Invited review

Nonconvulsive seizures: Developing a rational approach to the diagnosis and management in the critically ill population

J. Jirsch 1, L.J. Hirsch *

Comprehensive Epilepsy Center, Columbia University Medical Center, New York, NY, USA

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Abstract

Originally described in patients with chronic epilepsy, nonconvulsive seizures (NCSs) are being recognized with increasing frequency, both in ambulatory patients with cognitive change, and even more so in the critically ill. In fact, the majority of seizures that occur in the critically ill are nonconvulsive and can only be diagnosed with EEG monitoring. The semiology of NCSs and the associated EEG findings are quite variable. There are a number of periodic, rhythmic or stimulation-related EEG patterns in the critically ill of unclear significance and even less clear treatment implications. The field struggles to develop useful diagnostic criteria for NCSs, to standardize nomenclature for the numerous equivocal patterns, and to devise studies that will help determine which patterns should be treated and how aggressively. This review surveys the evidence for and against NCSs causing neuronal injury, and attempts to develop a rational approach to the diagnosis and management of these seizures, particularly in the encephalopathic population.

Keywords: Nonconvulsive seizure; Nonconvulsive status epilepticus; Critically ill; Intensive care unit; EEG; Periodic discharges

1. Introduction

Early descriptions of convulsive seizures are found in Babylonian tablets from 2000 BC that emphasize the supernatural nature of these events. Centuries later, Hippocrates wrote on the “sacred disease” and argued that epileptic convulsions were manifestations of a diseased brain and recommended physical treatments. Detailed accounts of less overt epilepsies began in the 18th and 19th century with the French description of “petit mal” seizures and Hughlings Jackson’s “uncinate fits” (Kaplan, 2002). The advent of EEG in the 20th century allowed physicians to discover unequivocal seizures in previously unsuspected circumstances, yet the field still struggles to define the extent of EEG patterns that should be considered ictal and to determine when these events should be treated. This review examines nonconvulsive seizures in the critically ill population, particularly emphasizing controversies as to which EEG patterns should be considered ictal, and exploring the evidence whether such seizures are intrinsically harmful. Whenever possible the American Academy of Neurology classification of evidence scheme is used (Appendix, for example, see Armon and Evans, 2005).

2. Nonconvulsive seizures in encephalopathic patients

The clinical spectrum in nonconvulsive seizures (NCSs) is protean (Table 1). In the community, NCSs present most frequently in patients who are confused but remain ambulatory, while in the hospital NCSs are most frequently diagnosed in the intensive care unit (ICU). We focus on the obtunded or comatose patients for this article, and in these cases the clinical diagnosis is often challenging as manifestations are often absent or may consist of only subtle myoclonic limb, facial or ocular movements. In fact, approximately 90% of critically ill patients with seizures recorded have purely nonconvulsive seizures that are unrecognized at the bedside and can only be diagnosed...
with CEEG (Claassen et al., 2004; Pandian et al., 2004). Ictal activity may be generalized (Fig. 1) or focal (Fig. 2) in these patients.

Technological advances over recent years have allowed an ever-increasing number of critically ill patients to be monitored using continuous digital EEG (CEEG), and it has become clear that ictal activity is common in this environment. The rate of NCSs has varied in published series to date depending on the patient population studied. The series from our center involved 570 patients monitored to detect subclinical seizures or for unexplained depressed level of consciousness, and found 18% were having NCSs and 10% were in nonconvulsive status epilepticus (NCSE). Similar studies of consecutive neurologic ICU patients have found 27–34% with electrographic seizures (Jordan, 1993; Pandian et al., 2004). Notable critically ill subpopulations are patients with diagnoses of intracerebral hemorrhage (29% had NCSs) (Vespa et al., 2003), CNS infection (26%) (Claassen et al., 2004), brain tumor (23%) (Claassen et al., 2004), severe head trauma (22%) (Vespa et al., 1999), subarachnoid hemorrhage (18%) (Claassen et al., 2004; Dennis et al., 2002), and a prior history of epilepsy (31%) (Claassen et al., 2004). Comatose patients who had convulsive status epilepticus prior to CEEG monitoring frequently later demonstrated electrographic seizures (13–48%) (DeLorenzo et al., 1998; Treiman et al., 1998), and focal or generalized periodic epileptiform discharges on EEG also appear to be significant predictors for NCSs (Class III and IV evidence). Finally, Towne et al. (2000) studied 236 consecutive patients with unexplained coma excluding those that had prior seizures or subtle movements that could be ictal, and found that 8% were having NCSs.

