



Factors associated with the duration of the postictal state after a generalized convulsion



Junichiro Ohira^a, Hajime Yoshimura^{a,*}, Takeshi Morimoto^{b,c}, Koichi Ariyoshi^d, Nobuo Kohara^a

^a Department of Neurology, Kobe City Medical Center General Hospital, 650-0047, 2-1-1 Minatojima-Minamimachi, Chuou-ku, Kobe, Hyogo, Japan

^b Clinical Research Center, Kobe City Medical Center General Hospital, 650-0047, 2-1-1 Minatojima-Minamimachi, Chuou-ku, Kobe, Hyogo, Japan

^c Department of Clinical Epidemiology, Hyogo College of Medicine, 663-8501, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, Japan

^d Department of Emergency Medicine, Kobe City Medical Center General Hospital, 650-0047, 2-1-1 Minatojima-Minamimachi, Chuou-ku, Kobe, Hyogo, Japan

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ABSTRACT

Purpose: Few studies have assessed the duration of the postictal state after a generalized convulsion (GC) in adults. This study aimed to investigate the postictal duration after a GC and the factors associated with it.

Methods: Patients aged ≥ 16 years who presented to the emergency department of a community general hospital with an unprovoked GC from January 2015 through December 2016 were evaluated retrospectively. A GC was defined as a bilateral convulsion with apparent impaired consciousness including a generalized tonic-clonic seizure.

Results: We evaluated 209 consecutive GCs (median age, 42 years) with the median postictal duration of 0.75 h. The univariate analyses indicated that the median duration of the postictal state was significantly longer: in elderly patients (aged ≥ 65 years) than in younger patients (aged < 65 years) (2 h vs. 0.7 h, $p = 0.0005$); in patients with higher modified Rankin scale (mRS) scores (≥ 3) at baseline than in those with lower scores (≤ 2) (2.5 h vs. 0.7 h, $p < 0.0001$); in patients with longer seizure duration (≥ 30 min) than in those with shorter duration (55 h vs. 0.7 h, $p < 0.0001$); in patients who were given emergency antiepileptic drugs than in those who were not (16 h vs. 0.6 h, $p < 0.0001$); and in patients who were intubated than in those who were not (63.5 h vs. 0.75 h, $p = 0.0009$). Multiple linear regression analyses indicated that older age, higher mRS scores at baseline, longer seizure duration, and administration of emergency antiepileptic drugs were independently associated with longer postictal duration.

Conclusion: Age, baseline functional disability, and seizure duration were factors associated with the duration of the postictal state after a GC.

1. Introduction

Most epileptic seizures have a postictal state, an abnormal condition characterized by impaired consciousness, sensory, motor, cognitive function, or emotions that lasts from the end of the seizures until the return to the presumed baseline [1,2]. The mechanisms of the postictal state are poorly understood, although electrophysiological changes in the brain and cerebral blood flow alterations are thought to be involved in the mechanisms [2,3].

Although a generalized convulsion (GC), which encompasses some types of seizures including a generalized tonic-clonic seizure (GTCS), is a common medical neurological emergency, studies on the postictal duration after a GC are scarce. A previous pediatric study demonstrated that the postictal duration was longer in acute symptomatic seizures, and in seizures for which emergency antiepileptic drugs (AEDs) were

used [4]. However, there are no studies of the postictal duration after a GC in a large number of adult patients, and there are no established data on the factors affecting the duration.

Therefore, we aimed to investigate the postictal duration after a GC and its associated factors for several hundred GCs of adult patients.

2. Methods

2.1. Study design and participants

We retrospectively searched the outpatient database of Kobe City Medical Center General Hospital, a community general hospital in Kobe, Japan, from January 2015 through December 2016 for patients aged 16 years or older who presented to the emergency department with a GC. A bilateral convulsion with apparent impaired consciousness

* Corresponding author.

