Non-convulsive status epilepticus in adults: clinical forms and treatment

Hartmut Meierkord, Martin Holtkamp

Non-convulsive status epilepticus (NCSE) is one of the great diagnostic and therapeutic challenges of modern neurology. Because the clinical features of this disorder may be very discrete and sometimes hard to differentiate from normal behaviour, NCSE is usually overlooked and consequently not treated properly. It is important to be familiar with the clinical subtypes such as absence, simple and complex partial, and subtle status epilepticus because each requires tailored management. In order to improve overall care of patients with NCSE, strict diagnostic criteria are needed that should be based on clinical alterations and ictal electroencephalographic changes. NCSE should be terminated rapidly to prevent patients from serious injuries, particularly if consciousness is impaired.

Lancet Neurol 2007; 6: 329–39

Department of Neurology Charité, Universitätsmedizin Berlin, Germany (H Meierkord MD, M Holtkamp MD)

Correspondence to:
Dr H Meierkord, Department of Neurology, Charité, Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
hartmut.meierkord@charite.de

Introduction

Non-convulsive status epilepticus (NCSE) can take several forms and broadly refers to prolonged seizure activity in the absence of major motor signs. In neurological clinics and emergency settings, this disorder is often considered and neurologists seem to be familiar with this problem. This is in contrast to the fact that agreement on diagnostic criteria, clinical forms, consequences, and treatment is scarce. NCSE is not an entirely satisfactory term because it denotes a heterogeneous clinical disorder consisting of various subtypes.

In this Review, we summarise the most important aspects of this elusive disorder in adults. Neurologists or emergency physicians need robust criteria to make a correct diagnosis of NCSE. This implies sophisticated knowledge of the different subtypes because, from a prognostic point of view, these are quite heterogeneous and require individually tailored treatment strategies.

The focus of this Review is on definitions, epidemiology, clinical features, and causes of the subtypes of NCSE. The four major types of NCSE are absence status epilepticus, simple partial status epilepticus (SPSE) without motor features, complex partial status epilepticus (CPSE), and status epilepticus in coma including subtle status epilepticus.

We also summarise experimental animal and human studies on neuronal and clinical consequences to gain a better insight into the outcome of the various clinical forms of NCSE compared with generalised convulsive status epilepticus (GCSE). Finally, we merge currently available outcome data with results from retrospective treatment trials to guide decisions on methods of pharmacological management and their degree of aggressiveness.

The advent of electroencephalography in the 1930s has allowed reliable diagnoses and further differentiation of NCSE. The first descriptions of absence status epilepticus date back to Lennox[1] and CPSE was first reported by Gastaut and colleagues.[2] Cases of "spike-wave stupor" were identified by Niedermeyer and Khalifeh[3] as status epilepticus and this contributed substantially to the emerging concept of NCSE, and the idea of "subtle" GCSE as opposed to "overt" status epilepticus was suggested by Treiman and colleagues.[4] Convulsive status epilepticus, the counterpart of NCSE, was recently reviewed in this journal.[5]

Definition

We define NCSE as a change in behaviour and/or mental processes from baseline associated with continuous epileptiform discharges in the electroencephalogram. However, there is as yet no universially accepted definition of NCSE. Some suggested definitions have included different components such as clinical changes that usually incorporate impaired consciousness, ictal electroencephalographic abnormalities, and response to treatment.[6–9] It is important to decide which components are essential for a widely acceptable definition. Most authors agree that alterations in the clinical state and associated plausible electroencephalographic changes should be the basis of the definition.[10] Clinical changes alone are not sufficient because these may be very subtle and sometimes hard to differentiate from normal behaviour or non-epileptic medical disorders.[11] Important differential diagnoses of NCSE are summarised in the panel. However, the definition must not exclusively rely on electroencephalographic changes because no single pattern can be regarded as pathognomonic. A positive electroclinical response to acute anticonvulsant treatment may be helpful in the diagnostic process, but no response does not exclude the diagnosis. There is an ongoing debate regarding the duration of an episode before a diagnosis of NCSE can be made. In agreement with

***Panel:* Differential diagnoses**

Disorders mimicking non-convulsive status epilepticus
Metabolic encephalopathy
Migraine aura
Posttraumatic amnesia
Prolonged postictal confusion
Psychiatric disorders
Substance de- or intoxication
Transient global amnesia
Transient ischaemic attack

others,[12,13] we suggest a definition of NCSE as 30 min of ongoing epileptic activity.[12,13] It should be noted that in clinical practice, continuing non-convulsive epileptic activity, if instantly diagnosed, should be treated with anticonvulsants earlier than 30 min after onset, regardless of whether the disorder is termed as a prolonged seizure or status epilepticus.

