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Factors Associated with Prolonged Impairment of Consciousness in Adult Patients Admitted for Seizures: A Comprehensive Single-center Study

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Abstract

Seizures are common neurological emergencies that occasionally cause prolonged impairment of consciousness. The aim of this retrospective single-center study is to clarify factors associated with prolonged impairment of consciousness for admitted adult patients investigating patient backgrounds, blood tests, electroencephalographic patterns, and MRI findings. The patients who were admitted to the hospital due to epileptic seizures were classified into two groups: (1) early recovery group, in which patients recovered their consciousness within 6 hr, and (2) delayed recovery group, in which patients showed impairment of consciousness more than 6 hr. Factors associated with prolonged impairment of consciousness were compared between these groups. In this study, 42 cases (33 patients), with a mean age of 67.8 years, were included. Fifteen cases (13 patients) and 27 cases (20 patients) were classified into the early and delayed recovery groups, respectively. The populations of older patients and patients from a nursing home were significantly higher in the delayed recovery group. With regard to radiological analyses, a high grade of periventricular hyperintensity (PVH), high Evans index score, and enlarged bilateral atrial widths were significantly associated with prolonged impairment of consciousness. Multivariable analyses showed that a high grade of PVH was significantly associated with delayed recovery of consciousness independent of age and status epilepticus. In conclusion, we proposed that diffuse white matter degeneration around the lateral ventricles contributes to prolonged impairment of consciousness.

Keywords: status epilepticus, impairment of consciousness, prognosis, white matter hyperintensity, ventricular enlargement

Introduction

Seizures are common and a previous study reported a prevalence of 10.3% in a population aged 65 years or older.[1)] Seizures are also common neurological emergencies, accounting for 1.2% of all visits to the emergency department.[2)] The duration of seizures is usually brief. However, seizures are sometimes multiple and prolonged, presenting with impairment of consciousness or neurological deficits, a state known as status epilepticus (SE). This definition involves two longitudinal time points. The first is the time point at which the seizures should be considered as an abnormally lasting state. The second is the time point at which patients are at risk for long-term morbidity.[3)] In cases of convulsive SE (CSE), the first and second time points are set as 5 and 30 min, respectively, based on animal models and clinical research.[3)] The outcome of SE can be quite severe; overall mortality is estimated as about 20% in adult cases.[4)]

Although the duration of seizures is usually short, seizures, including SE, sometimes cause prolonged impairment of consciousness. The number of studies

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reporting factors associated with delayed recovery of consciousness is limited. One study reported that factors such as age, baseline modified Rankin Scale, and duration of seizures are associated with postictal consciousness impairment in cases of generalized convulsion.[5] However, to the best of our knowledge, very few studies have comprehensively investigated factors associated with impairment of consciousness, including radiological features, blood tests, and electroencephalographic (EEG) patterns. The aim of this study was to clarify factors that contribute to delayed recovery of consciousness in adult patients admitted with seizures, based on patient backgrounds, values of serum lactate, EEG patterns, and MRI findings.

Materials and Methods

Study design

We retrospectively investigated adult patients who were admitted to the Department of Neurosurgery, Nishichita General Hospital between November 2018 and October 2019, due to epileptic seizures. The therapeutic flow of seizures in the emergency department was as follows: vital signs of patients were monitored, and an intravenous line was secured for injection. If seizure attacks were detected, intravenous diazepam was injected (5 mg at once, the maximum dose was 10 mg). Anti-epileptic drug (AED), mostly 500 mg levetiracetam, was used in some cases of SE. Blood test and MRI were performed at the emergency department, but EEG was performed after patients were moved to the ward in most cases. If the seizures were not controlled well after moving to the ward or NCSE was confirmed by EEG patterns, administration of continuous intravenous midazolam was performed.

