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Should We Treat Electroencephalographic Discharges in the Clinic or in the Intensive Care Unit, and if so When and How?

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The important question that often emerges in the clinic is how aggressive the therapy for nonconvulsive status epilepticus and electrical status epilepticus in sleep ought to be and how continuous the discharges in each of these 2 entities should be before therapy is aimed at them. Additionally, as the use of electroencephalographic monitoring continues to expand to include the clinic and intensive care unit populations, it is important to identify epileptiform patterns that warrant identification and treatment. This review will present the state-of-the-art data and suggest algorithms to manage these conditions.
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Introduction

It is well established that status epilepticus (SE) and acute repetitive seizures may cause brain injury or add to injury caused by an underlying brain insult.[1] Clear treatment protocols exist.[2,3] In the inpatient setting, there is disagreement regarding the treatment needed, or how aggressively to treat, nonconvulsive seizures (NCS), the electroencephalographic (EEG) patterns on the ictal-interictal continuum, or even nonconvulsive SE (NCSE). A similar situation exists in the outpatient setting in patients with epileptic encephalopathies, with or without NCSE, and electrical SE of sleep (ESES). This article will review the rationale and treatment of these various conditions.

EEG Patterns

There is consensus regarding the initial treatment of SE or acute repetitive seizures and clear guidelines exist[2,3] (Table 1). SE was originally defined as a lasting and enduring epileptic condition[4] with an increased risk of subsequent injury when its duration exceeds 30 minutes.[1,5,6] An increased morbidity and mortality occurs when SE is associated with an acute brain insult, adding additional injury, or occurs de novo in hospitalized patients.[7]

Continuous EEG (CEEG) monitoring in the critically ill patient captures the electrographic patterns associated with convulsive seizures, overt SE (Fig. 1A), electrographic seizures (nonconvulsive seizures [NCS]) and EEG patterns that may be ictal, especially when associated with altered awareness. Less clear is the need to treat subclinical electrographic activity, including NCSE (Fig. 1B), NCS, abundant epileptiform activity, or the EEG patterns considered as an ictal-interictal continuum.[8,9] This is defined as persistence of periodic EEG patterns ranging from those with less to greater potential for secondary neuronal injury[8,9]—suppression-burst pattern, triphasic waves, periodic lateralized epileptiform discharges (PLEDS), generalized periodic epileptiform discharges (GPEDs), stimulus-induced rhythmic, periodic, or ictal discharges, PLEDS-proper, and repetitive patterns in-between spikes to overt ictal patterns, such as convulsive and NCSE[8-11] (Table 2). These periodic patterns usually appear in patients with altered awareness and a poor outcome with PLEDs and GPEDs, now lateralized periodic discharges (LPDs) (Fig. 2) and generalized periodic discharges (PEDs) (Fig. 3), respectively.[8-11] Claassen[9] suggests that we move beyond the dichotomy of the terms ictal vs interictal and use "harmful vs non-harmful patterns," as this is really the clinical question—What patterns harm the brain and need to be treated vs which are nonharmful and do not need aggressive treatment?

SE has clinical and electrographic stages.[6] Clinical SE may evolve from increasing myoclonus or confusion to then repetitive clinical seizures, with these evolving into convulsive

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Table 1 AES Guideline for Treatment of Status Epilepticus[3]

Initial therapy of choice: a benzodiazepine (level A)
IV lorazepam, 0.1 mg/kg/dose, maximum 4 mg, may repeat once (level A)
IV diazepam, 0.15-0.2 mg/kg/dose, maximum 10 mg, may repeat once (level A)
IM midazolam, 10 mg for >40 kg, 5 mg for 13-40 kg, single dose (level A)
If none of these are available:
IV phenobarbital, 15 mg/kg/dose, single dose (level A)
Rectal diazepam, 0.2-0.5 mg/kg, maximum dose, 20 mg/dose, single dose (level B)
Intranasal or buccal midazolam, 0.2 mg/kg, maximum 10 mg (level B)
If seizures continue: choose 1 of the following second-line agents and give single dose
IV fosphenytoin, 20 mg PE/kg, maximum 1500 mg PE/dose (level U)
IV valproic acid, 40 mg/kg, maximum 3000 mg, single dose (level U)
IV levetiracetam, 60 mg/kg, maximum 4500 mg, single dose (level U)
Or IV phenobarbital, if not previously given
If seizures continue, no clear evidence to guide (level U)
Anesthetic doses of thiopental, midazolam, pentobarbital, or propofol
Some protocols in children use midazolam first; starting at 0.2 mg/kg/dose, maximum 10 mg. If seizures continue for another 5 min, another 0.2 mg/kg and start infusion of 0.1 mg/kg/h; if seizures continue, another 0.2 mg/kg/dose and increase infusion to 0.2 mg/kg/h. If seizures continue, repeat midazolam, 0.2 mg/kg/h and start pentobarbital, 5 mg/kg, followed by infusion of 1 mg/kg/h, increase as needed to 3 mg/kg/h.[2]

IM, intramuscular; IV, intravenous; PE, phenytoin equivalents.

