Nonconvulsive Status Epilepticus in the Neurosurgical Setting

Yuichi KUBOTA,[1,2] Hidetoshi NAKAMOTO,[1,2] and Takakazu KAWAMATA[2]

[1]Stroke and Epilepsy Center, Department of Neurosurgery,
Asakadai Central General Hospital;
[2]Department of Neurosurgery, Tokyo Women's Medical University

Abstract

Herein, we review the current state of nonconvulsive status epilepticus (NCSE). NCSE has recently been recognized as one of the causes of unexplained impaired consciousness in the neurosurgical or neurocritical setting. The causes of NCSE include not only central nervous system disorders such as craniotomy, stroke, traumatic brain injury, and central nervous system inflammation, but also severe critical conditions such as sepsis and uremia, among others. NCSE shows no overt clinical manifestations; therefore, prompt and correct diagnosis is difficult. The diagnosis of NCSE should be made by electroencephalogram (EEG), especially continuous EEG (CEEG) monitoring, because NCSE is caught only by prolonged recording. However, the interpretation of the EEG findings is also challenging because of the varying EEG characteristic of NCSE. While the diagnosis should be based on temporal or spatial EEG changes, several definitions and criteria have been proposed, and uniform, universal criteria are still lacking. Once NCSE is diagnosed, antiepileptic drugs (AEDs) should be aggressively administrated. Although there are no standardized international therapeutic guidelines, several AEDs have been attempted in clinical practice in other countries, including fosphenytoin, midazolam, levetiracetam, and valproate. Particularly, several AEDs should be considered prior to using anesthetics. Finally, the prognosis of NCSE depends on the cause thereof; however, in general, earlier intervention for NCSE appears important in terms of better recovery.

Key words: nonconvulsive status epilepticus (NCSE), continuous electroencephalogram monitoring (CEEG), antiepileptic drugs (AEDs), stroke, traumatic brain injury (TBI)

Introduction

Status epilepticus (SE) is a clinical entity characterized by perpetuating or repeating seizures for a certain period of time. Recently, a new definition of SE was proposed by the International League Against Epilepsy; this definition mentions a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormal, prolonged seizures.[1] Similarly, nonconvulsive status epilepticus (NCSE) is defined as prolonged or repetitive electrographic seizures without any motor manifestations lasting for more than 5 minutes.[1] Its cause was previously considered as a prior history of epilepsy or epileptic encephalopathy; however, recent advances in digital electroencephalography (EEG) have enabled us to record electrographic seizures accompanying craniotomy, stroke, and traumatic brain injury (TBI) in the neurocritical care or neurosurgical setting, as well as critical surgical conditions such as sepsis, liver dysfunction, and renal failure.[2] Continuous EEG (CEEG) monitoring is thought to be essential for diagnosing NCSE, which is otherwise difficult to diagnose, as its clinical presentation does not include overt symptoms or only includes extremely non-specific signs such as altered mental status, subtle eye movements like nystagmus, and severe disturbance of consciousness. Minimal motor manifestations such as facial jerking, blinking, and eyelid myoclonus are also considered as the symptoms of NCSE. NCSE is considered a treatable entity if diagnosed early, but may be difficult to detect and thus often goes undiagnosed. Regarding the treatment, how aggressively NCSE should be treated is still unclear. Therefore, large, well-controlled, prospective studies are needed to establish the appropriate treatment regimen. Husain et al. recently launched the Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS) study, which aims to compare the efficacy and tolerability of fosphenytoin and lacosamide in patients with NCSE, as noted by CEEG.[3]

In the present review, we summarize the current knowledge on NCSE in the neurosurgical setting, focusing particularly on the diagnosis and treatment thereof.

EEG Characteristic of NCSE

In general, the main principle of diagnosing NCSE is to find 'temporal and spatial changes' on EEG. For that purpose, a longer duration of EEG recording is required. According to Claassen et al., EEG recordings of less than one hour detect less than 50% of electrographic seizures.[4] In other words, the longer the EEG recordings, the higher the probability of detecting NCSE.