We classified the patients into two groups according to the duration of impairment of consciousness: (1) early recovery group and (2) delayed recovery group. The patients were placed in the early recovery group, if their consciousness level recovered to baseline within 6 hr after arrival at the hospital or after the final attack if patients manifested seizures after arrival at the hospital. The patients were then placed in the delayed recovery group if their consciousness level did not recover to baseline within 6 hr after arrival at the hospital or the final seizure attack. We included cases that were diagnosed with epileptic seizures and excluded cases that were considered to be acute provoked seizures. We investigated patient backgrounds, including past history, types of seizures, AEDs administered before and after admission, use of diazepam and AEDs at the emergency department, use of continuous intravenous midazolam in a hospital, and Glasgow Coma Scale scores at admission and discharge, in both groups. In addition, we recorded serum lactate values at the time of visiting the hospital, EEG patterns, and radiological features based on MRI. Then, we analyzed which factors were associated with prolonged consciousness impairment, comparing each factor between the early and delayed recovery groups. This study was approved by the ethical committee of Nishichita General Hospital (accession number 2020017).

Blood tests, EEG, and MRI

Serum lactate is a useful biomarker for differentiating generalized seizures from nonepileptic, but similar symptoms such as syncope and psychogenic nonepileptic seizures.[6] Serum lactate was measured in the emergency department. Because the rate of detection of epilepsy is higher with early performance of EEG,[2] EEG was performed as soon as possible after the patient was admitted to the hospital (Neurofax 1200, Nihon Kohden, Tokyo, Japan). Nonconvulsive SE (NCSE) was diagnosed according to the Salzburg criteria.[7] We used 1.5 or 3 T MRI systems (Ingenia, Philips, Amsterdam, the Netherlands) in our hospital. We inspected space-occupying lesions (SOLs), such as brain tumors, and low intensity regions in T2*-weighted images to detect a history of bleeding and superficial hemosiderosis, because the most common risk factor for epilepsy in adults is cerebrovascular disease,[8] and a previous study reported that post-subarachnoid hemorrhage hemosiderosis detected by T2*-weighted is a significant predictor of epilepsy.[9] We did not consider microbleeds or lacunar infarctions in the past history of cerebrovascular diseases. We also evaluated the grade of periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) based on fluid-attenuated inversion recovery image, and calculated the Evans index (EI) and bilateral atrial widths (AWs). AW was measured, and the maximum value on each side was used for analysis. Although EI and AW are usually used for evaluating pediatric hydrocephalus, we used these two indices as markers for enlarged anterior horn and trigones of the lateral ventricle, i.e., atrophy around ventricles, in this study. PVH and DWMH grades were evaluated according to a previous study.[10]

Statistical analysis

The association of seizures with each factor was analyzed using Fisher's exact test for variables that could be separated into two categories as well as

Student's *t*-test for continuous variables. Logistic regression analysis was used for detecting the factors associated with prolonged impairment of consciousness in admitted patients due to epileptic seizures. All tests were performed using the EZR software. For these tests, p <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Forty-two cases (33 patients) were included in this study. The mean age of the 33 patients was 67.8 years (range, 20–96 years), and 22 patients (66.7%) were aged 65 years or older. The seizures in most cases were diagnosed as focal seizures (87.9%) and SE in 26 cases (61.9%). Stroke was the most common event in the patients' history (36.4%). The number of patients who were administered with continuous intravenous midazolam, were intubated, did not recover from coma, and died were 17 (40.5%), 4 (9.5%), 1 (2.4%), and 2 (4.8%), respectively. The mean durations of impairment of consciousness in the early recovery group and the delayed recovery group were 1.2 hr and 10.4 days, respectively, including recurrent cases. These data are summarized in Table 1.

Factors associated with prolonged impairment of consciousness

Fifteen cases (13 patients) were classified in the early recovery group, whereas 26 cases (20 patients) were classified in the delayed recovery group. The number of older patients, patients living in a nursing home, and patients with lower Glasgow Coma Scale scores before admission were significantly higher in the delayed recovery group (p = 0.008, 0.002, and 0.03, respectively). Unexpectedly, serum lactate values in the early recovery group was higher than those in the delayed recovery group (6.1 vs 4.2 mmol/L, p = 0.23). In EEG patterns, periodic discharges (PDs) were detected only in the delayed recovery group (p = 0.07). Regarding the radiological features, the detection of SOLs or low intensity regions, or both, in T2*-weighted images was less associated with prolonged impairment of consciousness (p = 1.00). In contrast, a high grade of PVH was significantly associated with delayed recovery of consciousness (p <0.001), whereas a high grade of DWMH was not. Moreover, the indices of ventricular enlargement, i.e., EI and bilateral AWs, were also significantly associated with delayed recovery of consciousness (p = 0.02 and p <0.001, respectively). Table 2 shows the comparisons of these two groups.