E-mail address: hajime-y@kcho.jp (H. Yoshimura).

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was considered a GC in this study. Only patients with a single GC were included; those with multiple GCs (i.e., repeated GCs without full recovery during intervals of GCs) were excluded to avoid inaccurate measurements of the seizure duration and postictal duration. Nonconvulsive status epilepticus (NCSE) developing from a GC and acute symptomatic seizures were also excluded. The 2013 working clinical criteria were used for the diagnosis of NCSE [5]. Electroencephalography (EEG) was performed as soon as possible after admission to rule out NCSE especially when the duration of impaired consciousness after a GC was longer than a few hours. We used the recommendations from 2010 for the definition of acute symptomatic seizures [6]. To rule out acute symptomatic seizures, a laboratory test including complete blood count, hepatic enzymes, creatinine, electrolytes, and glucose, and a brain computed tomography were performed in almost all patients, especially in those with first-ever seizures. Alcohol or benzodiazepine withdrawal was ruled out by the history. A brain magnetic resonance imaging, lumbar puncture, and drug intoxication screening test were performed when needed. Patients who had changed hospitals without recovery within one week of admission were excluded because their postictal duration was unknown. The study protocol was approved by the institutional review board of Kobe City Medical Center General Hospital.

2.2. Definitions and patient assessment

Postictal duration was defined as the time between the end of the convulsion and the recovery of consciousness and motor function. Medical staff checked patients' awareness; their responsiveness to questions; their orientation to time, place, and person; and their motor function, and then evaluated whether they recovered or not, taking into consideration the statements from the patients themselves or their families. In non-admission cases, emergency medical services personnel checked patients every minute during the ambulance ride and, once in the emergency department, medical staff examined patients approximately every 30 min to determine whether the patients had recovered and could safely leave. The time point of recovery or the time when the patient left the emergency room was documented in the patient's record. In admission cases, nursing staff examined patients at least every two to three hours during the day and during the night in some cases and recorded the changes they noticed. Attending physicians recorded the condition of the patients in their charts two or three times on admission day and at least once daily for the duration of their hospital stay to assess recovery. When patients fell asleep after the GCs, medical staff usually woke patients up to check their consciousness level in an interval as mentioned above. The postictal duration for patients who did not recover during hospitalization was specified as their entire hospitalization period.

Daily use of AEDs was defined as the use of AEDs for consecutive days when the GC occurred. Attending physicians determined whether patients had skipped a dose based on statements by the patients themselves or their families or the blood concentrations of the AEDs. The use of emergency AEDs was defined as administration of intravenous AEDs in the emergency department to stop a GC before the recovery of consciousness.

2.3. Potential factors associated with postictal duration

We dichotomized the age, the modified Rankin scale (mRS) score at baseline, and the seizure duration, based on the following clinical reasons. In general, people aged 65 years or older were considered elderly for clinical relevance. The mRS score was evaluated to measure the degree of dependence; a mRS score of three or higher indicated functional dependence [7,8]. We determined the mRS scores before a GC based on statements by the patients themselves or their families. Seizure activity for 30 min or longer can result in long-term consequences [9].

According to previous reports, elderly patients were suggested to have a longer postictal state after complex partial seizures [10], and children who were given benzodiazepines to stop convulsions were demonstrated to have a longer recovery time following a seizure [4]. Taking these reports into consideration, we assessed the association between the postictal duration and six variables: age, sex, mRS scores at baseline, daily use of AEDs, first-ever seizure, and seizure duration. Administration of emergency AEDs and intubation were assessed as confounding factors.