Epidemiology

Incidence figures of NCSE and the relative frequencies of its subtypes vary across studies. This is probably due to the heterogenous definitions and diagnostic criteria used, and the result of possible referral bias, because some reports originate from tertiary epilepsy centres whereas others are population-based.

For all types of status epilepticus, incidence figures of ten to 41 per 100 000 per year have been reported.[12–16] The fraction of absence status epilepticus, SPSE and CPSE and, if included, status epilepticus in coma is reported with a wide range from 5%[14] to 49%.[12] From these data, incidence rates of NCSE of between two and eight per 100 000 can be derived. NCSE may be even more common because the epileptic nature of the clinical features is not usually readily recognised, and electroencephalography may not be available out of hours. Other estimations include a range from ten to 20 cases of NCSE per 100 000.[17]

In adults, absence status makes up only 1–6% of all clinical forms of status epilepticus.[12,14,18,19] However, in patients with idiopathic generalised epilepsies, single or recurrent typical absence status epilepticus are common and occur in 2·6–9·4% of cases.[20,21] Late-onset de novo absence status epilepticus has been reported in every tenth elderly patient with protracted ictal confusion,[22] and the mean age in one study was about 60 years.[23] SPSE has been reported in 9–23% of all patients with status epilepticus;[12,14–16] however, most patients present with somatomotor features.[24]

For many years, CPSE was considered to be a rare disorder as indicated by an epidemiological study from the USA that showed that only 3% of all status epilepticus episodes were complex partial.[14] However, subsequent European studies have shown that CPSE amounts to 16–43% of all cases of status epilepticus.[12,15,16] The low fraction of CPSE in earlier studies may be explained by the use of the International Classification of Disease-9, which did not include this subtype of status epilepticus.

Published data on the frequency of status epilepticus in coma are rare and one study assessed electroencephalographic recordings in a population of 236 comatose patients in intensive care, which showed the presence of NCSE in 8% of patients.[25]

In general, the incidence of status epilepticus shows a strong age-dependency. In elderly people (over age 60 years), incidence rates of 55–86 per 100 000 have been reported.[12,14] In elderly people, the relative frequency of simple and complex partial forms of status epilepticus also increases.[13] This is in accordance with the well-known experimental and clinical observation that focal epileptic activity tends to generalise less often in old age.[26,27]

Economic burden

It has become increasingly important to look at a medical disorder from an economic perspective. Although a few studies have analysed the costs of epilepsy, in general there are as yet no studies assessing the direct and indirect costs of status epilepticus. A recent study from the USA estimated costs via reimbursements received per admission.[28] Compared with acute myocardial infarction, congestive heart failure, and intracranial haemorrhage, status epilepticus resulted in the highest direct inpatient costs amounting to 4 billion US dollars per year. Among patients with status epilepticus, a higher age group and an acute CNS cause were factors that caused profound rises in costs. Subanalysis of clinical forms of status epilepticus was not done, and therefore exact figures on the costs of the different clinical forms of NCSE are pending. Clearly, the rapid expansion of the elderly population will substantially increase the economic impact of this disorder and studies are required to better refine the costs of status epilepticus and its subtypes.

Aetiology and clinical forms

Information on the causes and clinical forms of NCSE is very important for the management of this disorder. There is general agreement that cause is the most relevant prognostic factor in individual patients, but unfortunately there is a paucity of reliable published causal data on the different subtypes. The different forms of NCSE may best be differentiated on the basis of clinical features, electroencephalographic patterns, and context of the syndrome.

