Original Article

Lateralized Periodic Discharges are Predictive of Seizures in Patients with Intracerebral Hemorrhage

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Abstract

Background: Patients with intracerebral hemorrhages (ICHs) have higher incidence of seizures. Previous studies have suggested that location and size of hemorrhage may increase epileptogenicity. We aim to evaluate seizure development risk factors from clinical examination, imaging, and continuous electroencephalography (cEEG) in critically ill patients with ICH. **Methods:** We reviewed 57 consecutive patients with ICH admitted to a neurocritical intensive care unit over a 24-month period who were monitored on cEEG. Their demographic and examination data, ICH score, Glasgow Coma Scale (GCS), location of bleed, cEEG patterns, and discharge status were analyzed. **Results:** Sixteen (28%) patients from our study cohort had seizures at a mean duration of 7.46 h from cEEG hookup. Fifteen (93%) of those patients had only electrographic seizures. The finding of lateralized periodic discharges (LPDs) was significantly ($P = 0.019$) associated with seizures. Other variables, such as ICH score, size and location of hemorrhage, GCS, mental status, and other cEEG patterns, were not significantly associated with seizures. **Conclusion:** We found that LPDs were predictive of seizures in ICH patients. cEEG for longer than 24 h is preferred for detection of seizures as they occurred at a mean later than 7 h and most were without clinical signs.

Keywords: Continuous electroencephalography, intracerebral hemorrhage, lateralized periodic discharges, seizure

Introduction

Intracerebral hemorrhage (ICH) is defined as bleeding into brain parenchyma that can extend into the ventricles and occasionally into the subarachnoid space.[1] Etiologies of spontaneous ICH are hypertension, amyloid angiopathy, vascular anomalies (arteriovenous malformation, cavernous angiomas, and venous angiomas), tumors, coagulopathies, cortical venous thrombosis, vasculitis, and hemorrhagic transformation of ischemic stroke.[1] ICH commonly occurs in the cerebral hemispheres, basal ganglia, thalamus, brain stem (predominantly the pons), and cerebellum.[1] The mortality rate after spontaneous ICH at 6 months ranges from 23% to 58%.[2-5] Volume of ICH (irrespective of location) and initial Glasgow Coma Scale (GCS) score are strong predictors of 30-day mortality.[2] Patients with ICH are at a higher risk for seizure compared to the general population.[6,7]

Seizures can be a presenting symptom as well as a late complication of ICH.[6,7] Seizures secondary to ICH can range from focal motor seizures with intact awareness to secondary generalization with loss of awareness and to nonconvulsive seizures detectable only with electroencephalography (EEG).[6] Patients with lobar hemorrhages have been suggested to have a higher incidence of seizures.[8] Other risk factors for the development of seizures include ICH volume, age <60, and posthemorrhagic communicating hydrocephalus.[9,10] ICH-associated seizures are independently associated with increased midline shift, increased hemorrhage volume, and overall worse outcome.[11,12] Thus, it is important to recognize seizures and treat them appropriately. Unfortunately, many seizures are without clinical signs.[11] Continuous EEG (cEEG) is a neuromonitoring tool that is becoming increasingly utilized to detect nonconvulsive seizures in neurocritically ill patients.[11,12]

It is the purpose of this retrospective study of prospectively collected data to evaluate risk factors from examination, imaging, and cEEG for the development of seizures in critically ill patients with ICH.

Methods

Patients

Consecutive patients >18 years of age who presented with ICH to the neurocritical intensive care unit over 24 months were included in this study. Demographic characteristics (age and sex), level of consciousness (LOC), GCS, radiological findings, cEEG patterns, and discharge status were obtained from chart review. LOC was defined as being awake, lethargic, stuporous, or comatose. The discharge status

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of patients was simply classified as home, rehabilitation, or death in hospital.

