Nonconvulsive status epilepticus: a diagnostic and therapeutic challenge in the intensive care setting

Martin Holtkamp and Hartmut Meierkord

Ther Adv Neurol Disord

(2011) 4(3) 169–181

DOI: 10.1177/

1756285611403826

© The Author(s), 2011.

Reprints and permissions:

<http://www.sagepub.co.uk/journalsPermissions.nav>

Abstract: Nonconvulsive status epilepticus (NCSE) comprises a group of syndromes that display a great diversity regarding response to anticonvulsants ranging from virtually self-limiting variants to entirely refractory forms. Therefore, treatment on intensive care units (ICUs) is required only for a selection of cases. The aetiology and clinical form of NCSE are strong predictors for the overall prognosis. Absence status epilepticus is commonly seen in patients with idiopathic generalized epilepsy and is rapidly terminated by low-dose of benzodiazepines. The management of complex partial status epilepticus is straightforward in patients with pre-existing epilepsy, but poses major problems if occurring in the context of acute brain lesions. Subtle status epilepticus represents the late stage of undertreated previous overt generalized convulsive status epilepticus and always requires aggressive ICU treatment. Within the intensive care setting, the diagnostic challenge may be seen in the difficulty in delineating nonepileptic conditions such as posthypoxic, metabolic or septic encephalopathies from NCSE. Although all important forms are considered, the focus of this review lies on clinical presentations and electroencephalogram features of comatose patients treated on ICUs and possible diagnostic pitfalls.

Keywords: anticonvulsant treatment, diagnostic pitfalls, electroencephalogram patterns, encephalopathies, nonconvulsive status epilepticus

Introduction

Status epilepticus (SE) represents an important challenge to modern neurology and epileptology. This is based on the difficulty in clearly delineating the condition and its various clinical forms and on our insufficient insight into the relevant underlying pathophysiological processes. Consequently, current treatment options are still unsatisfactory, and mortality and morbidity rates remain high. However, in a number of areas, progress has been made including agreed upon guidelines [Meierkord *et al.* 2010; Minicucci *et al.* 2006] and consensus recommendations [Shorvon *et al.* 2008; van Rijeckvorse *et al.* 2006] on the management of the condition.

A special problem is posed by the variant of non-convulsive status epilepticus (NCSE). Outside the intensive care unit (ICU) and hospital setting, the clinical features of this disorder may be very discrete and are sometimes hard to differentiate from normal behaviour. The diagnosis

is also a notorious problem within the ICU situation. This is because patients with NCSE in the vast majority of cases will be in a coma or be affected by severely impaired consciousness. Clearly, the clinical features of SE in comatose patients are always contaminated and usually blurred by the underlying cause and by the patient's drug regimens, such as anaesthetics, muscle relaxants and anticonvulsant drugs. Furthermore, in a number of patients, electroencephalogram (EEG) demonstrates patterns with periodic or rhythmic discharges that generally are not pathognomonic for NCSE, but relevantly contribute to the diagnostic confusion. It is therefore important for the neurologist consulting a patient on the ICU to consider a wide range of differential diagnoses including posthypoxic states, septic and various metabolic encephalopathies.

In this review we focus on NCSE in the intensive care setting, but we also briefly refer to the other

Correspondence to:
Martin Holtkamp, MD
Department of Neurology,
Charité –
Universitätsmedizin
Berlin, Charitéplatz 1,
10117 Berlin, Germany
martin.holtkamp@charite.de

Hartmut Meierkord, MD
Institute of
Neurophysiology, Charité –
Universitätsmedizin Berlin,
Germany

clinical variants of NCSE not necessarily treated on the ICU. Details on the clinical forms and treatment of NCSE have been covered by us in a previous review [Meierkord and Holtkamp, 2007].

Definition and diagnostic criteria

NCSE is defined as a change in behaviour and/or mental processes from baseline associated with continuous epileptiform discharges in the EEG. It is important to note that as yet no universally accepted definition of NCSE exists. Past suggestions have included different components such as clinical changes often incorporating impaired consciousness, ictal EEG abnormalities and response to treatment [Cockerell *et al.* 1994; Tomson *et al.* 1992; Treiman and Delgado-Escueta, 1983; Mayeux and Lueders, 1978]. Most authors agree that alterations in the clinical state and associated plausible EEG changes should represent the mainstay of the definition [Niedermeyer and Ribeiro, 2000]. Clinical changes alone are not sufficient because these may be very subtle and sometimes hard to differentiate from normal behaviour or nonepileptic medical conditions [Celesia, 1976]. On the other hand, the definition must not exclusively rely on EEG changes since no single pattern can be regarded as pathognomonic. A positive electroclinical response to acute anticonvulsant treatment may be helpful in the diagnostic process, but a lacking response certainly does not exclude the diagnosis. There is ongoing debate regarding the duration of an episode for the diagnosis of NCSE to be made. In agreement with other authors [Knake *et al.* 2001; Hesdorffer *et al.* 1998], we suggest 30 minutes of ongoing epileptic activity for the definition of NCSE.

Clinical forms and treatment

Absence SE

Typical absence SE occurs in patients with idiopathic generalized epilepsies, in particular in childhood and juvenile absence epilepsy [Tomson *et al.* 1992] and in juvenile myoclonic epilepsy [Baykan *et al.* 2002; Kimura and Kobayashi, 1996]. The core clinical feature is an altered state of consciousness but changes in behaviour may also be observed. The corresponding ictal EEG shows generalized spike-wave discharges at a frequency of around 3 Hz [Baykan *et al.* 2002; Kimura and Kobayashi, 1996]. Commonly, the condition is treated successfully by intravenous (iv) administration of

10 mg diazepam or 4 mg lorazepam [Osorio *et al.* 2000; Thomas *et al.* 1992; Tomson *et al.* 1992]. Owing to the favourable response to first-line anticonvulsants, management of typical absence SE rarely requires ICU facilities. The features and management of atypical and late onset *de novo* absence SE are described elsewhere [Meierkord and Holtkamp, 2007].