Pre-existing epilepsy and NCSE

The development of a number of potent antiepileptic drugs and general improvements in pharmacological approaches in the second half of the last century have completely changed the incidence of status epilepticus in patients with pre-existing epilepsy. By contrast with a report by Hunter in 1959,[29] status epilepticus today is generally more common in patients without a history of seizures.[13,15] With regards to NCSE, there are no published robust figures, but clinical experience suggests that this observation is not true for patients with typical absence status epilepticus and for those with SPSE. Typical absence status epilepticus probably occurs more often in the context of pre-existing epilepsy, most commonly due to insufficient medication. SPSE is encountered after epilepsy surgery and usually takes the form of aura continua.[30] There is some evidence that the number of patients without pre-existing epilepsy is increasing with age, making up more than 70% of patients that are over age 60 years.[14] This accounts especially for patients with localisation-related NCSE.

In daily clinical practise, it is important to note that acute systemic infection is an important risk factor for the development of NCSE in both patients with and without a history of seizures.[31,32]

Approaches to classification

The clinical forms of status epilepticus may be subdivided into convulsive and non-convulsive variants. NCSE includes all forms of continuing epileptic activity and on observation the patient will not typically have any major motor signs. In such cases absence status epilepticus, SPSE, CPSE, and status epilepticus in coma including subtle status epilepticus are considered to be forms of NCSE. On the basis of the diagnostic criteria described above, isolated electrographic status epilepticus and disorders with subclinical epileptiform discharges[33] were not considered in this Review. Electrographic status epilepticus in sleep is restricted to children and is therefore beyond the scope of this Review. The classification based on seizure type by the International League Against Epilepsy[34] and its dichotomy of focal and generalised onset is also used to categorise status epilepticus on the basis of the assumption that there is a status equivalent for every seizure type.[35] Confusion may arise if both ways of grouping are intermingled without clear definitions. Both approaches for classification have their merits and drawbacks and do not exclude each other. It is straightforward to diagnose a given event as convulsive or non-convulsive because this merely requires observation of the patient. A classification into focal or generalised forms will usually require additional information derived from neurological examination and from further investigations, such as electroencephalography and neuroimaging. Figure 1 shows the two main classification systems of status epilepticus. A further approach based on a semiological seizure classification has also recently been suggested.[36] Reservations regarding this classification mainly result from the fear that it may be too complicated and not clinically useful.[37]

With either grouping—convulsive/non-convulsive and focal/generalised—it is important to note that status epilepticus is an evolving disorder with highly dynamic changes affecting both clinical and electroencephalographic features. Indeed, most forms of GCSE will develop into subtle status epilepticus if not terminated early in the course.[38] Status epilepticus with focal onset tends to generalise electrophysiologically and clinically within a short period after onset.[39] The physician therefore must consider the time that has elapsed from onset and possible changes in the clinical picture, and we suggest using both classifications in a stepwise fashion. Examination of the patient will allow subdivision into convulsive or non-convulsive forms, and additional clinical or electrophysiological information may in a second step allow the diagnosis of focal or generalised status epilepticus.

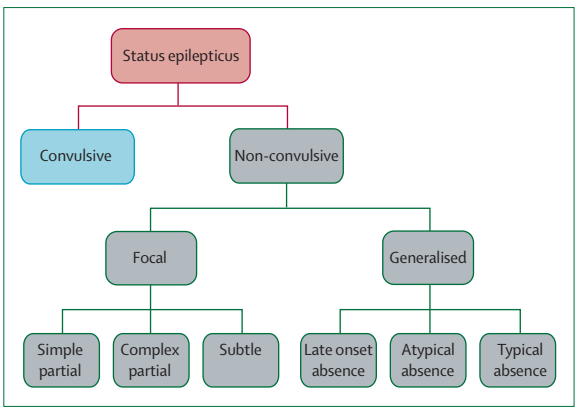

Figure 1: **Stepwise approach to classification of status epilepticus**
Careful examination of the patient can be used to determine between convulsive or non-convulsive forms. The seizure type classification of the International League Against Epilepsy[34] requires additional information from the neurological examination and investigations such as electroencephalogram and neuroimaging. Status epilepticus is a highly dynamic disorder with rapidly changing clinical and electroencephalographic features as a result of mechanisms that spread seizures. Therefore, time from onset needs to be considered to interpret the clinical picture. For example, subtle status epilepticus usually presents with bilateral clinical and electroencephalographic features but results from focal brain lesions and is not known to occur in idiopathic generalised epilepsy. This also shows that in time, there can be a transition from convulsive to non-convulsive forms of status epilepticus.