These results suggested that white matter degeneration, especially around the lateral ventricles, and ventricular enlargement might be associated with delayed recovery of consciousness. However, such radiological findings are frequently detected in elderly people. Moreover, the delayed recovery groups had more cases of SE than the early recovery cases did, and this could be a confounding factor. Therefore, multivariable analyses were performed and consequently indicated that a high grade of PVH is significantly associated with delayed recovery of consciousness (Table 3). The diagnosis of SE is time-dependent, and the duration of seizures sometimes depends on observations that cannot be objectively confirmed. We used variables, such as PVH, bilateral AWs, age, and use of diazepam injection instead of SE, and performed multivariable analyses. Consequently, a high grade of PVH was also an independent factor that was significantly associated with prolonged consciousness impairment (p = 0.042).

Patient outcomes

Two patients died in this study, and the mortality rate was 4.8%, including recurrent cases. Moreover, two patients did not recover consciousness for more than 1 month. These patients were defined as the poor prognostic group. The two patients who died did not receive AEDs before admission (Table 4). One patient was admitted to the hospital in a state of cardiopulmonary arrest because of CSE. The patient was intubated and temporarily rescued but finally died due to anoxia. The other patient was admitted because of the first focal to bilateral tonic clonic seizures and suddenly died of an unknown cause. Both patients who did not recover consciousness after more than 1 month were >75 years old, and none of them had received AEDs previously. Both patients were brought to the hospital in a state of CSE. After CSE had been controlled, EEG analysis revealed PDs, suggesting that both patients were experiencing the transition from a state of CSE to NCSE, which contributes to high mortality and morbidity.[11] One patient finally recovered her consciousness to baseline after 45 days but was transferred to the nursing home due to impairment of activities of daily living, although she lived in her own house before admission, whereas the other patient was transferred to a nursing home in a state of coma (Table 4). We also investigated poor prognostic factors by comparing patients in the poor prognostic group with the other patients in the delayed recovery group. No factors significantly contributed to the prevention of dismal seizure outcomes.

Table 1 Background of patients admitted cases due to seizures, including past history

Characteristic	All patients 42 cases 33 patients	Early recovery 15 cases 13 patients	Delayed recovery 27 cases 20 patients
Mean age (range)	67.8 years (20–96 years)	57.0 years (20–88 years)	75.8 years (48–96 years)
Female	16 (48.5%)	4 (30.8%)	12 (60.0%)
Residence			
Own home	23 (69.7%)	13 (100%)	10 (50.0%)
Nursing home	10 (30.3%)	0 (0%)	10 (50.0%)
Mean GCS score before admission (range)*	14.0 (9–15)	14.8 (14–15)	13.5 (9–15)
Seizure, focal (%)	29 (87.9%)	11 (84.6%)	18 (90.0%)
Status epilepticus*	26 (61.9%)	6 (40.0%)	20 (74.1%)
Mean duration of impaired consciousness*	–	1.2 hr (0–6 hr)	10.4 days (1–115 days)
Past history			
Stroke	12 (36.4%)	4 (30.8%)	8 (40.0%)
Epilepsy	11 (33.3%)	2 (15.4%)	9 (45.0%)
Dementia	10 (30.3%)	1 (7.7.%)	9 (45.0%)
Brain tumors	4 (12.1%)	2 (15.4%)	2 (10.0%)
Trauma	3 (9.1%)	1 (7.7%)	2 (10.0%)
Central nervous system infection	3 (9.1%)	1 (7.7%)	2 (10.0%)
Congenital disease	1 (3.0%)	0 (0%)	1 (5.0%)
Use of intravenous diazepam at ER*	20 (48.8%)	5 (33.3%)	15 (57.7%)
Use of intravenous AED** at ER*	14 (34.1%)	4 (26.7%)	10 (38.5%)
Use of continuous intravenous midazolam*	17 (40.5%)	2 (13.3%)	15 (55.6%)
Intubated*	4 (9.5%)	0 (0%)	4 (14.8%)
Prognosis*			
Coma	1 (2.4%)	0 (0%)	1 (3.7%)
Dead	2 (4.8%)	0 (0%)	2 (7.4%)

*Recurrent cases were included.
**Levetiracetam was used in 13 cases and fosphenytoin was used in 1 case.
AED: anti-epileptic drug, ER: emergency room, GCS: Glasgow Coma scale.