Simple partial SE

The vast majority of patients with simple partial SE (SPSE) presents with somatomotor features [Scholtes *et al.* 1996b] and are not covered in this review. By definition, the clinical changes in non-convulsive SPSE do not include an altered contact with the environment, and 'consciousness is preserved' as opposed to complex partial SE (CPSE). Treatment is similar to that of CPSE and is discussed in the following. Owing to the mild clinical disturbances in nonmotor SPSE, this condition is rarely treated on an ICU.

CPSE

For many years, CPSE was thought to be a rare condition as reflected by an epidemiological study from the US reporting a fraction of only 3% regarding all clinical forms of SE [DeLorenzo *et al.* 1996]. However, subsequent European studies have shown that CPSE amounts to 16–43% of all SE cases [Vignatelli *et al.* 2003; Knake *et al.* 2001; Coeytaux *et al.* 2000].

CPSE may be regarded as the result of a more widespread and often bilateral seizure discharge in some cases also explaining the higher complexity of clinical features compared with SPSE. A wide variety of clinical features may make it difficult to distinguish CPSE from absence SE [Kaplan, 1996; Celesia, 1976]. CPSE has been identified to be a recurrent problem often occurring at regular intervals, as seen in 17 out of 20 patients with a diagnosis of epilepsy in one study [Cockerell *et al.* 1994].

It is widely accepted that CPSE may present a very broad range of clinical features. By definition, impairment of consciousness must be present, often manifesting itself as altered contact with the environment. In most cases, evolution is gradual, occasionally starting with prolonged or serial auras of any kind. A number of reports indicate that many cases originate from the temporal lobes [Cockerell *et al.* 1994; Wieser *et al.* 1985; Wieser, 1980]. However, CPSE can

certainly not be equated with temporal lobe SE. A depth-electrode study has indicated that CPSE may well originate from extratemporal regions with special preference to frontal structures [Williamson *et al.* 1985]. As yet, there are no reliable figures on the relative frequencies of regions of onset.

Given the wide variety of clinical presentations that are possible, confirmation and documentation with EEG is required for the diagnosis to be made [Celesia, 1976]. EEG alterations are variable with regional, hemispherical or bilateral spikes, spike waves or rhythmic discharges (Figure 1A).

The response to initial anticonvulsant drugs in SP and CPSE generally is far better if SE occurs in patients with pre-existing epilepsy compared with patients with *de novo* SE resulting from acute or progressive central nervous system disorders.

In patients with a history of frontal or temporal lobe epilepsy, partial forms of SE may terminate spontaneously or rapidly respond to iv administration of 10 mg diazepam or 4 mg lorazepam. These doses are repeated in case of persistence or recurrence of epileptic activity. If necessary, additional phenytoin (15–18 mg/kg) or equivalent fosphenytoin is recommended [Meierkord *et al.* 2010; Tomson *et al.* 1986]. Alternatively, levetiracetam at 30–40 mg/kg or valproic acid at 25–45 mg/kg may be administered rapidly [Shorvon *et al.* 2008]. The latter is contraindicated in severe hepatic disorders such as hepatitis or cirrhosis, in urea cycle disorders such as ornithine transcarbamylase deficiency, and in mitochondrialopathies such as MELAS or POLG1 mutations [Engelsen *et al.* 2008], all of which may cause or contribute to CPSE. In the case of pre-existing epilepsy, recurrence of CPSE is not unusual [Cockerell *et al.* 1994]; however, refractoriness towards benzodiazepines and second-line agents is rare. In contrast, *de novo* CPSE in many cases is refractory towards first-line treatment and frequently requires further management on the ICU. Autoimmune-mediated encephalitis associated with antibodies against voltage-gated potassium channels [Vincent *et al.* 2004], glutamic acid decarboxylase [Malter *et al.* 2010] or NMDA receptors [Dalmau *et al.* 2008] may cause difficult-to-treat forms of CPSE. In particular, anti-NMDA receptor encephalitis has been described to be

associated with CPSE refractory to nonanaesthetic and anaesthetic anticonvulsants for months [Johnson *et al.* 2010]. Anti-NMDA receptor encephalitis and, if associated, CPSE may respond to steroids, plasmapheresis, iv immunoglobulins and in some cases to cyclophosphamide or the monoclonal antibody rituximab [Dalmau *et al.* 2008].

After failure of first- and second-line agents, iv phenobarbital at 20 mg/kg or phenytoin, valproic acid or levetiracetam if not administered before may be given [Holtkamp, 2007]. Furthermore, iv lacosamide [Kellinghaus *et al.* 2010] or enteral topiramate [Bensalem and Fakhoury, 2003] and pregabalin [Novy and Rossetti, 2010] may be successful in this condition.

Owing to the favourable clinical outcome of CPSE itself and the lack of neurological or neuropsychological sequelae [Scholtes *et al.* 1996a; Cockerell *et al.* 1994; Williamson *et al.* 1985], further treatment escalation including iv anaesthetics should be performed reluctantly [Driscoll, 2000; Kaplan, 2000]. Aggressive pharmacological treatment seems to have a greater risk concerning morbidity and mortality [Ropper, 2003] than continuing nonconvulsive seizure activity [Kaplan, 1999]. Subsequently, a European survey indicated that neurologists are more hesitant to administer anaesthetics in CPSE as compared with generalized convulsive status epilepticus (GCSE) [Holtkamp *et al.* 2003].

If CPSE cannot be terminated with the armamentarium of nonanaesthetizing agents, generalized anaesthesia may be considered in patients of younger age that do not have additional medical problems. A recently developed prognostic score (Status Epilepticus Severity Score [STESS]), relying on four outcome predictors, suggests that early aggressive treatment could not be routinely warranted in patients with a favourable STESS (determined by younger age, positive history of seizures, simple and complex partial seizures *versus* nonconvulsive SE in coma and no or slight *versus* severe consciousness impairment), who will almost certainly survive their SE episode [Rossetti *et al.* 2008]. These findings indicate that the decision to introduce generalized anaesthesia needs to be tailored to the individual patient. We discuss common anaesthetic treatment regimens with subtle SE in the following.