Absence status epilepticus

Typical absence status epilepticus

The main clinical feature of absence status epilepticus is an altered state of consciousness but changes in behaviour may also be reported (table)[40–50]. Patients with typical absence status epilepticus may be able to eat and drink, withdraw from pain, walk about, and respond to simple commands.[40,51] The duration of typical absence status epilepticus may range from minutes to days, or weeks.[40,52] The disorder can start or end with, or is interrupted by, a generalised convulsive seizure.[40,50]

An electroencephalogram during typical absence status epilepticus shows generalised spike-wave discharges that occur at a frequency of around 3 Hz (figure 2).[53] In the later stages of status epilepticus, electroencephalographic features may become more irregular and slow.[8,54,55]

Typical absence status epilepticus occurs in patients with idiopathic generalised epilepsies, particularly in patients with absence epilepsy[8] or juvenile myoclonic epilepsy.[53,56] The disorder is commonly triggered by inappropriate antiepileptic drugs such as carbamazepine,[57] fever, hyperventilation, grief, excitement, fatigue, or can be associated with the menstrual or sleep–wake cycles.[40,53]

Atypical absence status epilepticus

On clinical grounds alone, the distinction between typical and atypical absence status epilepticus may be difficult, particularly if there is no other information available about the history and characteristic cluster of symptoms and signs. Alteration of consciousness is said to be more severe in atypical than in typical absence status epilepticus (table).

	Phenomenology	EEG
Absence status epilepticus	Impaired consciousness of variable degree; behavioural changes: disorientation, decreased spontaneity, slow speech, hallucinations; rhythmic blinking; slight myoclonic jerking[40]	2–3 Hz spike-wave discharges
Typical	Shorter/less severe episodes than in atypical ASE; abrupt onset	Interictal background activity normal
Atypical	Additional features such as eye-lid blinking and grimacing	Interictal background activity slow
Late onset	Similar to typical absence status epilepticus; spectrum: mild amnesia to stupor	0·5–4 Hz spike-wave discharges
Simple partial status epilepticus	Preserved consiousness; acoustic,[39] aphasic,[24,41,42] dysaesthetic,[43] gustatory,[44] olfactory,[45] psychic,[44] vegetative,[44] or visual[46,47] symptoms or altered behaviour[48]	Variable with focal spike and spike-waves; surface EEG usually negative[44]
Complex partial status epilepticus	Impaired consciousness; "epileptic twilight state" with confusion and strange behaviour; oral or manual automatisms; gradual development of symptoms[7,49,50]	Similar features as in simple partial status epilepticus but less restricted in space; surface EEG with better sensitivity
Subtle status epilepticus	Lost consciousness; no or subtle movements such as rhythmic twitching of the arms, legs, trunk, or facial muscles, tonic-eye deviation, or nystagmoid eye jerking[4]	Generalised or lateralised spike or spike-wave discharges; flat periods[38]

ASE= absence status epilepticus. EEG=electroencephalogram

Table: **Clinical features and electroencephalographic abnormalities in subtypes of NCSE**

The electroencephalogram that is recorded during atypical absence status epilepticus is not very helpful in separating typical from atypical absence status epilepticus. Unfortunately, neither the morphology of spike-wave discharges nor their frequency are specific for either form.[58] However, interictal background activity in patients developing atypical absence status epilepticus is commonly slow but this information is usually not available during status epilepticus.