Data acquisition

The start time of cEEG was noted. cEEG data were recorded using 21 electrodes placed according to the international 10–20 system by certified EEG technologists and interpreted by board-certified epileptologists. EEG findings were classified according to the American Clinical Neurophysiology Society (ACNS) criteria as lateralized periodic discharges (LPDs), generalized periodic discharges (GPDs), GPDs with triphasic morphology (TW), continuous slowing/background slowing, burst suppression, and seizures. EEG seizures were defined as evolving rhythms in frequency, distribution, and/or morphology at >2 Hz for >10-s duration. Seizures were also classified as convulsive or nonconvulsive. Convulsive seizures were classified if semiology included tonic-clonic, clonic, tonic, automotor, versive, or dyskinetic posturing. Nonconvulsive seizures were considered if semiology included subtle movements, such as eye deviation were seen on video but not clinically or if there were EEG seizures without video or clinical findings, and if the ictal patterns lasted >10 s with a frequency of >2 Hz. In addition, the time to first seizure was noted.

Initial computed tomography (CT) scans were reviewed for this study. Hemorrhages were described by volume based on the ABC/2 method in axial dimension.[13] Hemorrhages were further classified as being subcortical or lobar and/or having intraventricular extension.

ICH score was calculated using the validated formula based on the GCS score, ICH volume, presence of intraventricular hemorrhage, infratentorial origin of ICH, and age of the patient.[14]

Data analysis

Continuous and categorical data were summarized with descriptive statistics including means with standard deviations, median with ranges, and frequencies. Categorical analysis was performed using odds ratio (OR) and Fisher's exact tests. Student's *t*-test was used to analyze continuous data. $P < 0.05$ was considered statistically significant. Data were analyzed using GraphPad 7.0 (La Jolla, CA, USA).

Results

Patient characteristics

Fifty-seven patients were identified as having ICH and were monitored on cEEG. Sixteen patients were identified as having seizures. Patients were then divided into either the seizure group (n = 16; 28%) or nonseizure group (n = 41; 71.9%) [Table 1].

The average age in the seizure group was 64.4 years as compared to 62.6 years in the nonseizure group (P = 0.64). In the seizure group, the majority were lethargic (43.75%; n = 7) or stuporous (43.75%; n = 7). In the nonseizure group, 3 (7.3%) patients were classified as awake, 17 (41.5%) patients as lethargic, 14 (34.1%) as stuporous, and 7 (17.1%) as comatose. No significant difference was found based on LOC. The mean ICH score and GCS score were 2 and 12, respectively, in the seizure group versus 1 and 10, respectively, in the nonseizure group. No significant difference was found between these scores [Table 1].

There was a significant difference in the number of patients who died during hospitalization who had seizures (56.25%) versus those who did not have seizures (17.1%; P = 0.0069; OR: 0.16; confidence interval [CI]: 0.051–0.54). There was no significant difference in the discharge status to either rehabilitation or home between the two groups [Table 1].

Continuous electroencephalography

On cEEG monitoring, the average time to first seizure was 7.46 ± 12.2 h. Fifteen (93.5%) patients had nonconvulsive seizures. Eight patients (50%) in the seizure group had LPDs, 12 patients (75%) had continuous slowing, and 15 (93.5%) patients had nonconvulsive seizures. In the nonseizure group, 7 patients (17.1%) had LPDs, 35 patients (85.4%) had continuous slowing, and 5 patients (12.2%) had burst suppression. A statistically significant increased risk of seizure was noted in patients with LPDs (P = 0.019; OR: 4.857; CI: 1.393–15.75). Other cEEG patterns were not found to be significantly associated with seizures [Table 2].

Neuroimaging

On CT head, the average blood volume of ICH in the seizure group was 42.9 ± 36.0 cc as compared to 32.9 ± 23.7 cc in nonseizure group. About 50% (n = 8) of patients in the seizure group had intraventricular extension or primary intraventricular bleed, as compared to 51.2% (n = 21) of patients in nonseizure

Table 1: Patient Characteristics

	Seizure	No Seizure	*P* Value
Total	16	41	
Age (Average, SD)	64.4, 12.7	62.6, 13.1	NS
Sex M (n, %)	8, 50	18, 43.9	NS
Level of consciousness (*n*, %)			
Awake	1, 6.25	3, 7.3	NS
Lethargy	7,43.8	17, 41.5	NS
Stupor	7, 43.8	14, 34.1	NS
Coma	1, 6.25	7, 17.1	NS
ICH Score (Median, Range)	1, 1 to 3	2, 0 to 4	NS
GCS Score (Median, Range)	10, 7 to 15	12, 3 to 15	NS
Seizures			
Time to first seizure hrs (average, SD)	7.46, 12.2	NA	
Discharge (n,%)			
Home	0, 0	4, 9.8	NS
Rehab	7, 43.8	30, 73.2	NS
Dead	9, 56.3	7, 17.1	NS