2.4. Statistical analysis

We present the median and range or interquartile range (IQR) for continuous variables, and report numbers and percentages for categorical variables. We described the postictal duration divided by 1 h; postictal duration of less than 1 h was divided by 0.5 h. Univariate analyses were conducted to identify variables significantly associated with longer postictal duration using the Mann-Whitney U test for potential factors. After taking the natural logarithm of the postictal durations so they resemble a normal distribution, multiple linear regression analyses were performed using all variables significantly associated with longer postictal duration in the univariate analyses. The coefficients of each parameter were taken exponential and recalculated to evaluate the extent of the contribution of each factor to the postictal duration. The Kruskal-Wallis test was used to compare postictal durations among 4 groups: first-ever seizures, recurrent seizures without AEDs prescribed, recurrent seizures with AEDs skipped, and recurrent seizures with daily use of AEDs. A two-tailed p-value < 0.05 was considered statistically significant. All data were analyzed using JMP version 10.0.2 for Windows.

3. Results

We identified 355 consecutive GCs in patients aged 16 years or older who presented to the emergency department (Fig. 1). We excluded 86 multiple GCs, one NCSE developing from a GC, 57 acute symptomatic seizures, and two GCs which were not followed up. In total, we included 209 unprovoked single GCs.

The clinical characteristics of these 209 GCs (185 patients; 117 males and 68 females) are summarized in Table 1. Eighteen patients had a GC twice and three patients had a GC three times during the study period. The median age was 42 years; 48 GCs (23.0%) occurred in patients aged 65 years or older. The median mRS score at baseline was

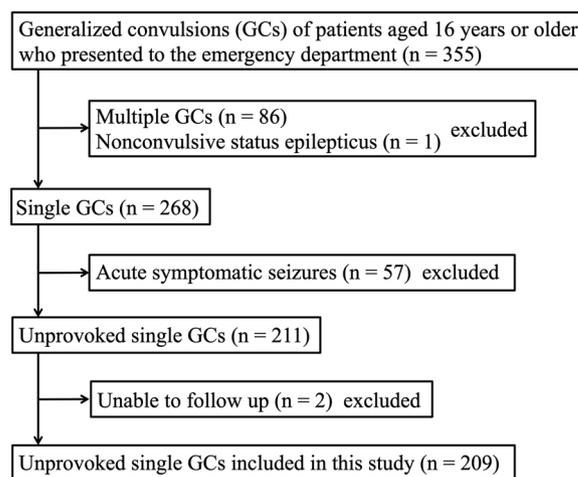


Fig. 1. Study flowchart.

This flowchart describes the inclusion and exclusion process of our study. Multiple GCs were defined as repeated GCs without full recovery during seizure intervals.

Table 1
Demographics of the 209 generalized convulsions.

Characteristic	Value (n = 209)
Age, median (range), years	42 (16–101)
≥ 65, n (%)	48 (23.0)
Male, n (%)	131 (62.7)
mRS score at baseline, n (%)	
0	149 (71.3)
1	16 (7.7)
2	8 (3.8)
≥ 3 (dependent)	36 (17.2)
Underlying condition, n (%)	
Present, n (%)	95 (45.5)
Stroke	43 (20.6)
Developmental delay	18 (8.6)
Dementia	13 (6.2)
Brain tumor	13 (6.2)
Traumatic brain injury	10 (4.8)
Others*	3 (1.4)
Absent or unknown, n (%)	114 (54.5)
Daily use of AEDs, n (%)	81 (38.8)
1 AED	52 (24.9)
2 AEDs	19 (9.1)
≥ 3 AEDs	10 (4.8)
First-ever seizure, n (%)	72 (34.4)
Seizure duration, median (IQR), min	3 (2–5)
≥ 30 min	11 (5.3)
Epilepsy classification, n (%)	
Symptomatic focal	89 (42.6)
Symptomatic generalized	2 (1.0)
Idiopathic generalized	8 (3.8)
Unknown	110 (52.6)
Use of emergency AEDs, n (%)	34 (16.3)
Diazepam	23 (11.0)
Fosphenytoin	26 (12.4)
Levetiracetam	7 (3.3)
Midazolam	2 (1.0)
Phenobarbital	1 (0.5)
Propofol	3 (1.4)
Intubation, n (%)	4 (1.9)
Admission, n (%)	53 (25.4)

mRS: modified Rankin scale; IQR: interquartile range; AED: antiepileptic drug.
* A residual of encephalitis, Postoperative of an arachnoid cyst, and chronic subdural hemorrhage.