In a series of 148 patients with atypical absence status epilepticus, 11 patients had Lennox-Gastaut syndrome.[59] Absence status epilepticus with atypical features may also be seen in patients with idiopathic generalised epilepsy and the disorder can be triggered by initiation or dosage increase of antiepileptic drugs, such as carbamazepine, gabapentin, phenytoin, or vigabatrin.[57]

Late-onset de novo absence status epilepticus

This variant presents an important cause underlying prolonged states of confusion or assumed psychiatric disorders in elderly patients.[23,60–62] Most prominent are variable degrees of altered contact with the environment so that a patient may be in stupor or present with only mild amnesia.[23]

The electroencephalographic features seen in typical absence status epilepticus with 3 Hz spike-wave discharges are present only in a few cases with late-onset de novo absence status epilepticus. Commonly, irregular spike-wave discharges with a frequency of 0·5–4 Hz are reported.[23]

Late-onset de novo absence status may occur in patients with remitted idiopathic generalised epilepsy or in patients without any seizure history. In a series published by Dunne and colleagues,[32] ten of 18 patients with de novo absence status epilepticus had pre-existing idiopathic generalised epilepsy and five of these were older than age 50 years. In many cases, a long remission period of 2–40 years precedes the onset of status epilepticus.[32] However, in a couple of cases, there was no history of pre-existing epilepsy.[23,63] Late-onset absence status epilepticus is usually triggered by psychotropic substance intoxication or detoxication such as benzodiazepine withdrawal as reported in eight of 11 patients.[23]

SPSE

In terms of pathophysiology, seizure spread in SPSE is restricted in space and discharges remain circumscribed. SPSE without motor features is difficult to recognise because the prevailing features are exclusively subjective and typically non-spectacular.[64] 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 CPSE. As already pointed out by Gloor,[65] consciousness is an unsatisfactory term, particularly if used to subdivide partial seizures and status epilepticus, but it is still in use. Depending on the area that is activated by the epileptic discharges, the main clinical features during status epilepticus indicate the region of onset (reported clinical symptoms are given in the table).

Epilepsia partialis continua is a distinctive syndrome involving SPSE and is refractory in most cases. In view of the presence of continuous clonic focal motor symptoms—although these may be quite discrete—the disorder should not be considered as a form of NCSE.

Electroencphalographic alterations, if recorded with surface electrodes, may be variable with focal spikes and spike-wave complexes. Both SPSE and CPSE may occur in patients with pre-existing lesional or non-lesional localisation-associated epilepsy, or de novo due to acute, progressive, or remote CNS injuries. The frequency of both causal types is difficult to determine because the large epidemiological studies do not report on causes of the clinical status epilepticus subtypes.

CPSE

CPSE may be the result of a more widespread, and usually bilateral, seizure discharge, in some cases also explaining the higher complexity of clinical features compared with SPSE (table). Various clinical features may make it difficult to distinguish CPSE from absence status epilepticus.[11,66]