Chong et al., proposed the following definition of NCSE:[5] (Table 1) any pattern lasting at least 10 seconds and satisfying any one of the following three primary criteria:

Primary criteria

1. Repetitive generalized or focal spikes, sharp-waves, or spike-and-wave or sharp-and-slow wave complexes (three per second).

Table 1 Chong's classification

Chong et al. (2005)		
Any pattern lasting at least 10 seconds any one of the following 3 primary criteria:		
Primary criteria	1	Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at 3/sec.
	2	Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at <3/sec and the secondary criterion.
	3	Sequential rhythmic, periodic, or quasi-periodic waves at >1/sec and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/sec, e.g. from 2 to 3/sec), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not adequate to satisfy evolution in morphology.
Secondary criteria		Significant improvement in clinical state or appearance of previously-absent normal EEG patterns (such as a posterior dominant rhythm) temporally coupled with acute administration of a rapidly-acting AED. Resolution of the "epileptiform" discharges leaving diffuse slowing without clinical improvement and without appearance of previously-absent normal EEG patterns would not satisfy the secondary criterion.

2. Repetitive generalized or focal spikes, sharp waves, or spike-and-wave or sharp-and-slow wave complexes (fewer than three per second), plus the secondary criterion.

3. Sequential rhythmic, periodic, or quasi-periodic waves (more than one per second) and unequivocal evolution in frequency (gradually increasing or decreasing by at least one per second, e.g., from two to three per second), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not adequate to satisfy the criterion of evolution in morphology.

Secondary criteria

Significant improvement in the clinical state or appearance of previously-absent normal EEG patterns (such as a posterior dominant rhythm) temporally coupled with acute administration of a rapidly-acting antiepileptic drug (AED). Resolution of the "epileptiform" discharges leaving diffuse slowing without clinical improvement and without appearance of previously-absent normal EEG patterns does not satisfy the secondary criterion.

Subsequently, the following criteria for NCSE were published at the Oxford conference on NCSE in 2005 (Table 2).[6] These criteria, which

Table 2 Oxford consensus' classification

Oxford conference (2005)	
1	Frequent or continuous focal electrographic seizures, with ictal patterns that wax and wane with change in amplitude, frequency and/or spatial distribution.
2	Frequent or continuous generalized spike wave discharges in patients without a prior history of epileptic encephalopathy or epilepsy syndrome.
3	Frequent or continuous generalized spike wave discharges, which show significant changes in intensity or frequency (usually a faster frequency) when compared to baseline EEG, in patients with an epileptic encephalopathy/syndrome.
4	PLEDs (periodic lateralized epileptiform discharges) or biPEDs (bilateral periodic epileptiform discharges) occurring in patients with coma in the aftermath of a generalized tonic-clonic SE (subtle SE).
5	Frequent or continuous EEG abnormalities (spikes, sharp waves, rhythmic slow activity, PLEDs, BiPEDs, GPEDs, triphasic waves) in patients whose EEG showed no previous similar abnormalities, in the context of acute cerebral damage (e.g. anoxic brain damage, infection, trauma).
6	Frequent or continuous generalized EEG abnormalities in patients with epileptic encephalopathies in whom similar interictal EEG patterns are seen, but in whom clinical symptoms are suggestive of NCSE.

are considered highly applicable for neurocritical practice, include:

a. Frequent or continuous focal electrographic seizures, with ictal patterns that wax and wane with changes in amplitude, frequency, and/or spatial distribution.

b. Frequent or continuous generalized spike wave discharges in patients without a prior history of epileptic encephalopathy or epilepsy syndrome.

c. Frequent or continuous generalized spike wave discharges that show significant changes in intensity or frequency (usually a faster frequency) when compared to the baseline EEG in patients with an epileptic encephalopathy/syndrome.

d. Periodic lateralized epileptiform discharges or bilateral periodic epileptiform discharges occurring in patients with coma in the aftermath of a generalized tonic-clonic SE (subtle SE).