![Fig. 1. An example of NCSE with generalized epileptic discharges. This 55-year-old man with AIDS presented with fluctuating mental status change and was later found to have cryptococcal meningitis. The patient was subsequently given 2 mg of lorazepam with abrupt cessation of ictal activity and improvement of mental status.](image)

Table 1

<table>
<thead>
<tr>
<th>Negative symptoms</th>
<th>Positive symptoms</th>
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<tr>
<td>Anorexia</td>
<td>Agitation/aggression</td>
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<tr>
<td>Aphasia/mutism</td>
<td>Automatisms</td>
</tr>
<tr>
<td>Annesia</td>
<td>Blinking</td>
</tr>
<tr>
<td>Catatonia</td>
<td>Crying</td>
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<tr>
<td>Coma</td>
<td>Delirium</td>
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<tr>
<td>Confusion</td>
<td>Delusions</td>
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<tr>
<td>Lethargy</td>
<td>Echolalia</td>
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<td>Staring</td>
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Largely extracted (and expanded) from Kaplan (1996).
Clearly, NCSs are common in neurocritical care patients and it has become evident that the majority of these events would be missed without prolonged EEG studies. The series by Pandian et al. (2004) illustrates this point well where all patients in their series had 30 min routine EEGs at the beginning of their monitoring. The authors found that more than half of all seizure cases would have been missed without prolonged recording (routine EEG found seizures in 11% of patients vs. 27% with cEEG; median duration of CEEG was 2.9 days). Similarly, our institution found seizure activity present at the beginning of the EEG record in 16 of 110 (15%) patients who would eventually develop ictal activity during monitoring, and in about half of patients by 1 h.

The duration of monitoring required to exclude the presence of seizures in critically ill patients remains somewhat unclear. Claassen et al. (2004) found that of 110 patients with seizures during CEEG, 95% of noncomatose patients had their first seizure identified within 24 h of recording, but the first seizure had been recorded in only 80% of the comatose patients. Furthermore, 13% of the comatose patients with seizures did not have their first seizure until more than 48 h of recording. The presence of certain interictal patterns may help predict a delayed time to first seizure, and a finding of periodic lateralized epileptic discharges (PLEDs) should prompt the clinician to continue EEG monitoring beyond 24 h as 21% of these patients had their first seizure after the first full day of cEEG compared with 8% in those without PLEDs (Class III evidence). There are almost certainly other important EEG monitoring variables to help improve the sensitivity of NCS detection in the ICU, and to date little is known about the optimal number of channels or electrodes required in these patients.

The specificity and accuracy of CEEG monitoring for seizure detection is also incompletely understood. Large centers that review abundant EEG monitoring records in critically ill patients recognize that a clear division of EEG patterns as either ictal or interictal is elusive or nonexistent, and interpretation varies considerably among different electroencephalographers. Indeed the strength of evidence suggesting various periodic EEG patterns are predictive of NCSs is weakened in many studies by a lack of independent definitions of the two. EEG patterns that have historically been considered non-ictal are on occasion reportedly ictal. A case in point is triphasic waves, which commonly occur in metabolic encephalopathies but also in cortical degenerative diseases, CNS infections, and sepsis (Sundaram and Blume, 1987; Young et al., 1990). They are...
classically characterized by generalized, frontally dominant periodic discharges at 1–2 Hz (but occasionally faster than this), often with fronto-occipital lag. Triphasic waves, however, can be difficult to distinguish from NCSE because with both patterns patients typically have altered consciousness, and discharges may fluctuate at greater than 1 Hz (Sheridan and Sato, 1986). Phase two amplitude predominance and antero-posterior lag on referential montage are features of triphasic waves that are absent in NCSE according to some authors (Boulanger et al., 2006) but not most others (Drake and Erwin, 1984; Hormes et al., 1988; Kaplan, 2004; Chong and Hirsch, 2005). Moreover, even the response to benzodiazepines, which has traditionally helped guide epileptologists in identifying ictal patterns, can eliminate or markedly attenuate classic triphasic waves (Fig. 3; Fountain and Waldman, 2001).