Figure 1. (A) Electroencephalogram (EEG) recorded during a prolonged episode of complex partial status epilepticus (SE). The clinical features that gave rise to the assumption of SE had started several hours earlier. The 63-year-old female patient suffered from left mesial temporal lobe epilepsy with hippocampal sclerosis as demonstrated by MRI. Note that the changes are bilateral and widespread with high-amplitude rhythmic discharges and alpha–beta activities of lower amplitude. Electroencephalogram (EEG) normalized after pharmacological treatment with 10 mg iv diazepam in parallel to the clinical features. (B) EEG recorded during subtle SE. The 39-year-old female patient suffered from viral encephalitis and developed secondary generalized convulsive SE that in this context may also be termed ‘overt’ SE. The patient was partially treated with benzodiazepines and phenytoin but this did not terminate SE. She was referred from another hospital to our neurological intensive care unit. The comatose patient presented with mild bilateral facial twitching, and the EEG revealed generalized periodic discharges interrupted by short generalized flat periods. The diagnosis of subtle SE was suggestive taking into account the history, clinical findings and the EEG features. The concept of so-called ictal to interictal continuum has been proposed by some authors, but it is unclear whether such patterns represent epiphenomena or may indicate the danger of additional brain injury [Claassen, 2009]. The current patient was put under generalized anaesthesia with thiopental until an EEG burst suppression pattern was achieved. In the following weeks, several attempts to taper the anaesthetic resulted in recurrence of seizure activity. After various infectious complications, the patient died from electromechanical dissociation. EEG changes as seen in (A) and (B) are by no means specific to nonconvulsive SE and may also be encountered in nonepileptic conditions treated on the intensive care unit (see Figures 2 and 3).

Subtle SE

The concept of 'subtle' SE is very useful and has the potential to guide the clinician in cases where the correct diagnosis is immediately relevant for treatment decisions. The idea of subtle SE loses much of its diagnostic power if not used in the strict sense as representing the end point of 'overt' SE, the latter denotes GCSE [Treiman *et al.* 1998, 1990]. Subtle SE is a form of NCSE that evolves from GCSE if the latter has been treated insufficiently or has not been treated at all. The clinical hallmarks of subtle SE include a comatose state and the absence of prominent motor features. However, discrete ('subtle') muscle twitching may be present and the EEG mostly shows generalized periodic discharges (Figure 1B), but lateralized and regional discharges may also occur. In the initial report, the concept of subtle SE was used in a wider sense, and also those patients were included in whom the condition was believed to be caused by severe encephalopathy and subtle SE may be an unrecognized cause of coma [Treiman *et al.* 1984]. In order to retain the cutting edge of the concept, we suggest that the diagnosis of subtle SE should only be made in the presence of EEG changes and if there is evidence of previous overt epileptic seizures or SE. For the same reason, we do not include postanoxic myoclonus (also misleadingly termed myoclonic status *epilepticus*) as done by Treiman [Treiman, 1993] since there is no agreement regarding its epileptic nature [Meierkord and Holtkamp, 2008; Rossetti *et al.* 2007; Wijdicks *et al.* 2006; DeLorenzo *et al.* 1996]. Subtle SE evolves from overt GCSE and should be treated as aggressively as the overt variant. In a randomized controlled trial with 134 patients, the iv administration of lorazepam (0.1 mg/kg), diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), phenobarbital (18 mg/kg) or phenytoin (18 mg/kg) terminated SE in only 8–24% of cases; success rates were not significantly different in the study groups [Treiman *et al.* 1998]. The response rate in early overt GCSE was 44–65%, and the dramatic loss in efficacy of the predominantly GABAergic substances may be explained by modification of the GABA_A receptor due to continuing seizure activity [Kapur and Macdonald, 1997]. Refractory subtle SE should be treated like overt GCSE not responding to first-line drugs, and in this situation European treatment guidelines recommend anaesthetics such as midazolam (0.2 mg/kg bolus, 0.05–0.4 mg/kg/h infusion), propofol (bolus of 2–3 mg/kg, followed by further boluses

at 1–2 mg/kg until seizure control, then continuous infusion at 4–10 mg/kg/h), thiopental (starting with a bolus of 3–5 mg/kg, then further boluses of 1–2 mg/kg every 2–3 min until seizures are controlled, thereafter continuous infusion at a rate of 3–7 mg/kg/h), or pentobarbital, the first metabolite of thiopental that is marketed in the US (bolus dose of 5–15 mg/kg over 1 h followed by an infusion of 0.5–1 mg/kg/h, increasing if necessary to 1–3 mg/kg/h) [Meierkord *et al.* 2010]. There are no reliable clinical data on how long iv anaesthetics should be administered, but a minimum duration of 24 h is generally recommended [Meierkord *et al.* 2010]. To assess the recurrence of epileptic activity after tapering, continuous EEG monitoring should be performed up to 5 days after withdrawal of continuous iv anaesthetics [Holtkamp *et al.* 2005a]. The drawbacks of anaesthetic substances include severe side effects and limited efficacy. A propofol infusion syndrome is characterized by cardiac failure, severe metabolic acidosis, rhabdomyolysis and renal failure, and may occur with a treatment duration longer than 48 h [Vasile *et al.* 2003]. Prolonged use of large doses of propofol to treat Refractory Status Epilepticus (RSE) is associated with significant mortality and morbidity [Iyer *et al.* 2009]. Continuous administration of iv barbiturates commonly causes pressor-requiring arterial hypotension, severe gastroparesis and immunosuppression facilitating infections and sepsis [Ropper, 2003]. Progressive erosion of inhibition due to depletion of postsynaptic GABA receptors with ongoing epileptic activity [Naylor *et al.* 2005] may result in loss of efficacy of anaesthetics such as propofol, barbiturates and midazolam. Recurrence of seizure activity after tapering of anaesthetics has been described in more than 50% of cases [Claassen *et al.* 2001], and for this difficult-to-treat and prognostically poor variant we suggest the term 'malignant' status epilepticus [Holtkamp *et al.* 2005a]. However, recent data indicate that duration of CPSE and subtle SE is not an independent predictor for outcome, and patients with prolonged SE still have the chance to survive [Drislane *et al.* 2009].