0; 36 GCs (17.2%) occurred in functionally dependent patients (the mRS score ≥ 3). 72 GCs (34.4%) were first-ever seizures. AEDs were used daily in 81 GCs (38.8%). AEDs were prescribed for the epilepsy but were skipped in 18 recurrent seizures (8.6%). In 41 recurrent seizures (19.6%), AEDs were not prescribed for the following reasons: the last seizure was the first seizure, patients did not consult doctors after one or more seizures, etc. Skipped AEDs were valproic acid (11 GCs), levetiracetam (6), carbamazepine (3), phenytoin (2), and zonisamide (1), and did not include benzodiazepine or barbiturates, which are well known to trigger withdrawal seizures. The median duration of GCs was 3 min, and 11 GCs (5.3%) were long-lasting (≥ 30 min). Emergency AEDs were used for 34 GCs (16.3%). Four GCs (1.9%) required intubation; and 53 GCs (25.4%) required the admission.

The median duration of the postictal state was 0.75 h (IQR 0.5–2.4 h); and 132 GCs (62%) had the postictal duration of 1 h or shorter, while 22 GCs (11%) had the postictal duration longer than 10 h (Fig. 2). The postictal durations of two GCs which did not recover during hospitalization were specified as the hospitalization periods (16 d and 48 d). The postictal duration in patients who had a GC more than once during the study period ranged from 0.1 to 5.3 h. All GCs accompanied impaired consciousness to various extents during the postictal state.

The univariate analyses indicated that the duration of the postictal state was significantly longer in elderly patients (aged ≥ 65 years) compared with younger patients (aged < 65 years) (median, 2 h vs. 0.7 h, respectively; $p = 0.0005$); in patients with higher mRS scores

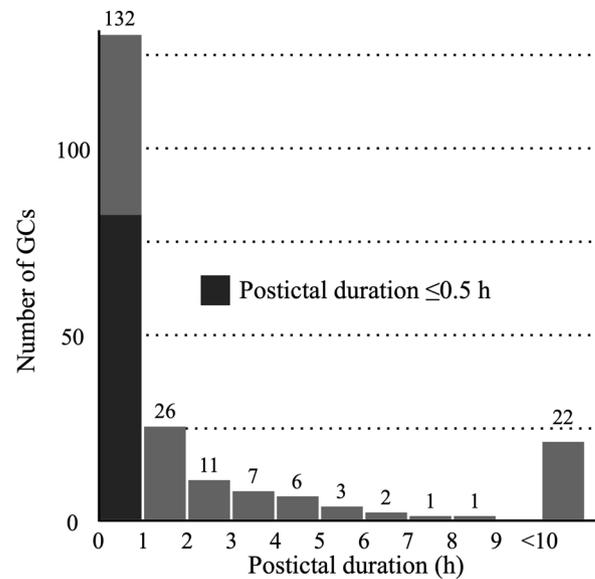


Fig. 2. Histogram of the duration of the postictal state. The postictal duration of 86 GCs was 0.5 h or shorter, while that of 22 GCs was more than 10 h. GC: generalized convulsion.

(≥ 3) at baseline compared with those with lower mRS scores (≤ 2) (median, 2.5 h vs. 0.7 h, respectively; $p < 0.0001$); in patients with longer seizure duration (≥ 30 min) compared with those with shorter one (< 30 min) (median, 55 h vs. 0.7 h, respectively; $p < 0.0001$); in patients who were given emergency AEDs compared with those who were not (median, 16 h vs. 0.6 h, respectively; $p < 0.0001$); and in patients who were intubated compared with those who were not (median, 63.5 h vs. 0.75 h, respectively; $p = 0.0009$) (Table 2). The difference in postictal durations was not statistically significant among the following 4 groups: first-ever seizures, recurrent seizures without AEDs prescribed, recurrent seizures with AEDs skipped, and recurrent seizures with daily use of AEDs (Supplementary Table 1).