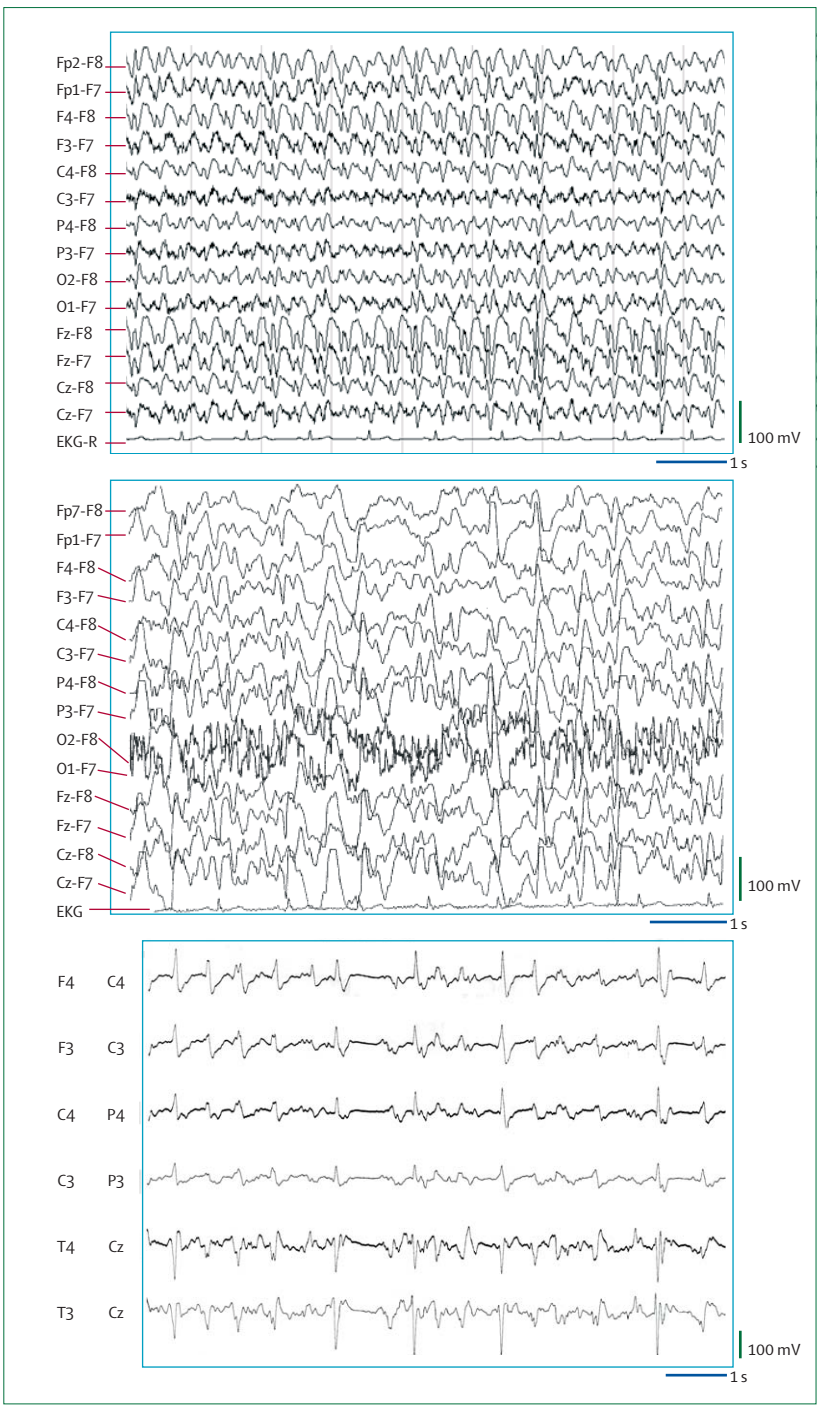

Figure 2: **Electroencephalograms during status epilepticus**
Top; this is recorded during an episode of typical absence status epilepticus in a patient age 18 years with juvenile absence epilepsy. Status epilepticus developed in the context of non-compliance. The electroencephalogram was recorded about 1 h after the patient was reported to react slower than normal. A pattern of not-quite regular 3 Hz spike-wave discharges is shown. Absence status epilepticus was stopped with low doses of benzodiazepines and reinstalling the patient's regular medication. Middle; this is recorded during an episode of complex partial status epilepticus. The patient, age 63 years, had a history of left mesial temporal lobe epilepsy with hippocampal sclerosis as shown by MRI. Note that the changes are bilateral and widespread with high-amplitude rhythmic discharges and alpha-beta activities of lower amplitude.Bottom; this is recorded during subtle status epilepticus. The patient, age 39 years, had a history of acute viral encephalitis and developed secondary generalised convulsive status epilepticus ("overt" status epilepticus). The patient was partially treated with benzodiazepines and phenytoin but this did not terminate status epilepticus. The comatose patient presented with mild bilateral facial twitches and electroencephalography showed generalised epileptiform discharges interrupted by short generalised flat periods. Diagnosis of subtle status epilepticus was indicated on the basis of history, clinical findings, and electroencephalographic features. The patient was put under generalised anaesthesia with thiopental until there was an electroencephalographic burst suppression pattern. 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.

Early reports of CPSE that included electroencephalographic documentation resulted in the assumption that there are two variants: continuous and cyclic forms.[6,46,67] However, further well-documented cases have shown that continuous and discontinuous clinical and electrographic seizure activity may occur within one episode, suggesting that continuous and cyclic types do not represent separate entities.[8,18,52,68,69] CPSE has been identified to be a recurrent problem usually occurring at regular intervals, as seen in 17 of 20 patients in one study.[9]