Discussion

In this study, we classified patients into two groups depending on the duration of impairment of consciousness and found that patients with a high grade of PVH had significantly higher rates of delayed recovery of consciousness. However, these factors seemed to be less associated with the dismal prognosis of seizures, such as death and coma. To the best of our knowledge, this is the first study to investigate factors associated with prolonged consciousness impairment, especially radiological findings.

White matter hyperintensities (WMHs), i.e., PVHs and DWMHs, and ventricular enlargement are frequently detected by MRI in elderly people. However, multivariable analyses indicated that a high grade of PVH is associated with delayed recovery independent of age and SE. Therefore, we investigated the effects of atrophy or degeneration of white matter around the ventricles upon recovery of consciousness after brain damage because Blumenfeld proposed that postictal impairment of consciousness was similar to the disorder of consciousness.[12] A previous study showed that patients in a state of consciousness impairment after severe brain

Table 2 Comparison between the early and delayed recovery groups

Factors	Early recovery	Delayed recovery	*p* value
Age, mean (years)	57.0	75.8	**0.008**
Gender, female (%)	4/13 (30.8%)	12/20 (60.0%)	0.19
Residence, nursing home (%)	0/13 (0%)	10/20 (50.0%)	**0.002**
Mean GCS score before admission	14.8	13.5	**0.003**
Status epilepticus*	6 (40.0%)	20 (74.1%)	0.06
AEDs, administered before admission (%)	2/13 (15.4%)	9/20 (45.0%)	0.13
Use of intravenous diazepam at ER*	5 (33.3%)	15 (57.7%)	0.19
Serum lactate, mean (mmol/L) *	6.1	4.2	0.23
PDs in EEG, detected*	0/13 (0%)	7/27 (25.9%)	0.07
Low intensity regions in T2*-weighted images and/or SOLs, detected (%)**	6/13 (46.2%)	9/19 (47.4%)	1.00
PVH grade, grade II, III, or IV (%)**	3/13 (23.1%)	16/19 (84.2%)	**0.0009**
DWMH grade, grade II, III, or IV (%)**	6/13 (46.1%)	15/19 (78.9%)	0.24
Evans index, mean	0.28	0.31	**0.02**
Bilateral atrial widths, mean (mm)	26.7	38.7	**0.0009**

*Recurrent cases were included.
**A case contraindicated for MRI was excluded.
AED: anti-epileptic drug, DWMH: deep white matter hyperintensity, EEG: electroencephalography, GCS: Glasgow Coma Scale, PD: periodic discharge, PVH: periventricular hyperintensity, SOL: space-occupying lesion.

Table 3 Multivariable analysis for factors associated with delayed recovery of consciousness

Variables	OR	95% CI	*p* value
Age	0.98	0.89–1.10	0.81
Status epilepticus	4.17	0.25–32.10	0.40
Bilateral atrial widths	1.11	0.98–1.26	0.10
PVH grade	2.83	1.01–17.10	**0.048**

CI: confidence interval, OR: odds ratio, PVH: periventricular hyperintensity.

injury had extensive atrophy of the thalamus, caudate nucleus, putamen, globus pallidus, hippocampus, and brain stem.[13] Another study proposed that reduced activity of the posterior cingulate cortex (PCC) was associated with low states of arousal and awareness.[14] In addition, the medial parietal cortex and adjacent PCC were key regions differentiating patients in a minimally conscious state from those in a vegetative state.[15] Apart from consciousness impairment, the basal ganglia play key roles in sleep-waking regulation.[16] Considering these previous studies, brain regions near the lateral ventricles, such as the thalamus, caudate nucleus, hippocampus, anterior cingulate cortex, medial frontal cortex, PCC, and medial parietal cortex, seem to be associated with arousal and awareness after brain damage.