Multiple linear regression analyses of the five factors, which were significant in the univariate analyses, revealed that older age, higher

Table 2
Univariate and multiple linear regression analyses of the factors associated with the postictal duration after a generalized convulsion.

Variable	Postictal duration, median (h)	Univariate P-value	Multiple regression	
			Exponential coefficient	P-value
Sex	Female 0.55 Male 1.0	0.054	–	–
Age	< 65 years 0.70 ≥ 65 years 2.0	0.0005	–	0.042
mRS score at baseline	≤ 2 0.70 ≥ 3 2.5	< 0.0001	–	0.037
Daily use of AEDs	Yes 0.60 No 1.0	0.46	–	–
First-ever seizure	No 0.70 Yes 1.0	0.11	–	–
Seizure duration	< 30 min 0.70 ≥ 30 min 55	< 0.0001	–	< 0.0001
Use of emergency AEDs	No 0.60 Yes 16	< 0.0001	–	< 0.0001
Intubation	No 0.75 Yes 64	0.0009	–	0.20

Significant p-values are shown in bold font.
mRS: modified Rankin scale; AED: antiepileptic drug.

mRS scores at baseline, longer seizure duration, and the use of emergency AEDs were independently associated with longer postictal duration after a GC (Table 2). The factors most strongly correlated with longer postictal duration were the use of emergency AEDs followed by the seizure duration, the mRS scores at baseline, and the age as indicated by exponential coefficients (3.1, 2.5, 1.3, 1.2, respectively).

4. Discussion

In the present study, we showed that 60% of GCs had the postictal duration of 1 h or shorter, while 10% had that of longer than 10 h. We also showed that older age, higher mRS scores at baseline, longer seizure duration, and the use of emergency AEDs were independently associated with longer postictal duration.

Reports on the postictal duration after a seizure in adults are scarce and, to the best of our knowledge, this retrospective study represents the largest cohort examined on this topic to date. One small case series suggested that patients with diffuse structural abnormalities or developmental delay tended to have a prolonged postictal state after a GTCS [11]. Another study suggested that patients aged 60 years or older had a longer postictal state after complex partial seizures than younger patients [10]. There were two pediatric studies on postictal duration after seizures from the same research group in 2007 [12] and 2009 [4] with a larger number of participants in the latter study: the study was a prospective analysis of 128 children who presented to the hospital with various types of seizures, including GTCSs, complex partial seizures, clonic seizures, and tonic seizures [4]. It showed that the median duration of the postictal state in children after a GTCS was 0.70 h (range, 0.00–85.50 h), which was similar to our results observed in a generalized convulsion (including GTCS) of adult patients. The study also reported that the postictal duration was longer in acute symptomatic seizures of children with previously known brain disorders than in remote symptomatic seizures, and in seizures for which emergency AEDs were used. In the present study, we excluded acute symptomatic seizures because the patients might not return to baseline due to the acute brain disorders that triggered the seizures. It is plausible that sedative effect of AEDs may have prolonged the postictal state in the previous pediatric study and our adult study, since emergency use of AEDs was associated with a prolonged postictal state in both studies.