SE (CSE) (Table 3). Even overt CSE may stop as SE duration increases, leaving the patient with altered awareness or unresponsive yet still with electrographic SE; this is NCSE, similar to the cardiac phenomenon of electromechanical disassociation. Treiman et al[12] have demonstrated that the electrographic stages of SE correlate with the clinical stages (Table 4). Mikati et al[13] have confirmed that these same stages occur in the younger animal.

CEEG monitoring shows that even when overt CSE is controlled, NCSE may continue,[14] occurring in about 15% of adults and in 16% of children.[15] The presence of this ongoing seizure activity may lead to further brain injury. There is no debate regarding the treatment of persistent NCSE after the control of CSE, but its identification requires the availability of EEG monitoring. There is debate on how aggressively NCS or patterns on the ictal-interictal continuum, such as PEDs (GPEDS) or LPDs (PLEDS) should be treated. However, there is an increased morbidity and mortality with NCS in stroke, intracranial hemorrhage, and subarachnoid hemorrhage. For example, Vespa et al[16] showed an increased midline shift and mortality when NCS occurred in intracerebral hemorrhage. Recently, similar findings have been reported in neonates with hypoxic-ischemic encephalopathy[17,18]; increasing seizure activity is associated with greater magnetic resonance imaging (MRI) damage, although it remains unclear if this is a direct cause and effect relationship.

Recent articles have addressed the treatment of EEG patterns in the ictal-interictal continuum.[19,20] They are defined depending on the frequency of the periodic discharges: If the frequency of EEG patterns is 3 Hz or greater than 3 Hz they are generally considered "ictal" whereas those with a frequency at 1 Hz or less are "interictal"; those patterns with frequencies between 1 and 3 Hz are "ictal-interictal continuum."[8,19,20] Treatment can be with a benzodiazepine or different intravenous antiepileptic drugs (AEDs) (Table 1) with a positive response defined as clinical and EEG improvement.

The setting in which EEG discharges occur, and whether to treat, may differ between the inpatient and outpatient setting. Akman[21] has differentiated this into ambulatory NCSE, that seen with the exacerbation of a pre-existing epilepsy vs NCSE with an acute neurologic insult in the critically ill patient. The PEDs (GPEDs) pattern is an example defined as a periodic EEG pattern with bisynchronous sharp wave complexes occurring in periodic intervals between 0.5 and 4 seconds.[22] PEDs may be present in an outpatient with chronic encephalopathy, such as a dementia, vs following the control of CSE in the intensive care unit (ICU). This has also been divided into ambulatory vs nonambulatory. We studied children with GPEDs in the pediatric ICU: the GPEDs pattern was present in children treated with refractory SE, usually the EEG pattern present after treatment, in a continuum from the suppression-burst pattern, into GPEDs, subclinical seizures and ultimately, a clinical seizure.[23,24] Therefore, the clinical situation in which an EEG pattern is detected has important clinical implications. LPDs, previously known as PLEDs, have the same concern, are these ictal or interictal patterns? LPDs are well described in vascular diseases and central nervous system (CNS) infections, but can also evolve into electrographic seizure activity on EEG. Diffusion-weighted MRI, single-photon emission computed tomography scan, positron emission tomography scan, or perfusion-MRI may determine whether a pattern is ictal or interictal.[9] Signal change on diffusion-weighted imaging, increased metabolism on positron emission tomography scan, or increased blood flow on single-photon emission computed tomography scan should be seen in the ictal state.

The concept of an epileptic encephalopathy, which applies mainly to the outpatient setting, has also changed how we manage epileptiform activity on EEG. We were taught "to treat the patient not the EEG," with the implication that we should treat seizures but not interictal epileptiform EEG activity. An epileptic encephalopathy is defined as a disorder in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (such as a cortical malformation), and that these impairments may worsen over time.[25] Clinical manifestations caused by epileptiform activity include cognitive and behavioral dysfunction, motor dysfunction, or regression in abilities, with clinical improvement noted if the epileptiform activity can be improved. However, the epileptiform activity may also be an epiphenomenon: the EEG abnormality is caused by the underlying etiology, which also causes the spikes, and even if the spikes are