Many other periodic EEG patterns in the critically ill are equally ambiguous. Generalized periodic epileptic discharges (GPEDs) have been divided according to inter-discharge interval into periodic short interval diffuse discharges (PSIDDs with intervals of 0.5–4 s), and periodic long interval diffuse discharges (PLIDDs, 4–30 s). PLIDDs are very rare and classically occur with subacute sclerosing panencephalitis. Less rare are PSIDDs, which occur most often with anoxia–ischemia, Creutzfeld–Jacob disease or after convulsive status epilepticus (Fig. 4). Yemisci et al. (2003) found GPEDs with a variety of etiologies to be associated with convulsive seizures (Class IV evidence). Husain et al. (1999) and others (Brenner and Schaul, 1990; Nei et al., 1999) argued that many instances could be considered ictal with evolving discharge patterns and/or clinical improvement in response to antiepileptic drugs. We recently presented preliminary data from our center comparing 98 consecutive patients with generalized periodic discharges (GPDs) to matched controls also undergoing CEEG monitoring. Patients with GPDs were more likely to have seizures of any kind (52% vs. 41%), NCSs (29% vs. 13%), and poor outcome (83% vs. 63%) (Abou Khaled et al., 2006; Class III evidence).

Another EEG pattern in the critically ill is periodic lateralized epileptic discharges (PLEDs). PLEDs most commonly occur following acute focal destructive lesions (e.g. infarct, infection or tumor) or with a combined structural lesion and metabolic insult (Fig. 5). The pattern has traditionally been considered an interictal epileptiform disturbance, however the discharges have occasionally been described time-locked to focal motor movements and in these cases are therefore ictal. Moreover, PLEDs have also been associated with negative symptoms sometimes seen with NCSs (e.g. aphasia, cognitive changes, even hemiparesis) and these may improve immediately following AED treatment (Kuroiwa and Celesia, 1980; Snodgrass et al., 1989; Ono et al., 1997; Brussiere et al., 2005). Reiher et al. (1991) recognized a continuum of periodic discharges from so-called “PLEDs-proper” through “PLEDs-plus” and finally ictal activity. PLEDs-plus were distinguished morphologically by having low-voltage rhythmic discharges associated in time and spatial distribution with the epileptiform discharges (Fig. 6), and these complexes were even more highly associated with seizures than PLEDs-proper. This subcategorization would appear to be useful but remains to be confirmed. In prolonged recordings, we rarely see a recording with PLEDs-proper without also seeing PLEDs-plus or definite electrographic seizures.

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Fig. 3. Typical triphasic waves are shown from a patient with hepatic encephalopathy before (a) and after (b) intravenous injection of diazepam. Mental status did not improve after benzodiazepine injection. Calibration is 1 s (horizontal) and 50 μV (vertical). [From Fountain and Waldman, 2001, with permission.]
A recent meeting of The American Clinical Neurophysiology Society proposed standardized terminology to describe rhythmic and periodic EEG patterns in the critically ill patient (Hirsch et al., 2005). Generic terminology was emphasized that avoids using clinical terminology such as “ictal”, “epileptiform” or “triphasic waves”, because there is no consensus regarding whether many of these patterns are related to seizures, when they are associated with ongoing neuronal injury, or even the neurophysiological mechanisms underlying their generation. Moreover, criteria for NCSs are evolving and may also help generate uniformity in the community. The criteria of Young et al. (1996), more recently modified by Chong and Hirsch (2005), are shown in Table 2. The 3 Hz cutoff used as a criterion for the frequency of repetitive epileptic discharges in NCSs is somewhat arbitrary. It is important to note that when these criteria are not fulfilled, NCSE has not been excluded, it simply cannot be ruled in definitively. In other words, the criteria in the Table are specific but not sensitive. In many real-world situations the ultimate interpretation of ictal vs. non-ictal remains unclear even with expert EEG’ers and proper trials of benzodiazepines.