SD=Standard deviation; M=Male; ICH=Intracerebral hemorrhage; GCS=Glasgow Coma Scale; Sz=Seizure; n=Number; NA=Not applicable; NS=Not significant

group. Nearly 37.5% (n = 6) of patients in the seizure group had lobar bleed, as compared to 34.1% (n = 14) patients in nonseizure group. No significant risk of seizure was associated with size of hemorrhage, lobar location of hemorrhage, or intraventricular extension/location of hemorrhage [Table 2].

Table 2: Continuous electroencephalography (CEEG) and computed tomography (CT) comparison between patients who had seizures and those who did not

	Seizures	No Seizures	*P* Value
EEG (*n*, %)			
LPDS	8, 50	7,17.1	0.019
LPDS	2, 12.5	2,4.9	NS
TW	0, 0	0, 0	NS
Continuous Slowing	12, 75	35,85.4	NS
Burst Suppression	0, 0	5,12.2	NS
Non Convulsive seizures	15, 93.8	NA	
CT Head			
IVH (*n*, %)	8, 50	21, 51.2	NS
Lobar (*n*, %)	6, 37.5	14, 34.1	NS
Volume, cc (Average, SD)	42.9, 36	32.9, 23.7	NS

EEG=Electroencephalography; LPDs=Lateralized periodic discharges; GPDs=Generalized periodic discharges; TW=GPDs with triphasic morphology; CT=Computed tomography; n=Number; sz=Seizure; NA=Not applicable; NS=Not significant

Discussion

Our study demonstrated that ICH patients with the finding of LPDs on cEEG monitoring were at increased risk for developing seizures. As per the American Heart Association/American Stroke Association guidelines for the management of ICH, seizure prophylaxis with an antiepileptic drug (AED) is not routinely recommended.[15] However, due to the high association of LPDs with clinical and subclinical seizures, the presence of these discharges in critically ill patients with ICH may validate the use of a prophylactic AED. In addition, we found that the average time to first seizure was 7.46 h. The majority of seizures occurred without any clinical signs. These findings highlight the importance of cEEG monitoring in critically ill patients with ICH.

Seizures can have a deleterious effect on the overall outcome of critically ill patients with ICH. They can result in raised intracranial pressure and can cause brain injury reflected by elevation in neuron-specific enolase.[16,17] Risk of seizures is highest within the first few days after ictus in patients with ICH.[18-20] More than 50% of seizures occur in the first 24 h.[18-20] Clinical seizures are seen in 5.5%–24% of the patients with ICH.[11,16] The incidence of early seizures in patients with ICH is reported to be 28%–31% on cEEG monitoring.[11,16] The underlying cause of early seizures is believed to be immediate metabolic and physical disturbances in the brain caused by increased extracellular concentration of glutamate following ICH.[21] Late seizures are seen less frequently in patients with ICH and are believed to be caused by underlying gliotic scarring.[22,23] In addition, we found a significant increase in patients who died in the seizure group compared to those who did not have seizures. The patients with seizures did have a more severe GCS score but not ICH score. Death in the hospital was highest in ICH patients with seizures. Seizures in this patient population may be an epiphenomenon reflecting the patients' overall critical state.

LPDs were first described by Chatrian *et al*. in 1964.[24] They were defined as periodic spike/sharp waves followed by slow wave occurring at a frequency of 1–2 s in one hemisphere.[24] Owing to the heterogeneity of LPDs and observer differences, various modifiers have been used to describe them.[25] ACNS has introduced guidelines on using the term LPDs with plus modifiers based on amplitude, phases, rhythmicity, spike/sharp and slow wave, prevalence, duration, frequency, polarity, stimulus-induced, fluctuating, and evolving patterns.[25]

Various studies described LPDs as predictors of seizures irrespective of their etiology.[26] Rodriguez Ruiz *et al*. conducted a large multicenter trial with 4000 critically ill patients and concluded that LPDs had the highest association with seizures irrespective of frequency, and the association was higher when a plus modifier (superimposed fast activity/fast and rhythmic activity/fast and spike or sharp wave activity/rhythmic or quasi-rhythmic activity) was present.[27]

