatic	26/66 (39.4)	5.20 (1.10–24.5)	**0.02**
Cryptogenic	2/18 (11.1)	1.00 (reference)	
Seizure type			
Nonconvulsive	5/9 (55.6)	2.15 (0.54–8.54)	0.30
Convulsive	36/98 (36.7)	1.00	
Refractory status epilepticus			
Yes	24/33 (72.7)	8.94 (3.50–22.8)	< **0.001**
No	17/74 (23.0)	1.00	
EEG patterns			
LPDs	15/22 (68.2)	6.71 (2.31–19.6)	< **0.001**
GRDA or LRDA	2/11 (18.2)	0.70 (0.14–3.59)	> 0.99
Conventional seizure patterns	8/10 (80.0)	12.5 (2.40–65.6)	**0.001**
None of the other three patterns	15/62 (24.2)	1.00 (reference)	
Abnormal hyperintensities on DWI			
Yes	19/26 (73.1)	7.98 (2.86–22.3)	< **0.001**
No	17/67 (25.4)	1.00	

Significant p-values are shown in bold font.
CI, confidence interval; DWI, diffusion-weighted imaging; EEG, electroencephalography; GRDA, generalized rhythmic delta activity; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; mRS, modified Rankin Scale; OR, odds ratio.
[a] Data are presented as number/total number (percentage) of patients.

Table 4
Multivariate logistic regression analysis of prognostic factors of status epilepticus in the elderly (n = 91).

Variable	Adjusted OR (95% CI)	p value
Previous diagnosis of epilepsy		
Yes	0.34 (0.09–1.39)	0.13
No	1.00 (reference)	
Etiology		
Acute symptomatic	2.88 (0.33–25.0)	0.34
Remote symptomatic	4.58 (0.62–33.6)	0.14
Cryptogenic	1.00 (reference)	
Refractory status epilepticus		
Yes	5.36 (1.28–22.4)	**0.02**
No	1.00 (reference)	
EEG patterns		
LPDs	0.97 (0.18–5.29)	0.97
GRDA or LRDA	0.46 (0.06–3.60)	0.46
Conventional seizure patterns	5.78 (0.46–73.3)	0.18
None of the other three patterns	1.00 (reference)	
Abnormal hyperintensities on DWI		
Yes	6.13 (1.72–21.9)	**0.005**
No	1.00 (reference)	

Significant p-values are shown in bold font.
CI, confidence interval; DWI, diffusion-weighted imaging; EEG, electroencephalography; GRDA, generalized rhythmic delta activity; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; OR, odds ratio.

To the best of our knowledge, this retrospective study represents the largest cohort of the oldest elderly patients with both CSE and NCSE, where sufficient EEG and MRI data were available. Two previous studies on elderly SE were reported from Hong Kong [17] and India [18]. The retrospective study in Hong Kong included 80 elderly patients with only CSE with a median age of 74.2 years, which did not mention EEG and MRI data [17]. The prospective study in India reported 64 elderly patients with new-onset SE or cluster seizures with a mean age of 68.0 years, in which only 34 patients with SE and MRI data of 14 patients were included [18]. The percentage of patients with a previous diagnosis of epilepsy was low in our study (30%) as well as in the Hong Kong study (18.5%) [17], compared with that in overall adult SE (42–50%) [19]. It seems that elderly people are more likely to suffer from SE as their first seizure. Despite the retrospective study, we would not have missed most of the encephalopathic patients with NCSE, because EEG was routinely performed in any patients with altered mental status in our institution. However, this study is mainly a reflection of CSE in the elderly, because only 9 patients (8.4%) experienced NCSE alone, although CSE developed into NCSE in other 15 patients (14.0%).

We assessed the functional outcome of elderly people with SE by comparing their disabilities before and after SE using an objective score, namely mRS, because many elderly people have some physical and/or mental disabilities at baseline. To date, no study has evaluated their functional outcome elaborately in the same way. Although patients' disabilities after SE were judged at different time points, namely at the time of discharge, we considered their outcomes comparable, because all patients were discharged after their general and neurological conditions had recovered completely or become stable in the short term. We could not compare our results with those in previous studies on adult SE [20–23], because definitions of poor functional outcome and inclusion criteria of patients varied in each study. The case-fatality rate was lower than that of elderly patients in previous epidemiological studies from the late 1990s to the early 2000s (6.5% vs. 16–38%) [2,6]. This difference is probably because of the exclusion of postanoxic SE and advanced medical care of critically ill patients in the present study. In fact, a more recent large cohort study in the United States reported lower in-hospital mortality of elderly people with SE (8.0%), despite including postanoxic SE [24].