The key findings of our study were that older patients (≥ 65 years), patients with higher mRS scores (≥ 3) at baseline, and those who experienced a longer GC (≥ 30 min) had significantly longer postictal states after a GC. Elderly patients tend to have impaired brain function at baseline compared with younger patients because aging is associated with declining brain function [13]. Functional disabilities represented by the mRS score in this study were caused by stroke, dementia, developmental delay, traumatic brain injuries, and other brain disorders, though rarely involved orthopedic disorders. Therefore, most of the patients who were functionally disabled were considered to have impaired brain function due to their brain disorders. Furthermore, since seizures lasting 30 min or longer in animal models can result in irreversible neuronal damage [9,14], it is conceivable that a longer GC (≥ 30 min) damaged the brain severely and contributed to longer postictal duration. Therefore, our study results suggest that patients with impaired brain function at baseline due to older age or brain disorders and patients whose brain function was damaged by a longer GC had longer postictal duration, and occasionally may not return to the functional baseline.

We included all patients with bilateral convulsions and apparent impaired consciousness in this study. Therefore, various types of seizures such as GTCSs, generalized tonic seizures, generalized clonic seizures, or hyperkinetic seizures could be included. However, GTCSs would be predominant in adults in an emergency room setting as shown in a pediatric prospective study in the emergency department (4).

It is conceivable that underlying diseases can affect the postictal duration. In the present study, however, we did not include underlying

conditions in multiple linear regression analyses, because “absent or unknown” category accounted for more than half of all GCs partly due to the retrospective study design, which would lower the reliability of the analyses. Furthermore, underlying conditions are pathophysiologically associated with mRS scores at baseline and we were primarily interested in the association between the postictal duration and baseline functional disability itself, rather than underlying conditions, which cause functional disability. Well-designed prospective studies are needed to reveal whether baseline functional disability is associated with the postictal duration independently of underlying conditions.

Emergency AEDs were mostly used to stop persistent convulsions at the emergency department. Intubations were usually performed to protect airways in patients with severe impaired consciousness or to support respiration in patients to whom anesthetic agents were administered to stop refractory GCs. Therefore, these 2 factors were naturally associated with severe GC cases. Actually, seizure duration was significantly longer in GCs which required emergency AEDs and those which required intubation (data not shown). Accordingly, we included these 2 factors in multiple linear regression analyses as confounding factors.

We conducted this study in an emergency room setting to recruit unselective patients with GCs. Performing the study in an epilepsy monitoring unit (EMU) setting may allow for more accurate measurement of postictal duration, but then the study would be limited to patients who are hospitalized for the accurate diagnosis of epilepsy or pre-surgical evaluation; however, future studies with this alternate design may offer additional insights concerning postictal duration.

There are several limitations to our study. First, the measurement of the postictal duration might not be precise due to the retrospective study design. Although the evaluation of admitted patients tended to be infrequent from the day after admission, they were frequently evaluated on the day of admission, when evaluation was more important because approximately 90% of seizures had the postictal duration of 10 h or shorter (Fig. 2). Second, the seizure duration was mostly based on the statements of patient’s family, which may not be accurate. However, as we just focused on whether the duration was longer than 30 min or not, we considered that the accuracy would be acceptable in this study. Third, as subtle cognitive deficits and subtle psychiatric symptoms could not be assessed when determining the time point of recovery, the postictal durations could be underestimated. Such minor abnormalities, however, are undetectable without examining patients in detail at baseline before the onset of a GC and would be difficult to recognize even in a prospective study. Fourth, NCSE developing from a GC could be mistaken for the postictal state, making the postictal duration artificially longer; however, EEG was performed on the earliest weekday after admission to rule out NCSE. Fifth, we could not investigate the relationship between epilepsy classifications and the postictal duration, as it was difficult to classify epilepsy syndromes due to the retrospective study design. Despite these limitations, this is the first large-scale study on postictal duration after a GC in adults; the results reveal general characteristics and associated factors of postictal duration. Well-designed prospective studies are needed to further substantiate our results.

5. Conclusion

In conclusion, age, baseline functional disability, and seizure duration were independently associated with postictal duration after a GC. Patients with impaired brain function at baseline and patients whose brain function was damaged by a prolonged GC experienced a longer postictal state.

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Declarations of interest

None.

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.seizure.2019.01.001>.

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