Although WMHs are frequently detected by MRI in older people, their pathophysiology is not fully understood. Axonal loss, demyelination, hypoperfusion, and inflammation are thought to be correlated with WMHs.[17] WMHs cause impairment of memory function and gray matter atrophy are associated with cognitive dysfunction and dementia.[17,18] In contrast, another MRI study proposed that a high grade of DWMH, but not high grade of PVH, was associated with low cognitive performance, suggesting that PVHs and DWMHs affect cognitive functions differently.[19] In our study, a high grade of PVH, but not high grade of DWMH, was strongly associated with prolonged impairment of consciousness, supposedly negatively affecting brain regions such as the thalamus, caudate nucleus, medial frontal, and cingulate gyri, after epileptic seizures. There are very few studies that discuss the relations between WMH and prolonged consciousness impairment; thus, this study may be the first report discussing the relation between PVHs and prolonged impairment of consciousness.

However, this study has some limitations. First, we classified the early or delayed recovery group based on the patients' arrival time to the hospital. The duration of impairment of consciousness may not be accurate, but it is difficult to precisely record the onset time or duration of seizures detected outside the hospital. For the same reasons, the diagnosis of SE might not be accurate because it depends on the duration of seizures. Second, in this study, impaired consciousness of patients might be caused by continuous NCSE or reveal delayed recovery from postictal vague state. It is difficult to precisely discriminate between these two states without continuous EEG monitoring. Therefore, we analyzed factors associated with delayed recovery of consciousness without separating these two states. Third, the AEDs administered were not uniform in

Table 4 Summary of admitted patients who resulted in a poor seizure prognosis

Case	Age, sex	Past history	Presenting symptoms	Lactate (mmol/L)	EEG patterns	AED*	Outcome	Periods**
1	96, F	Dementia	Impaired consciousness	2.59	LPDs	None	Recovered	45 days
2	69, F	SAH	FBTCS, CPA	15.81	Electrocerebral inactivity	None	Dead	6 days
3	78, F	CI, AD	FBTCS	4.96	GPDs	None	Coma	115 days
4	65, F	Encephalitis	FBTCS, todd paralysis	2.42	Continuously low amplitude	None	Dead	2 days

*AEDs administrated before admission to the hospital.
**Days until recovery of consciousness for the recovered cases (case 1) or discharge for the cases of death or coma (cases 2–4).
AD: Alzheimer's disease, AED: anti-epileptic drug, CI: cerebral infarction, CPA: cardiopulmonary arrest, EEG: electroencephalography, FBTCS: focal to bilateral tonic-clonic seizure, GPDs: generalized periodic discharges, LPDs: lateralized periodic discharges, SAH: subarachnoid hemorrhage.

this study (Table 1). In a randomized controlled trial comparing three AEDs (levetiracetam, fosphenytoin, and valproate) in patients with benzodiazepine-refractory SE, there were no significant differences among the three drugs in cessation of SE and improvement of consciousness.[20] In addition, the use of intravenous AED was not significantly different between the early and delayed recovery groups. Taken together, we assumed that the difference in AEDs and the use of AEDs were not associated with patient outcomes. The use of continuous intravenous midazolam might affect delayed recovery of consciousness. However, the midazolam was used after hospitalization in this study and could be started within 6 hr in dismal prognostic or recurrent cases; thus, we assumed that the use of the midazolam was less associated with grouping of the enrolled patients. Finally, serum lactate values and EEG patterns can be changeable and may be dependent on the time after seizures. Serum lactate reflects tissue hypoxia, and its level is also elevated in other diseases, such as tumors and sepsis.[6] In a few cases, venous serum lactate was measured. In a previous study, although the venous lactate level was higher than the arterial lactate level, the mean difference between them was 0.25 mmol/L[21]; therefore, we included the cases with arterial or venous lactate values in this study.

Conclusion

In this study, we retrospectively investigated factors associated with prolonged impairment of consciousness. The results showed that a high grade of PVH contributes to prolonged impairment of consciousness. We assume that the diffuse degeneration of white matter delayed the recovery of consciousness in patients with grand mal seizures, supposedly due to the impaired function of arousal and awareness. In contrast, diffuse white matter degeneration around the lateral ventricles or ventricular enlargement was less associated with the dismal outcomes of the seizures. Furthermore, we believe that these findings will be useful for the neurocritical care of patients with epileptic seizures including SE.

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Conflicts of Interest Disclosure

None.

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