Our suggested method for performing a benzodiazepine trial is listed in Table 3. At our center this is performed by the neurologist or epileptologist with proper nursing support and monitoring of vitals (i.e. ECG, blood pressure, pulse oximetry). Midazolam is our drug of choice in diagnostic cases because of its rapidly acting pharmacodynamic properties, as well as its short half-life. Sequential 1 mg doses are slowly infused intravenously while monitoring the EEG as well as the patient’s clinical state, EKG, blood pressure, respirations, and oxygen saturation, until a maximum dose of approximately 0.2 mg/kg. After each dose, a new EEG and neurological examination assessment is initiated, and the trial is stopped if there has been definite improvement in either of these two variables, or if there is evidence of respiratory depression or hypotension. This multiple small-step approach is stressed in order to avoid over-sedation and consequently the window to make the diagnosis. NCSE cannot be definitively diagnosed simply based on the resolution of an EEG pattern without clinical improvement in the typical scenario if one large bolus of benzodiazepine is given. The test is only considered diagnostic of NCSE if there has been an improvement in the
clinical state or if there has been a return of normal EEG rhythms (e.g. posterior-dominant “alpha” rhythm).

Although we know of no studies to explore the issue, it seems evident that video and audio recording alongside EEG is a simple measure to help improve the diagnostic specificity during the evaluation of rhythmic electrographic patterns. Particularly chewing, chest percussion, patting in infants, and vibrating bed artifact can challenge even experts as these may mimic seizures. Video and audio have the additional utility in helping to characterize non-ictal paroxysmal spells that are common in ICU patients as well as identifying reactive EEG patterns such as the recently recognized stimulus-induced rhythmic, periodic or ictal discharges (SIRPDs) (Hirsch et al., 2004).

3. Nonconvulsive seizures: evidence for neuronal injury

Much of the evidence for the deleterious effects of NCSs is derived from animal models or from human studies in epileptic patients. The concepts of excitotoxicity and selective CNS vulnerability that have emerged from this literature are likely applicable to the emerging field involving the critically ill population. The still limited range of studies involving the critically ill is explored later.

The detrimental effects of prolonged seizures have long been emphasized in the neurological community, as SE has an associated mortality rate of 26% in adults (De Lorenzo et al., 1996). This statistic may however be somewhat misleading and etiology is probably ultimately more important in the prognosis (Scholtes et al., 1996; Drislane, 2006). Mortality in patients with SE following brain anoxia is much higher than that of patients with SE due to low AED levels (71% vs. 4%). Instead, the more pressing risk is probably lasting intellectual morbidity as evidenced by the acute and chronic radiologic changes, as well as pathological changes particularly in the hippocampus following SE (Yaffe et al., 1995; VanPaesschen et al., 1997; VanLandingham et al., 1998; Cole, 2004).

Classic studies by Meldrum and Brierley (1973) on baboons showed that the intense, prolonged electrochemical excitatory stimulation of SE results in pathological changes, particularly in the hippocampus. Other animal studies have shown that repeated NCSs and induced NCSE result in epilepsy and behavioral effects (Milgram et al., 1988; Liu et al., 1994; Lothman and Bertram, 1993; Matthews et al., 1993). Early life seizures may be particularly harmful to the vulnerable immature nervous system as evidenced by associated deficiencies in a variety of behavioral and cognitive domains with anxiety, exploratory, and memory impairments in demonstrated in rats (Lee et al., 2001; Stafstrom, 2002) and humans (Austin and Dunn, 2002; Neyens et al., 1999; Dodrill and Wilensky, 1990).
Pediatric SE is clearly not monolithic. Absence SE is associated with recurrence (Guberman et al., 1986), but does not appear to cause lasting effects (Ellis and Lee, 1978; Granner and Lee, 1994; Cockerell et al., 1994). Moreover, neurocognitive effects may be less important in adult humans as demonstrated in one prospective study that eliminated cases of progressive illness and acute symptomatic SE, and showed no cognitive deterioration in 15 adults with SE after two years of follow-up (Adachi et al., 2005).

Consensus opinion is that status epilepticus can induce neuronal injury through a variety of mechanisms. Neuronal death occurs by a combination of necrosis and apoptosis mechanisms with excessive glutamate release (excitotoxicity) resulting in the activation of intracellular

Table 2
Criteria for non-convulsive seizure (from Chong and Hirsch, 2005, who modified the criteria of Young et al., 1996; reproduced with permission)

<table>
<thead>
<tr>
<th>Any pattern lasting at least 10 s satisfying any one of the following three primary criteria</th>
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<tr>
<td><strong>Primary criteria</strong></td>
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<tr>
<td>• Repetitive generalized or focal spikes, sharp-waves, spike-and-wave complexes at ≥3/s</td>
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<tr>
<td>• Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at ≤3/s and the secondary criterion</td>
</tr>
<tr>
<td>• Sequential rhythmic, periodic, or quasi-periodic waves at ≥1/s and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/s, e.g. 2–3/s), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not enough to satisfy evolution in morphology</td>
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**Secondary criterion**