EEG patterns that are less easy to interpret include:

e. Frequent or continuous EEG abnormalities (spikes, sharp waves, rhythmic slow activity, periodic lateralized epileptiform discharges, bilateral periodic epileptiform discharges, generalized periodic epileptiform discharges, or triphasic waves) in patients whose EEG showed no previous similar abnormalities, in the context of acute cerebral damage (e.g., anoxic brain damage, infection, trauma).

f. Frequent or continuous generalized EEG abnormalities in patients with epileptic encephalopathies in whom similar interictal EEG patterns are seen, but in whom the clinical symptoms are suggestive of NCSE.

Categories (c) and (f) reflect the problem of deciding the significance of spike wave discharges in the setting of epileptic encephalopathy (e.g., Lennox Gastaut syndrome), in which the ictal and interictal EEG patterns may be very similar. The differentiation of the two is problematic. Category (e) reflects the difficulty of differentiating patterns of epileptic discharges that may lie along an ictal-interictal continuum.

To avoid these confusions, the American Clinical Neurophysiology Society published standardized critical care EEG terminology guidelines in 2012.[7] In neurocritical care, there is no uniformly accepted nomenclature for the EEG patterns frequently encountered in these patients, such as periodic discharges, fluctuating rhythmic patterns, and combinations thereof. Similarly, there is no consensus on which patterns are associated with ongoing neuronal injury, which patterns need to be treated, or how best to treat them. The first step in addressing these issues is to standardize the terminology to allow multicenter research projects and to facilitate communication. One of the main goals is to eliminate terms with clinical connotations,

intended or not, such as "triphasic waves," a term that implies a metabolic encephalopathy with no relationship to seizures for many clinicians. In the 2012 guidelines, the use of "ictal," "interictal," and "epileptiform" for the equivocal patterns that are the primary focus of this report are also avoided. These EEG terminology guidelines are currently well accepted, especially in the neurocritical setting, as well as in our center. In this nomenclature, the localizations are classified as generalized, lateralized, bilateral, independent, and multifocal. Moreover, the waveform patterns are divided into periodic discharges, rhythmic delta activity, and spike-and-wave or sharp-and-wave patterns (Figs. 1–3). The diagnosis of NCSE is finally determined by a combination of the EEG waveform changes and the clinical symptoms of the patient.
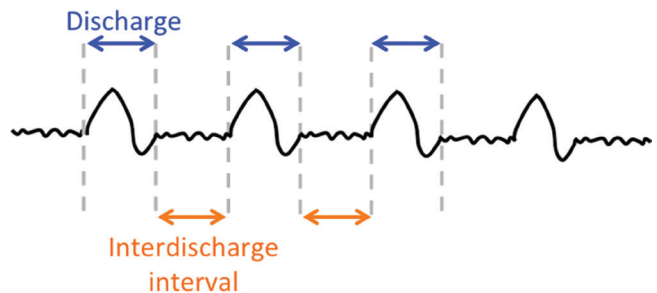

Fig. 1a Periodic Discharges (PDs). **"Periodic" indicates repetition of a waveform with relatively uniform morphology and duration, with a quantifiable interdischarge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals. "Discharges" are defined as waveforms with no more than three phases (i.e., crosses the baseline no more than twice) or any waveform lasting 0.5 seconds or less, regardless of the number of phases. This is as opposed to bursts, defined as waveforms lasting more than 0.5 seconds and with at least four phases (i.e., crosses the baseline at least three times).**
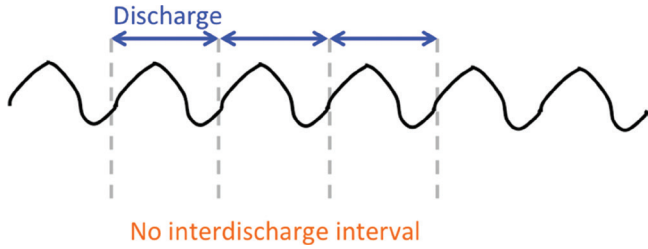