NCSE in the ICU

Those clinical forms of NCSE that usually respond well to first-line anticonvulsants include absence SE and, if occurring in the context of chronic epilepsy, simple and complex partial SE. These conditions generally do not require intensive care treatment, in contrast to *de novo* CPSE owing to acute brain insults. The rationale

behind such a procedure derives from data that have identified acute brain lesions as predictors of refractoriness [Holtkamp *et al.* 2005b]. The treatment of subtle SE evolving from previous overt GCSE [Treiman *et al.* 1984] always needs to be done under intensive care conditions.

In cases with refractory CPSE, consciousness is usually severely impaired, and in subtle SE, patients are comatose per definition. The EEG in either group may show continuous, periodic or rhythmic, generalized or regional discharges. Unfortunately, such pattern are neither specific for epileptic seizures nor for SE.

EEG patterns

The brain under the clinical condition of coma produces a variety of periodic and rhythmic EEG changes that have been discussed in a proposal by a subcommittee of the American Clinical Neurophysiology Society to be standardized [Hirsch *et al.* 2005]. These EEG changes most importantly include, in traditional terminology, periodic lateralized epileptiform discharges (PLEDs), bilateral independent periodic lateralized epileptiform discharges (BiPLEDs), generalized periodic epileptiform discharges (GPEDs) and stimulus-induced rhythmic periodic ictal-like discharges (SIRPIDs). Owing to unjustified clinical connotations that such terms are associated with, the subcommittee aims at replacing them, i.e. 'periodic lateralized epileptiform discharges' are proposed to be replaced by 'lateralized periodic discharges'. The goal is also to simply describe EEG patterns regarding localization, morphology and frequency. The new terminology was tested amongst seven board-certified clinical neurophysiologists. Unfortunately, inter-observer and intraobserver agreement is marginal for many of the new terms, and a simplification of the proposed terminology has been suggested [Gerber *et al.* 2008].

Owing to recent technical advances, it is now possible to carry out continuing digital monitoring of surface and intracranial EEG in the critically ill patient [Friedman *et al.* 2009; Young *et al.* 2009]. A considerable number of patients with acute brain injury has been demonstrated to exhibit pure electroencephalographic discrete or continuous seizure activity [Waziri *et al.* 2009]. Although such EEG activity in traumatic brain injury may be associated with the development of hippocampal atrophy, a causal relationship has not been proven [Vespa *et al.* 2010].

Currently, the clinical and prognostic relevance of such EEG seizure activity is unclear. Therefore, antiepileptic treatment potentially harming the patient is not recommended.

When differentiating encephalopathies from NCSE, there is agreement that the overall picture of the EEG discharge should be taken into account, including its evolution in time and space. A clear incremental evolution of regional or generalized rhythmic discharges and decremental features with flat periods associated with clinical seizure activity strongly indicate NCSE [Treiman and Walker, 2006; Hirsch *et al.* 2005]. As other periodic and rhythmic EEG changes that are encountered in patients in coma are usually not pathognomonic, the diagnosis of NCSE generally should not be based on EEG changes alone.

Unfortunately, overdiagnosing NCSE is difficult to avoid if the diagnosis is based mainly on EEG changes. Towne and colleagues reported NCSE as the underlying cause of coma in 8% of more than 200 such patients [Towne *et al.* 2000]. In this study, the diagnosis was based on periodic or rhythmic EEG features only. Following iv benzodiazepines, improvement of the EEG was seen, but no amelioration of the patients' condition was reported. As any EEG activity is highly sensitive to benzodiazepines (Figure 2), we suggest to diagnose NCSE only if there is evidence from the recent course of the condition that seizures or SE have occurred in addition to indicative EEG features.

EEG recording in the intensive care setting is subject to disturbances from numerous sources resulting in physiologic and extraphysiologic artefacts [Young and Campbell, 1999]. Considering the latter only, the most common electrode artefact is the electrode popping. Morphologically, this appears as single or multiple sharp waveforms due to abrupt impedance change. It is identified easily by its characteristic appearance (e.g. abrupt vertical transient that does not modify the background activity) and its usual distribution, which is limited to a single electrode. If there is failure of adequate grounding on the patient, alternating current (60 Hz) artefacts from power lines may occur. The problem may arise when the impedance of one of the active electrodes becomes significantly large between the electrodes and the ground of the amplifier. The movement of other persons

(A)

(B)

Figure 2. Electroencephalogram (EEG) recorded from a 56-year-old comatose male patient 3 days after global cerebral hypoxia following ventricular fibrillation. (A) The EEG is dominated by generalized periodic discharges (GPDs) at a frequency of 2 Hz showing maximum amplitudes in bifrontal regions. Between the bursts the EEG activity is extremely flat. (B) Five minutes after administration of 2 mg iv lorazepam GPDs have disappeared and there is widespread low-amplitude activity at the end of the trace. The changes after administration of benzodiazepines were not associated with any clinical improvement. This patient did not suffer from status epilepticus but GPDs simply reflect severe posthypoxic encephalopathy.

around the patient (which usually cannot be completely avoided in the ICU) can generate artefacts, usually of capacitive or electrostatic origin. Such artefacts require proper notation on the records. Another artefact, probably due to electrostatic changes on the drops, can be introduced by a gravity-fed iv infusion. Morphologically, this appears as spike transient potentials at fixed intervals that coincide with drops of the infusion.

With the increasing use of automatic electric infusion pumps, a new type of artefact, infusion motor artefact (IMA), has arisen. Morphologically, IMA appears as very brief spiky transients, sometimes followed by a slow component of the same polarity. Its frequency does not relate directly to the drop rate. Lininger and colleagues have suggested that this artefact arises from electromagnetic sources [Lininger *et al.* 1981]. The artefact produced by respirators varies widely in morphology and frequency. Monitoring the ventilator rate in a separate channel helps to identify this type of artefact. In general, therefore, simultaneous video recording may help correctly interpret EEG features [Friedman *et al.* 2009].