We classified RPPs by using “main term 1” and “main term 2” of the 2012 ACNS's Standardized Critical Care EEG Terminology [9], because

these two terms were reported to have high interrater agreement [25], which was also true in our study. Only one prospective study has described RPPs of adult SE with this new terminology and evaluated its relevance to the outcome [26]. They reported that the classification of RPPs as a whole was associated with the outcome in univariate analysis, but was not an independent prognostic factor after adjusting for the Status Epilepticus Severity Score (STESS) [27] and the presence of a potentially fatal etiology. In our study, we investigated the relevance of PDs and RDA to the outcome separately, and found that PDs were associated with poor outcome in univariate analysis, while RDA was not. This association, however, did not remain significant in multivariate analysis. Future studies on a larger cohort with sufficient clinical, EEG and MRI data would further delineate the relevance of each RPPs to the outcome. Although continuous EEG (cEEG) was not performed in our study, the association between distinctive EEG patterns (i.e., LPDs and conventional seizure patterns) and poor outcome was similar to the result of the previous prospective study applying cEEG [28]. Therefore, even emergent routine EEG could adequately detect characteristic EEG patterns to predict the outcome of SE.

We, for the first time, demonstrated the presence of hyperintensities on DWI as an independent functional prognostic factor of SE. Although diffusion-weighted hyperintensities related to SE have been analyzed in association with the focality or laterality in focal epilepsy [29,30], no previous studies have investigated them specifically in association with the functional outcome. Diffusion-weighted hyperintensities are reversible in most SE patients [11], but occasionally leave irreversible changes (e.g., atrophy and/or increased signal on T2-weighted images) in the cortices and/or the white matters [31–33]. The hyperintensity on DWI could be a surrogate marker of the neuronal impairment due to SE. The pathophysiology of this abnormal signal has been assumed to be the excitotoxicity and the uncoupling between blood flow and metabolism induced by prolonged seizure activities [11,34], but is not completely elucidated. ADC is reduced in most cases [11,12], but sometimes normal or increased [12,33,34], and can be heterogeneous within the affected lesion. The reason why ADC values vary is unclear, but is probably partly because of the timing when MRI was performed after SE. Therefore, we judged diffusion-weighted hyperintensities visually regardless of ADC values with strict distinction from acute ischemic stroke and old lesions. Cerebellar diffusion-weighted hyperintensities contralateral to the epileptic focus are rarely associated with SE [10,12], and are speculated to be the result of crossed cerebellar diaschisis. Although not all patients underwent MRI or EEG in this study, the results of the statistical analysis would be less likely to be biased, because patients did not undergo MRI or EEG for various reasons (e.g., patients who had metallic implants or unstable general condition, or who were considered to have no need for it by treating physicians), and there were no statistically significant differences in variables assessed as prognostic factors between patients with and without missing data.

We also demonstrated that a previous diagnosis of epilepsy, etiology, and refractory SE were associated with the outcome using univariate analysis, as shown in previous studies [35–37]. Among these variables, only refractory SE remained as an independent prognostic factor with multivariate analysis. Refractory SE could be a more important factor for the functional outcome of SE than the etiology. The percentage of refractory SE in our elderly patients (30.8%) was almost similar to that in overall adult SE (25–43%) [36–39].

This retrospective study has some limitations. First, we might have selected a severe subset of SE patients because we adopted the seizure duration of >30 min in the definition of SE, although the ILAE Task Force on Classification of SE recently proposed 5 min as time point t_1 and 30 min as time point t_2 in the case of CSE [40]. This might worsen the morbidity, given that t_1 is the time point beyond which prolonged seizures are unlikely to stop on their own and t_2 is the time point after which there is likely to be irreversible cerebral damage. Second, the potential underrepresentation of NCSE might bias the results. Although routine EEG was recorded with a median interval of one day after admission, we might have missed some patients with NCSE who recovered spontaneously before routine EEG or in whom infrequent seizure patterns could not be detected by routine EEG. Third, the long-term functional outcome could be different from the short-term outcome, which we assessed in this study. Fourth, patients with SE who admitted to the neurosurgery department for surgical intervention, and patients in whom SE occurred during hospitalization were not included in this study. Despite these limitations, the results of this study could reflect general characteristics of SE in elderly people, because it was performed in a community general hospital that provides primary to tertiary care. The proportion of NCSE and mortality could be quite different in a tertiary referral center with an active neuro-intensive care unit.

5. Conclusions

We delineated the clinical, EEG and DWI features from the largest cohort of the oldest elderly people with SE in Japan—a real super-aged society. The presence of hyperintensities on DWI and refractory SE were demonstrated as independent functional prognostic factors, while RPPs classified by the 2012 ACNS's Standardized Critical Care EEG Terminology were not. Diffusion-weighted hyperintensities could help us to predict the outcome of elderly patients with SE. However, their prognostic significance in overall SE and usefulness as a variable of the prognostic score for SE, such as STESS [27] and Epidemiology-based Mortality score in SE (EMSE) [41], should be investigated in future studies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2016.09.062.

Conflicts of interest

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