In a retrospective review of 100 consecutive patients with LPDs, Newey *et al*. reported that LPDs with rhythmicity (OR: 13.91) were most significant for predicting status epilepticus and/or seizures.[28] This was followed by LPDs with overlying faster frequencies (OR: 5.16) and then sharply contoured morphology (OR: 4.09).[28] LPDs with blunt delta morphology (OR: 0.24) had the lowest risk for seizures.[28] The ictal-interictal continuum has classified various EEG patterns on the basis of likelihood of seizure association.[29] In the continuum, LPDs have been described as being toward the ictal side.[29] LPDs plus (LPDs+) are considered LPDs with accompanying low-amplitude fast activity, which is more frequently associated with independent seizures than LPDs proper.[29] Other cEEG findings, such as brief potentially ictal rhythmic discharges, stimulus-induced rhythmic, periodic, or ictal discharges, GPDs, and lateralized rhythmic delta activity, have also been found to be associated with seizures in critically ill patients.[27,30,31]

The duration of cEEG monitoring is an important aspect in diagnosing seizures in critically ill patients. In our study, the average time to first seizure was 7.46 h. The majority of seizures occurred without any clinical signs, which indicate that seizure detection may require longer EEG monitoring. cEEG monitoring is, therefore, necessary in detecting seizures in critically ill patients with ICH. The significance of longer EEG monitoring in critically ill patients has been previously described.[32] In a retrospective review, Claassen *et al*. reviewed cEEG data of critically ill patients and reported time to seizure duration.[32] Sixty-one percent of noncomatose patients had seizure during the 1st h of monitoring, whereas 95% of noncomatose patients had seizure in the first 24 h.[32]

In comparison to noncomatose patients, only 50% of comatose patients had seizure in the 1st h, but 80% had seizure in the first 24 h.[32] Eighty-seven percent of comatose patients reportedly had seizure within 48 h of monitoring.[32] The finding of LPDs was associated with delayed seizure onset.[32] This study concluded that comatose patients, especially those with LPDs, may require longer monitoring for detection of their first electrographic seizure.[32]

Previous studies have reported a higher seizure incidence in patients with larger ICH volumes and in those with accompanying intraventricular hemorrhage.[6,9,20,33] However, ICH size and location were not associated with occurrence of seizures in our study. Yang *et al*. reported that larger ICH volumes were significantly associated with the occurrence of early seizures.[9] They concluded that every 1 mm^3 increase in ICH volume increases the risk of seizure by 2.7%.[9] However, in a prospective study by De Herdt *et al*., ICH volumes were found unrelated to seizure occurrence.[33] This finding was similar to what we observed in our study. Other studies have reported that neither the volume of blood presents in brain parenchyma nor in the ventricular spaces affects the occurrence of seizures.[20,34] Although large cerebral hemorrhages may not cause seizures, the associated neurological deficits are much more severe in patients with larger ICH volume.[6,35] Nonetheless, more studies are required to provide further information on association between ICH volumes and location and seizure occurrence.

Cortical location of ICH bleeds was suggested to be associated with increased seizure incidence.[6,19,34-36] The underlying pathogenesis is related to the involvement of gray-white matter interface at the cortex causing an increased in paroxysmal activity.[37] Direct cortical irritation following ICH can precipitate seizure.[38] We did not find that cortical location of ICH associated with occurrence of seizures in this cohort.

Our study is limited by being a retrospective observational study. Our study is dependent on the inter-rater reliability of the EEG reader in identifying the observed EEG patterns as well as the EEG ordering behaviors of the physicians. It is possible that some patients with ICH were not monitored on cEEG. We strive to limit ordering behavior bias by allowing any physician to order an EEG without prior approval from an epileptologist/neurologist. All EEGs were interpreted by board-certified epileptologists.

Conclusion

We found that LPDs on cEEG monitoring in critically ill patients with ICH are associated with increased seizure occurrence. Other cEEG patterns were not significantly associated with seizures. We did not find that location of hemorrhage, neurological examination, or size of hemorrhage is to be predictive of seizure occurrence. The finding of a majority of seizures being electrographic only and occurring after 7 h of cEEG monitoring highlights the utility of this modality in managing critically ill patients with ICH.

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Conflicts of interest

There are no conflicts of interest.

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