Nonepileptic conditions mimicking features of NCSE

A number of conditions may resemble NCSE clinically, but are not associated with periodic or rhythmic EEG abnormalities. These include prolonged migraine auras, transient global amnesia, transient ischaemic attacks and psychiatric disturbances such as stupor or dissociative disorders. It should be kept in mind that status pseudoepilepticus may take various clinical forms. Bizarre and wild motor features are most common and therefore will per definition not be confused with NCSE. In some patients status pseudoepilepticus may take the form of feigned loss or impairment of consciousness without any motor features. Such cases should not be overlooked. None of the mentioned conditions is accompanied by periodic or rhythmic EEG abnormalities, thus excluding the diagnosis of NSCE. If EEG recording is not feasible, 2 mg iv lorazepam may be administered for diagnostic purposes. A clear clinical response to benzodiazepines indicates a diagnosis of NCSE, as none of the abovementioned other conditions improves with lorazepam. This is also true for the rare cases of NCSE with negative surface EEG.

In the following, we focus on conditions treated on the ICU that may be mistaken for NCSE from a clinical and electroencephalographical point of view.

Posthypoxic encephalopathy. Global cerebral hypoxia following cardiac arrest, ventricular fibrillation or severe respiratory failure commonly produces EEG alterations characterized by generalized periodic, often sharp or spiky, single or grouped discharges that occur against a flat or slow-activity background (Figure 2A) [Niedermeyer *et al.* 1999]. The overall EEG pattern may resemble changes as seen in SE, but rather reflects severe encephalopathy [Niedermeyer and Ribeiro, 2000]. Even more, these EEG features may be accompanied by myoclonus occurring within the first days after cerebral hypoxia, often resulting in the misdiagnosis of SE. Myoclonus in these patients usually is sensitive to stimuli, such as tracheal suction or to touch [Van Cott *et al.* 1996; Niedermeyer *et al.* 1977]. Early posthypoxic myoclonus needs to be separated from late myoclonus that is triggered by voluntary movements and may occur weeks after cerebral hypoxia. This syndrome has been well characterized, clinically and electrophysiologically, in the early 1960s by Lance and Adams, after whom it later has been named [Lance and Adams, 1963]. In contrast to early and late posthypoxic myoclonus, stimulus sensitivity is only seen in rare forms of reflex epilepsy [Ferlazzo *et al.* 2005]. Mild myoclonus may occur spontaneously in subtle SE but does not increase with external stimuli. Available data do not indicate that pharmacological treatment of either the EEG alterations or early posthypoxic myoclonus has any positive impact on the patient's prognosis [Wijdicks, 2002; Towne *et al.* 2000; Lowenstein and Aminoff, 1992]. Administration of anticonvulsants in such cases appears to be just EEG cosmetics [Meierkord and Holtkamp, 2008], and it is important to note that the comatose patient himself does not have any benefit from such treatment. However, less myoclonus may be a relief for nurses and family members and may be justified in special situations. Common treatment regimens include iv administration of piracetam 12 to 36 g/day, levetiracetam up to 3 g/day, valproic acid 2–3 g/day and the benzodiazepine clonazepam 1–4 mg/day. The latter has a stronger antimyoclonus effect than some other benzodiazepines, as, in addition to its GABAergic properties, clonazepam interacts with the glycine receptor [Young *et al.* 1974],

Figure 3. (A) Electroencephalogram (EEG) recorded from a 61-year-old female patient with hepatic encephalopathy occurring 1 week after liver transplantation. There are high-amplitude continuous 2 Hz generalized periodic discharges, occasionally displaying triphasic morphology. Clinically, the patient was stuporous and had asterixis. Ammonium level at the time of EEG recording was $139 \mu\text{mol/l}$ (normal range: $<48 \mu\text{mol/l}$). After normalization of the ammonium level, clinical presentation and EEG returned to normal. This patient did not suffer from status epilepticus but GPDs with triphasic morphology reflect severe metabolic encephalopathy. (B) EEG recording of a 71-year-old male patient with mixed septic and uraemic encephalopathy after endocarditis and secondary renal failure. Note the GPDs at a frequency of approximately 1 Hz, some of which are characterized by triphasic morphology. The patient died 5 days later from multiorgan failure. This patient did not suffer from status epilepticus but GPDs with biphasic and triphasic morphology indicate severe metabolic and septic encephalopathy.

that decisively is involved in the generation of posthypoxic myoclonus [Rajendra *et al.* 1997].

Metabolic, septic and toxic encephalopathies

Metabolic encephalopathies belong to the important conditions looked at in the early days of the EEG. Hans Berger observed EEG slowing induced by hypoglycaemia in schizophrenic patients treated with insulin in the 1930s [Berger, 1937]. The electroencephalographic changes seen in some patients with hepatic encephalopathy (HE) have been reported by Foley and colleagues in the 1950s describing high-voltage slow waves of patients with hepatic coma [Foley *et al.* 1950] that later were termed triphasic waves [Bickford and Butt, 1955] (Figure 3A). Further studies have demonstrated a loose relationship between EEG and behavioural alterations of HE [Parsons-Smith *et al.* 1957]. Triphasic waves, however, have been demonstrated to be rather nonspecific [Karnaze and Bickford, 1984], and are seen in other metabolic encephalopathies associated with severe nephropathy, intoxications, electrolyte dysbalances such hypercalcaemia or infectious conditions [Fisch and Klass, 1988; Allen *et al.* 1970] (Figure 3B). Characteristically, clinical and EEG disturbances in metabolic encephalopathies normalize rapidly following correction of the causal dysfunction, e.g. after lowering ammonium levels in patients with hepatic encephalopathy or administration of iv glucose in patients with hypoglycaemic encephalopathy [Niedermeyer, 2005]. Clinically and electroencephalographically, these conditions may mimic NCSE, and treatment with first-line anticonvulsants such as benzodiazepines may improve the EEG, but not the patients' condition.