Fig. 1b **Example of right LPDs**

Fig. 2a Rhythmic Delta Activity (RDA). "Rhythmic" indicates repetition of a waveform with relatively uniform morphology and duration, and without an interval between consecutive waveforms. RDA is defined as rhythmic activity < 4 Hz. The duration of one cycle (i.e., the period) of the rhythmic pattern should vary by <50% from the duration of the subsequent cycle for the majority (>50%) of cycle pairs to qualify as rhythmic.
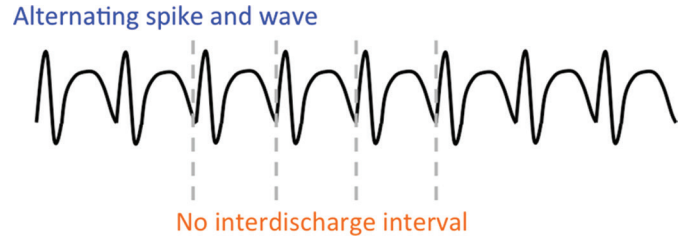

Fig. 3a Spike-and-wave or sharp-and-wave (SW) patterns. These are defined as polyspike, spike, or sharp waves consistently followed by a slow wave in a regularly repeating and alternating pattern (spike-wave-spike-wave-spike-wave), with a consistent relationship between the spike (or polyspike or sharp wave) component and the slow wave, and with no interval between one spike-wave complex and the next (if there is an interval, this would qualify as PDs, where each discharge is a spike-and-wave).
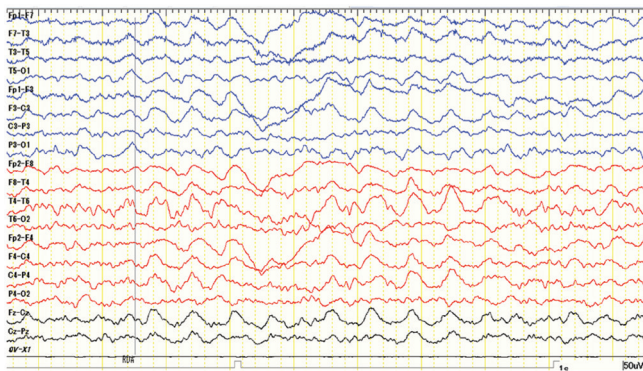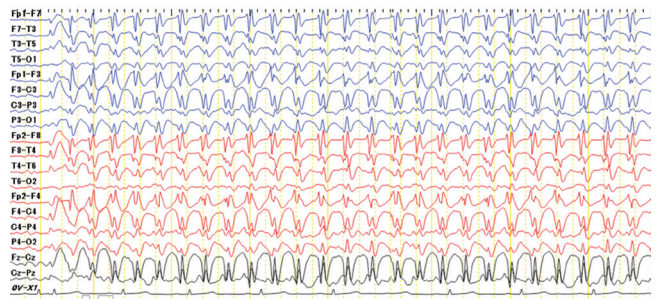

Fig. 2b Example of GRDA

Fig. 3b Example of GSWs

Treatment of NCSE

Although NCSE has been recognized as a neurocritical condition, the appropriate treatment of NCSE has not been established, owing to a lack of sufficient clinical trials. The American Neurocritical Care Society proposed guidelines for the evaluation and management of SE in 2012.[8] In these guidelines, the treatment of NCSE is similar to that of convulsive SE. However, it is difficult for physicians to promptly detect the onset of NCSE due to the lack of clinical signs in these patients. Therefore, it is important to consider this condition in the differential diagnosis of patients with unexplained impaired consciousness after convulsion, stroke, TBI, or craniotomy; in patients with subtle clinical manifestations such as subtle abnormal eye movements or facial myoclonus; and in patients with a characteristic EEG pattern for NCSE, including periodic discharges, despite the absence of evolving or fluctuating patterns. The principal aim of NCSE treatment is to stop both the clinical symptoms and electrographic seizures.

Previously, SE was mainly treated by anesthetics; however, recently, AEDs have been reported to be more appropriate, owing to the high rate of complications associated with the use of anesthetics. As an emergent treatment, benzodiazepines should be administered as soon as possible. Although benzodiazepines act very fast, they are only effective for a short duration. Therefore, subsequent treatment is needed, including by phenytoin/fosphenytoin, midazolam, and/or phenobarbital, which all have long half-lives. In terms of phenytoin, while there are large amounts of clinical data available, arrhythmias, hypotension, and purple glove syndrome are potential side effects. On the other hand, fosphenytoin, as a pro-drug of phenytoin, is safer than phenytoin in the setting of the purple glove syndrome. Further, midazolam and phenobarbital sometimes show serious adverse effects, including respiratory depression and hypotension. In Japan, although several reports have demonstrated its effectiveness and tolerability,[9,10] levetiracetam is used off-label for SE. Currently, the TRENdS study, which compares the efficacy and tolerability of fosphenytoin and lacosamide in patients with NCSE, as noted by

CEEG, is ongoing,[3] and the results are anticipated to impact on the treatment decision-making for these patients.