• Significant improvement in clinical state or appearance of previously absent normal EEG patterns (such as posterior-dominant “alpha” rhythm) temporally coupled to 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
proteases and nitric oxide, the generation of destructive free radicals and programmed cell death (Fujikawa, 2005). Systemic metabolic derangements associated with convulsive seizures are also neurotoxic (Meldrum and Brierley, 1973), as are the effects of raised intracranial pressure and increased metabolic demand (Scott et al., 2002).

Neuronal susceptibility to injury is probably not uniform and factors affecting vulnerability may include location (hippocampus and dentate gyrus), cell type (granule cells), age (mature group), previous seizure history, as well as other ill-defined genetic factors (DeGiorgio et al., 1992; Briellmann et al., 2002; Schauwecker, 2002; Zhang et al., 2002; Sutula and Pitkänen, 2003). The neuropsychological deficits described above likely result from seizure-induced alterations in neuronal circuits from receptor changes, fiber sprouting, and alterations in both excitatory and inhibitory connections (Lynch et al., 1996, 2000).

There is less robust evidence that the NCSE or NCSs most frequently encountered in the intensive care unit (ICU) are destructive. Instances of permanent dysfunction following prolonged NCSE without any alternate acute brain insult are in the realm of case reports, and in each instance seizures were very prolonged, lasting more than 36 h (Engel et al., 1978; Krumholz et al., 1995). Moreover, models such as that of Meldrum and Brierley (1973) that are commonly cited to show the damaging effects of SE on the brain may not be appropriate in the encephalopathic group because seizures in these animal models typically involve rapid epileptiform discharges that are much different from the slower, less intense discharges usually seen in the ICU (Drislane, 1999). In fact, the EEG pattern associated with NCSs in the critically ill often resembles the generalized spike and wave seen in absence seizures, an epileptic disorder that most accept does not cause permanent injury.

There are, however, several convincing epidemiological and laboratory findings suggesting that NCSs in the encephalopathic group may be harmful. The Virginia group found that continued ictal discharge after clinical SE was associated with a highly significant increase in morbidity and mortality (Jaitly et al., 1997; Class III evidence). Young et al. (1996), in their series of 49 patients with NCSs, found that death occurred in 13 of 23 (57%) patients in NCSE. Age, ICU length of stay and etiology were also significantly associated with mortality, but after multiple logistic regression analysis, only seizure duration and delay to diagnosis remained significant (Class III evidence). Lastly, in the rodent model of NCSs produced by acute middle cerebral artery occlusion, NCS events were found to be positively correlated with both infarct size and mortality. When NCSs were prevented with AEDs in this animal model, there was a resultant significant reduction in mortality (Williams et al., 2004).

There is also evidence that the acute symptomatic brain may be particularly prone to the damaging effects of seizures. The injured brain undergoes dynamic changes in neurochemistry that likely cause it to be vulnerable to increases in metabolic demand associated with seizure discharges (Bergsneider et al., 1997; Bullock et al., 1995). Vepsa et al. (1998) performed microdialysis in traumatic brain injury patients and found elevations of glutamate to toxic levels in association with seizures including NCSE. Moreover cerebral perfusion pressures positively correlated with increases in glutamate during seizure periods and, in the setting of altered cerebrovascular autoregulation and damaged blood–brain barrier, may lead to hyperemia and further cell injury. Vepsa et al. (2003) later showed that seizures detected by continuous monitoring after intracerebral hemorrhage were associated with significantly increased midline shift and a trend towards worse outcome. A limitation of this last study in the argument for treating nonconvulsive events, however, was that only 18 patients had seizures and a few of these were clinical (convulsive) events, yet both convulsive and nonconvulsive seizures were analyzed together. Moreover, multivariate analysis showed that neurological status and age were much greater predictors of outcome than the presence or absence of seizures. Certainly increased cerebral blood flow and intracranial pressure have been associated with seizures, and symptomatic posturing or herniation has been associated with seizures in patients with CNS infections (Solomon et al., 2002; Idro et al., 2005). However, we are unaware of any well-documented instance of herniation...
convincingly associated with NCSs alone. Although a causal relationship between seizures (including NCSs), cerebral edema and progressive midline shift is certainly possible and perhaps likely, this has not yet been proven.