Neurodegenerative disorders

Dementias and other degenerative disorders of the central nervous system, even in the absence of epilepsy, may be associated with nonspecific periodic and rhythmic EEG discharges [Naidu and Niedermeyer, 2005; Van Cott and Brenner, 2005]. The most prominent example of rhythmic EEG activity is the triphasic waves in Creutzfeldt–Jakob disease [Wieser *et al.* 2006], confirmation of these EEG alterations are part of the diagnostic work-up *intra vitam*. Although mental changes and periodic or rhythmic EEG abnormalities in neurodegenerative disorders evaluated cross-sectionally may resemble NCSE, the temporal evolution of the disorder

over months or years should help in distinguishing between the two conditions.

Summary: diagnostic criteria for NCSE in the intensive care setting

The hallmarks of NCSE in the ICU setting are: (1) the patient is comatose or suffers at least from severe impairment of consciousness; (2) there are no or only minimal motor features taking the form of facial or limb twitching; (3) the EEG displays generalized, lateralized or regional periodic or rhythmic patterns.

These features, however, are not pathognomonic, and the correct diagnosis of NCSE in the intensive care setting is a challenge even to the experienced neurologist. In general, it seems more likely to mistake diseases for NCSE than to overlook the condition. Since aggressive anticonvulsant treatment may add to morbidity and mortality of already critically ill patients, some diagnostic criteria may be useful.

A distinct electroclinical evolution of prolonged seizure activity is the mainstay to diagnose NCSE correctly. If EEG is not available, a clinical improvement in close temporal relationship to acute anticonvulsant treatment is suggestive for NCSE but a missing response does not exclude the diagnosis.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

None declared.

References

- Allen, E.M., Singer, F.R. and Melamed, D. (1970) Electroencephalographic abnormalities in hypercalcaemia. *Neurology* 20: 15–22.
- Baykan, B., Gokyigit, A., Gurses, C. and Eraksoy, M. (2002) Recurrent absence status epilepticus: clinical and EEG characteristics. *Seizure* 11: 310–319.
- Bensalem, M.K. and Fakhoury, T.A. (2003) Topiramate and status epilepticus: report of three cases. *Epilepsy Behav* 4: 757–760.
- Berger, H. (1937) Das Elektroenkephalogramm des Menschen. 12. Mitteilung, 106th edn, pp. 165–187.
- Bickford, R.G. and Butt, H.R. (1955) Hepatic coma: the electroencephalographic pattern. *J Clin Invest* 34: 790–799.

- Celesia, G.G. (1976) Modern concepts of status epilepticus. *JAMA* 235: 1571–1574.
- Claassen, J., Hirsch, L.J., Emerson, R.G., Bates, J.E., Thompson, T.B. and Mayer, S.A. (2001) Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology* 57: 1036–1042.
- Cockerell, O.C., Walker, M.C., Sander, J.W. and Shorvon, S.D. (1994) Complex partial status epilepticus: a recurrent problem. *J Neurol Neurosurg Psychiatry* 57: 835–837.
- Coeytaux, A., Jallon, P., Galobardes, B. and Morabia, A. (2000) Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 55: 693–697.
- Dalmau, J., Gleichman, A.J., Hughes, E.G., Rossi, J.E., Peng, X., Lai, M. *et al.* (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 7: 1091–1098.
- DeLorenzo, R.J., Hauser, W.A., Towne, A.R., Boggs, J.G., Pellock, J.M., Penberthy, L. *et al.* (1996) A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 46: 1029–1035.
- Drislane, F.W. (2000) Presentation, evaluation, and treatment of nonconvulsive status epilepticus. *Epilepsy Behav* 1: 301–314.
- Drislane, F.W., Blum, A.S., Lopez, M.R., Gautam, S. and Schomer, D.L. (2009) Duration of refractory status epilepticus and outcome: loss of prognostic utility after several hours. *Epilepsia* 50: 1566–1571.
- Engelsen, B.A., Tzoulis, C., Karlsen, B., Lillebo, A., Laegreid, L.M., Aasly, J. *et al.* (2008) POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection. *Brain* 131: 818–828.
- Ferlazzo, E., Zifkin, B.G., Andermann, E. and Andermann, F. (2005) Cortical triggers in generalized reflex seizures and epilepsies. *Brain* 128: 700–710.
- Fisch, B.J. and Klass, D.W. (1988) The diagnostic specificity of triphasic wave patterns. *Electroencephalogr Clin Neurophysiol* 70: 1–8.
- Foley, J.M., Watson, C.W. and Adams, R.D. (1950) Significance of the electroencephalographic changes in hepatic coma. *Trans Am Neurol Assoc* 51: 161–165.
- Friedman, D., Claassen, J. and Hirsch, L.J. (2009) Continuous electroencephalogram monitoring in the intensive care unit. *Anesth Analg* 109: 506–523.
- Gerber, P.A., Chapman, K.E., Chung, S.S., Drees, C., Maganti, R.K., Ng, Y.T. *et al.* (2008) Interobserver agreement in the interpretation of EEG patterns in critically ill adults. *J Clin Neurophysiol* 25: 241–249.
- Hesdorffer, D.C., Logroscino, G., Cascino, G., Annegers, J.F. and Hauser, W.A. (1998) Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. *Neurology* 50: 735–741.
- Hirsch, L.J., Brenner, R.P., Drislane, F.W., So, E., Kaplan, P.W., Jordan, K.G. *et al.* (2005) The ACNS subcommittee on research terminology for continuous EEG monitoring: proposed standardized terminology for rhythmic and periodic EEG patterns encountered in critically ill patients. *J Clin Neurophysiol* 22: 128–135.
- Holtkamp, M. (2007) The anaesthetic and intensive care of status epilepticus. *Curr Opin Neurol* 20: 188–193.
- Holtkamp, M., Masuhr, F., Harms, L., Einhaupl, K.M., Meierkord, H. and Buchheim, K. (2003) The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists. *J Neurol Neurosurg Psychiatry* 74: 1095–1099.
- Holtkamp, M., Othman, J., Buchheim, K., Masuhr, F., Schielke, E. and Meierkord, H. (2005a) A “malignant” variant of status epilepticus. *Arch Neurol* 62: 1428–1431.
- Holtkamp, M., Othman, J., Buchheim, K. and Meierkord, H. (2005b) Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 76: 534–539.
- Iyer, V.N., Hoel, R. and Rabinstein, A.A. (2009) Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. *Crit Care Med* 37: 3024–3030.
- Johnson, N., Henry, C., Fessler, A.J. and Dalmau, J. (2010) Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. *Neurology* 75: 1480–1482.
- Kaplan, P.W. (1996) Nonconvulsive status epilepticus in the emergency room. *Epilepsia* 37: 643–650.
- Kaplan, P.W. (1999) Assessing the outcomes in patients with nonconvulsive status epilepticus: non-convulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. *J Clin Neurophysiol* 16: 341–352.
- Kaplan, P.W. (2000) No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: “the cure may be worse than the disease”). *Neurophysiol Clin* 30: 377–382.
- Kapur, J. and Macdonald, R.L. (1997) Rapid seizure-induced reduction of benzodiazepine and Zn²⁺ sensitivity of hippocampal dentate granule cell GABAA receptors. *J Neurosci* 17: 7532–7540.
- Karnaze, D.S. and Bickford, R.G. (1984) Triphasic waves: a reassessment of their significance. *Electroencephalogr Clin Neurophysiol* 57: 193–198.
- Kellinghaus, C., Berning, S., Immisch, I., Larch, J., Rosenow, F., Rossetti, A.O. *et al.* (2011) Intravenous lacosamide for treatment of status epilepticus. *Acta Neurol Scand* 123: 137–141.