NCSE after Craniotomy

Most neurosurgeons have experienced a case of prolonged impaired consciousness after craniotomy. Al-Mefty et al. reported seven cases of delayed, progressive, postoperative decline in the level of consciousness to deep coma that was time-limited to several days with abrupt awakening, diagnosed using EEG recording after skull base surgery.[11] They called this clinical entity "postoperative nonconvulsive encephalopathic status". Several potential causes were discussed, including the anesthetic agents or medications used in the setting of craniotomy, as well as postoperative electrographic seizures. Postoperative NCSE was also described by Devarajan et al.[12] who experienced de novo NCSE in an elderly patient without a history of epilepsy. The entity occurred in the immediate postoperative period after uncomplicated resection of a convexity meningioma. CEEG monitoring showed electrographic seizure activity without any motor manifestations. In this case, the NCSE was successfully treated with several AEDs. The authors stressed that the NCSE may be more common than reported and should be considered early in the differential diagnosis of any patient with unexplained impairment of consciousness after intracranial surgery. Further, surgery for all supratentorial tumors, such as meningiomas, gliomas, and metastatic tumors, may have the possibility of causing NCSE. Hence, neurosurgeons should always keep NCSE in mind as a cause of delayed impaired consciousness after craniotomy.

NCSE in Patients with Stroke

Stroke in itself seems to be associated with the risk of NCSE. Concerning ischemic stroke, all types of ischemia, that is, not only cortical ischemia, but also lacunar infarction, have the possibility of developing subsequent NCSE. Among elderly critical ill patients, Litt et al. reported 24 NCSE episodes was found, within them five patients had a lacunar infarction. However the pathophysiology had not mentioned.[13] Early detection and intervention for secondary neuronal damage due to NCSE is a cornerstone of management in neurocritical care units; therefore, using CEEG to detect evolving or worsening cerebral ischemia or NCSE is desirable. Patients with stroke can have lateralized periodic discharges and other EEG findings on the ictal-interictal continuum that put them at risk for developing seizures.

Furthermore, subarachnoid hemorrhage is a known cause of NCSE. The incidence of developing NCSE in patients with subarachnoid hemorrhage is reported to range between 3 and 31%.[14,15] Of note, the presence of periodic discharges or NCSE, as well as the absence of normal sleep architecture and reactivity, have been independently associated with poor neurological outcomes, defined as a Modified Rankin Scale score greater than 4.[16]

The patients with intracranial hemorrhage (ICH) occasionally develop seizures. Periodic discharges on CEEG have been associated with worse outcome following ICH. Compared with deep ICH, such as thalamic or putaminal ICH, patients with subcortical ICH tend to develop NCSE more frequently. Thus, while it is still unclear whether CEEG can improve the outcomes in patients with stroke, awareness of EEG abnormalities in these patients is likely beneficial.

NCSE in TBI

TBI is also associated with a risk of subsequent NCSE, which is being increasingly recognized as harmful. In a retrospective study of patients with TBI undergoing CEEG, Claassen et al. found that 18% of patients experienced a seizure during the CEEG monitoring, all of which were subclinical seizures, while 8% developed NCSE.[4] On the other hand, in a pediatric population, Amdt et al. reported the usefulness of CEEG for the detection of subclinical early posttraumatic seizures; they found that subclinical seizures occurred in 16.1% of patients.[17]

Conclusion

NCSE is commonly observed in various neurosurgical or neurocritical care settings. Without EEG, it is hard to detect NCSE because of the lack of overt clinical signs. If neurosurgeons encounter unexplained impaired consciousness, CEEG should be applied to diagnose NCSE. As the outcomes of the NCSE are generally considered poor, prompt diagnosis and immediate intervention are needed.