One final line of evidence suggesting that NCSs may be deleterious involves a biomarker. Neuron specific enolase (NSE) is a key enzyme for energy metabolism and is a marker of acute brain injury as well as damage to the blood–brain barrier (Correale et al., 1998). DeGiorgio et al. (1999) prospectively measured levels of NSE in consecutive patients with SE and found significant elevations in CPSE and subclinical generalized SE patients, even when there were no other causes for acute brain injury beyond seizures. Moreover, this study found that absolute levels of NSE correlated with the duration of SE, suggesting that early treatment of NCSs is desirable.

4. Treatment of nonconvulsive seizures and status epilepticus

While it would appear that NCSs are damaging to the brain, it is far less obvious that single NCSs or NCSE needs to be treated as aggressively as convulsive varieties for reasons outlined above. Claassen et al. (2002) performed a systematic review comparing various continuous IV infusion AEDs and pentobarbital in patients treated for refractory convulsive and nonconvulsive status epilepticus, and found a poor outcome overall (50% mortality) regardless of the agent utilized or the titration goal (i.e. seizure suppression or background suppression). Pentobarbital treatment appeared to be more effective in preventing breakthrough seizures than other medications, even in cases of NCSE which are known to be more refractory to treatment than GCSE (Mayer et al., 2002), however it is frequently complicated by hypotension, and ultimate outcome was the same. While propofol has a shorter half-life than pentobarbital and would seem to be safer than long acting barbiturates, it has become clear that propofol infusion syndrome is an important complication. This serious complication is characterized by refractory metabolic acidosis, cardiac failure, rhabdomyolysis and renal failure, and occurs most often with prolonged infusion at >5 mg/kg/h for >48 h, and possibly traumatic or other acute brain injury (Vasile et al., 1998). The use of IV benzodiazepines was associated with increased mortality despite no difference in severity of illness. Aggressive ICU care in these patients prolonged hospitalization but did not lead to improved outcomes.

While the malignancy of NCSs remains debated, it is clear that severe outcomes in critically ill patients with NCSs are more affected by other factors. Underlying etiology and the length of ICU stay with its attendant mostly infectious complications are probably most important (Yaffe and Lowenstein, 1993). At our center, concerted effort is made to diagnose and treat NCSs as quickly as possible but with minimal sedation so as to avoid prolonging coma and intubation. Non-coma inducing agents such as IV fosphenytoin, valproate, and perhaps intermittent benzodiazepines are used in addition to the oral AEDs (via nasogastric tube) such as levetiracetam (Rosetti and Bromfield, 2005) (now available intravenously as well) and topiramate (Towne et al., 2003).

5. Future directions

Clearly our understanding of how best to manage patients with subclinical rhythmic or periodic EEG patterns is in its infancy. An important initial step to this end has begun with the proposal of standardized terminology for these patterns last year (Hirsch et al., 2005). Undoubtedly further refinement of this nomenclature will occur in the future, and perhaps even some agreement on the definition of a NCS. Deciding which EEG patterns are harmful, and how aggressively cessation of this activity should be pursued, will only be established through large multicenter clinical trials. In the nearer future, some direction may result from studying serial biomarkers (such as NSE) in these patients, imaging modalities (e.g. diffusion-weighted MRI, MR spectroscopy, positron emission tomography) or simultaneous cerebral microdialysis to gain insight into alterations in metabolic stress and to determine frank neuronal injury associated with EEG changes.

Appendix A

Classification of evidence (American Academy of Neurology scheme, see Armon and Evans, 2005):

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population. The following are required:

(a) Primary outcome(s) is(are) clearly defined.
(b) Exclusion/inclusion criteria are clearly defined.
(c) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
(d) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets A through D above OR a randomized, controlled trial in a representative population that lacks one criterion A through D.

Class III: All other controlled trials including well-defined natural history controls or patients serving as own controls in a representative population in which outcome assessment is independently assessed or independently derived by objective outcome measurement (objective outcome measurement is an outcome measure that is unlikely to be affected by an observer’s (patient, treating physician, investigator) expectation or bias [e.g. blood tests, administrative outcome data]).

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

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