- Kimura, S. and Kobayashi, T. (1996) Two patients with juvenile myoclonic epilepsy and nonconvulsive status epilepticus. *Epilepsia* 37: 275–279.
- Knake, S., Rosenow, F., Vescovi, M., Oertel, W.H., Mueller, H.H., Wirbatz, A. *et al.* (2001) Incidence of status epilepticus in adults in Germany: a prospective, population-based study. *Epilepsia* 42: 714–718.
- Lance, J.W. and Adams, R.D. (1963) The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain* 86: 111–136.
- Lininger, A.W., Volow, M.R. and Gianturco, D.T. (1981) Intravenous infusion motor artifact. *Am J EEG Technol* 21: 167–173.
- Lowenstein, D.H. and Aminoff, M.J. (1992) Clinical and EEG features of status epilepticus in comatose patients. *Neurology* 42: 100–104.
- Malter, M.P., Helmstaedter, C., Urbach, H., Vincent, A. and Bien, C.G. (2010) Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. *Ann Neurol* 67: 470–478.
- Mayeux, R. and Lueders, H. (1978) Complex partial status epilepticus: case report and proposal for diagnostic criteria. *Neurology* 28: 957–961.
- Meierkord, H., Boon, P., Engelsens, B., Gocke, K., Shorvon, S., Tinuper, P. *et al.* (2010) EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 17: 348–355.
- Meierkord, H. and Holtkamp, M. (2007) Non-convulsive status epilepticus in adults: clinical forms and treatment. *Lancet Neurol* 6: 329–339.
- Meierkord, H. and Holtkamp, M. (2008) Status epilepticus: an independent outcome predictor after cerebral anoxia. *Neurology* 70: 2015–2016.
- Minicucci, F., Muscas, G., Perucca, E., Capovilla, G., Vigeveno, F. and Tinuper, P. (2006) Treatment of status epilepticus in adults: guidelines of the Italian League against Epilepsy. *Epilepsia* 47(Suppl. 5): 9–15.
- Naidu, S. and Niedermeyer, E. (2005) Degenerative disorders of the central nervous system, In: Niedermeyer, E. and Lopes da Silva, F. (eds). *Electroencephalography*, 5th edn, Lippincott Williams & Wilkins: Philadelphia, PA, pp. 379–401.
- Naylor, D.E., Liu, H. and Wasterlain, C.G. (2005) Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neurosci* 25: 7724–7733.
- Niedermeyer, E. (2005) Metabolic central nervous system disorders, In: Niedermeyer, E. and Lopes da Silva, F. (eds). *Electroencephalography*, 5th edn, Lippincott Williams & Wilkins: Philadelphia, PA, pp. 439–453.
- Niedermeyer, E., Bauer, G., Burnite, R. and Reichenbach, D. (1977) Selective stimulus-sensitive myoclonus in acute cerebral anoxia. A case report. *Arch Neurol* 34: 365–368.
- Niedermeyer, E. and Ribeiro, M. (2000) Considerations of nonconvulsive status epilepticus. *Clin Electroencephalogr* 31: 192–195.
- Niedermeyer, E., Sherman, D.L., Geocadin, R.J., Hansen, H.C. and Hanley, D.F. (1999) The burst-suppression electroencephalogram. *Clin Electroencephalogr* 30: 99–105.
- Novy, J. and Rossetti, A.O. (2010) Oral pregabalin as an add-on treatment for status epilepticus. *Epilepsia* 51: 2207–2210.
- Osorio, I., Reed, R.C. and Peltzer, J.N. (2000) Refractory idiopathic absence status epilepticus: a probable paradoxical effect of phenytoin and carbamazepine. *Epilepsia* 41: 887–894.
- Parsons-Smith, B.G., Summerskill, W.H., Dawson, A.M. and Sherlock, S. (1957) The electroencephalograph in liver disease. *Lancet* 273: 867–871.
- Rajendra, S., Lynch, J.W. and Schofield, P.R. (1997) The glycine receptor. *Pharmacol Ther* 73: 121–146.
- Ropper, A.H. (2003) *Neurological and Neurosurgical Intensive Care*, Lippincott Williams & Wilkins: Boston, MA.
- Rossetti, A.O., Logroscino, G., Liaudet, L., Ruffieux, C., Ribordy, V., Schaller, M.D. *et al.* (2007) Status epilepticus: an independent outcome predictor after cerebral anoxia. *Neurology* 69: 255–260.
- Rossetti, A.O., Logroscino, G., Milligan, T.A., Michaelides, C., Ruffieux, C. and Bromfield, E.B. (2008) Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 255: 1561–1566.
- Scholtes, F.B., Renier, W.O. and Meinardi, H. (1996a) Non-convulsive status epilepticus: causes, treatment, and outcome in 65 patients. *J Neurol Neurosurg Psychiatry* 61: 93–95.
- Scholtes, F.B., Renier, W.O. and Meinardi, H. (1996b) Simple partial status epilepticus: causes, treatment, and outcome in 47 patients. *J Neurol Neurosurg Psychiatry* 61: 90–92.
- Shorvon, S., Baulac, M., Cross, H., Trinka, E. and Walker, M. (2008) The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London Colloquium on Status Epilepticus. *Epilepsia* 49: 1277–1285.
- Thomas, P., Beaumanoir, A., Genton, P., Dolisi, C. and Chatel, M. (1992) ‘De novo’ absence status of late onset: report of 11 cases. *Neurology* 42: 104–110.
- Tomson, T., Lindbom, U. and Nilsson, B.Y. (1992) Nonconvulsive status epilepticus in adults: thirty-two consecutive patients from a general hospital population. *Epilepsia* 33: 829–835.
- Tomson, T., Svanborg, E. and Wedlund, J.E. (1986) Nonconvulsive status epilepticus: high incidence of complex partial status. *Epilepsia* 27: 276–285.