Conflicts of Interest Disclosure

The authors hereby declare no conflict of interest regarding this article.

References

1) Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status

epilepticus – Report of the ilae task force on classification of status epilepticus. *Epilepsia* 56: 1515–23, 2015

2) Kurtz P, Gaspard N, Wahl AS, Bauer RM, Hirsch LJ, Wunsch H, Claassen J. Continuous electroencephalography in a surgical intensive care unit. *Intensive Care Med* 40: 228–234, 2014

3) Husain AM. Treatment of recurrent electrographic nonconvulsive seizures (TRENdS) study. *Epilepsia* 54 Suppl 6: 84–88, 2013

4) Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 62: 1743–1748, 2004

5) Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. *J Clin Neurophysiol* 22: 79–91, 2005

6) Walker M, Cross H, Smith S, Young C, Aicardi J, Appleton R, Aylett S, Besag F, Cock H, DeLorenzo R, Drislane F, Duncan J, Ferrie C, Fujikawa D, Gray W, Kaplan P, Koutroumanidis M, O'Regan M, Plouin P, Sander J, Scott R, Shorvon S, Treiman D, Wasterlain C, Wieshmann U. Nonconvulsive status epilepticus: Epilepsy research foundation workshop reports. *Epileptic Disord* 3: 253–296, 2005

7) Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, Mani R, Arif H, Jette N, Minazad Y, Kerrigan JF, Vespa P, Hantus S, Claassen J, Young GB, So E, Kaplan PW, Nuwer MR, Fountain NB, Drislane FW. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin Neurophysiol* 30: 1–27, 2013

8) Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr, Shutter L, Sperling MR, Treiman DM, Vespa PM; Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 17: 3–23, 2012

9) Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. *J Neurol* 259: 645–648, 2012

10) Atmaca MM, Orhan EK, Bebek N, Gurses C. Intravenous levetiracetam treatment in status epilepticus: A prospective study. *Epilepsy Res* 114: 13–22, 2015

11) Al-Mefty O, Wrubel D, Haddad N. Postoperative nonconvulsive encephalopathic status: identification of a syndrome responsible for delayed progressive deterioration of neurological status after skull base surgery. Clinical article. *J Neurosurg* 111: 1062–1068, 2009

12) Devarajan J, Siyam AM, Alexopoulos AV, Weil R, Farag E. Non-convulsive status epilepticus in the postanesthesia care unit following meningioma excision. *Can J Anaesth* 58: 68–73, 2011

13) Litt B, Wityk RJ, Hertz SH, Mullen PD, Weiss H, Ryan DD, Henry TR. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* 39: 1194–1202, 1998

14) Little AS, Kerrigan JF, McDougall CG, Zabramski JM, Albuquerque FC, Nakaji P, Spetzler RF. Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid hemorrhage. *J Neurosurg* 106: 805–811, 2007

15) Dennis LJ, Claassen J, Hirsch LJ, Emerson RG, Connolly ES, Mayer SA. Nonconvulsive status epilepticus after subarachnoid hemorrhage. *Neurosurgery* 51: 1136–1143, 2002

16) Claassen J, Hirsch LJ, Frontera JA, Fernandez A, Schmidt M, Kapinos G, Wittman J, Connolly ES, Emerson RG, Mayer SA. Prognostic significance of continuous EEG monitoring in patients with poor-grade subarachnoid hemorrhage. *Neurocrit Care* 4: 103–112, 2006

17) Arndt DH, Lerner JT, Matsumoto JH, Madikians A, Yudovin S, Valino H, McArthur DL, Wu JY, Leung M, Buxey F, Szeliga C, Van Hirtum-Das M, Sankar R, Brooks-Kayal A, Giza CC. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. *Epilepsia* 54: 1780–1788, 2013

Address reprint requests to: Yuichi Kubota, Stroke and Epilepsy Center, Asakadai Central General Hospital, 1-8-10 Nishibenzai, Asaka, Saitama, Japan.
e-mail: kubota.yuichi@twmu.ac.jp