- Towne, A.R., Waterhouse, E.J., Boggs, J.G., Garnett, L.K., Brown, A.J., Smith Jr, J.R. *et al.* (2000) Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology* 54: 340–345.
- Treiman, D.M. (1993) Generalized convulsive status epilepticus in the adult. *Epilepsia* 34(Suppl. 1): S2–S11.
- Treiman, D.M., DeGiorgio, C.M.A., Salisbury, S.M. and Wickboldt, C.L. (1984) Subtle generalized convulsive status epilepticus. *Epilepsia* 25: 653.
- Treiman, D.M. and Delgado-Escueta, A.V. (1983) Complex partial status epilepticus. *Adv Neurol* 34: 69–81.
- Treiman, D.M., Meyers, P.D., Walton, N.Y., Collins, J.F., Colling, C., Rowan, A.J. *et al.* (1998) A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 339: 792–798.
- Treiman, D.M. and Walker, M.C. (2006) Treatment of seizure emergencies: convulsive and non-convulsive status epilepticus. *Epilepsy Res* 68(Suppl. 1): S77–S82.
- Treiman, D.M., Walton, N.Y. and Kendrick, C. (1990) A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res* 5: 49–60.
- Van Cott, A.C., Blatt, I. and Brenner, R.P. (1996) Stimulus-sensitive seizures in postanoxic coma. *Epilepsia* 37: 868–874.
- Van Cott, A.C. and Brenner, R.P. (2005) EEG and dementia, In: Niedermeyer, E. and Lopes da Silva, F. (eds). *Electroencephalography*, 5th edn, Lippincott Williams & Wilkins: Philadelphia, PA, pp. 363–378.
- van Rijckevorsel, K., Boon, P., Hauman, H., Legros, B., Osseman, M., Sadzot, B. *et al.* (2006) Standards of care for non-convulsive status epilepticus: Belgian consensus recommendations. *Acta Neurol Belg* 106: 117–124.
- Vasile, B., Rasulo, F., Candiani, A. and Latronico, N. (2003) The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med* 29: 1417–1425.
- Vespa, P.M., McArthur, D.L., Xu, Y., Eliseo, M., Etchepare, M., Dinov, I. *et al.* (2010) Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. *Neurology* 75: 792–798.
- Vignatelli, L., Tonon, C. and D'Alessandro, R. (2003) Incidence and short-term prognosis of status epilepticus in adults in Bologna, Italy. *Epilepsia* 44: 964–968.
- Vincent, A., Buckley, C., Schott, J.M., Baker, I., Dewar, B.K., Detert, N. *et al.* (2004) Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 127: 701–712.
- Waziri, A., Claassen, J., Stuart, R.M., Arif, H., Schmidt, J.M., Mayer, S.A. *et al.* (2009) Intracortical electroencephalography in acute brain injury. *Ann Neurol* 66: 366–377.
- Wieser, H.G. (1980) Temporal lobe or psychomotor status epilepticus. A case report. *Electroencephalogr Clin Neurophysiol* 48: 558–572.
- Wieser, H.G., Hailemariam, S., Regard, M. and Landis, T. (1985) Unilateral limbic epileptic status activity: stereo EEG, behavioral, and cognitive data. *Epilepsia* 26: 19–29.
- Wieser, H.G., Schindler, K. and Zumsteg, D. (2006) EEG in Creutzfeldt–Jakob disease. *Clin Neurophysiol* 117: 935–951.
- Wijdicks, E.F. (2002) Propofol in myoclonus status epilepticus in comatose patients following cardiac resuscitation. *J Neurol Neurosurg Psychiatry* 73: 94–95.
- Wijdicks, E.F., Hijdra, A., Young, G.B., Bassetti, C.L. and Wiebe, S. (2006) Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 67: 203–210.
- Williamson, P.D., Spencer, D.D., Spencer, S.S., Novelly, R.A. and Mattson, R.H. (1985) Complex partial status epilepticus: a depth-electrode study. *Ann Neurol* 18: 647–654.
- Young, A.B., Zukin, S.R. and Snyder, S.H. (1974) Interaction of benzodiazepines with central nervous glycine receptors: possible mechanism of action. *Proc Natl Acad Sci U S A* 71: 2246–2250.
- Young, G.B. and Campbell, V.C. (1999) EEG monitoring in the intensive care unit: pitfalls and caveats. *J Clin Neurophysiol* 16: 40–45.
- Young, G.B., Sharpe, M.D., Savard, M., Al Thenayan, E., Norton, L. and Davies-Schinkel, C. (2009) Seizure detection with a commercially available bedside EEG monitor and the subhairline montage. *Neurocrit Care* 11: 411–416.

Visit SAGE journals online
<http://tan.sagepub.com>

SAGE JOURNALS
 Online