It is widely accepted that CPSE may present a very broad range of clinical features. By definition, impairment of consciousness must be present, typically manifesting itself as altered contact with the environment. In most cases, evolution is gradual, occasionally starting with prolonged or serial auras of any kind. Several reports indicate that many cases originate from the temporal lobes.[9,39,44] However, CPSE certainly cannot be equated with temporal lobe status epilepticus. A depth-electrode study has indicated that CPSE may originate from extra-temporal regions with special preference for frontal structures.[69] As yet, there are no reliable data on the relative frequencies of regions of onset. Thomas and colleagues[70] described two types of NCSE of frontal origin. Patients either showed mood disturbances with affective disinhibition that were associated with subtle impairment of cognitive functions without overt confusion, or patients had impaired consciousness.[70] Although the latter clearly represents CPSE, the authors suggest that the former may better be described as SPSE.

Given the various possible clinical presentations, confirmation and documentation with electroencephalography is needed for a diagnosis to be made.[11] Common electroencephalographic changes are given in the table and an example of the bilateral nature of the changes is shown in figure 2.

NCSE in coma

The diagnosis of NCSE in coma is a notorious problem. This is because the clinical features of status epilepticus 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. Pure electrographic status epilepticus without clinical evidence of seizures, even

before electroencephalographic examination, has been described in 38% of patients.[71] Additional diagnostic problems arise from the fact that there are no pathognomonic electroencephalograhic changes proving status epilepticus beyond doubt. In fact, even prominent generalised spike activity can indicate the expression of a severe encephalopathy, usually caused by anoxia rather than NCSE.[10] Thus, NCSE in patients in a coma is probably overdiagnosed if the diagnosis is based on electroencephalographic alterations alone.

Subtle GCSE

The concept of "subtle" status epilepticus 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 status epilepticus loses much of its diagnostic power if not used in the strict sense as representing the endpoint of overt status epilepticus, the latter denoting GCSE.[38,72] Subtle status epilepticus is a form of NCSE that develops from GCSE if the latter has been treated insufficiently or not treated at all. We are aware that in an initial report, patients were included in whom the disorder was believed to be caused by severe encephalopathy, and subtle status epilepticus may be an unrecognised cause of coma.[4] As GCSE occurring in idiopathic generalised epilepsy is almost never refractory,[73] it is likely that in most patients stubtle status epilepticus is due to focal brain pathology. Figure 2 shows an electroencephalogram of a patient who was referred to our intensive care unit. In order not to lose the force of the concept, we suggest that the diagnosis of subtle status epilepticus should be made only in the presence of electroencephalographic changes and if there is evidence for previous overt epileptic seizures or status epilepticus. For the same reason we do not include postanoxic myoclonus (also called myoclonic status epilepticus) as done by Treiman[74] because there is no agreement regarding its epileptic nature.

Coma induced by CNS disorders associated with status epilepticus

All other diagnoses of NCSE in coma should be made with caution, because the diagnosis of NCSE has to rely on changes in the clinical picture and on associated plausible alterations in the electroencephalogram. In a patient in a coma, it is very difficult to identify changes in the clinical state as ictal symptomatology, and to differentiate this from non-ictal symptoms, that reflect the underlying pathology. Electroencephalographic changes in coma are usually not pathognomonic and a diagnosis of NCSE should not be based on these electroencpehalographic changes alone. In a retrospective study by Towne and colleagues,[25] 236 patients in coma were reviewed regarding the possible different causes. Coma was most commonly induced by hypoxia (42% of cases) and by stroke (22%). The authors diagnosed NCSE in 8% of cases on the basis of electroencephalographic findings; however, this may mean overdiagnosing of the disorder. In such situations, we suggest making a diagnosis of NCSE only if, in addition to the electroencephalographic changes, there is clinical evidence from the patient's history or if there have been recent episodes of seizures or status epilepticus.

Electroencephalographic patterns

During a coma, the brain produces various periodic and rhythmic electroencephalographic changes that are currently being standardised by a subcommittee of the American Clinical Neurophysiology Society.[75] These electroencephalographic changes include, most importantly, periodic lateralised epileptiform discharges, bilateral independent periodic lateralised epileptiform discharges, periodic epileptiform discharges, generalised periodic epileptiform discharges, stimulus-induced rhythmic periodic ictal-like discharges, and triphasic waves. A major goal of the subcommittee is to eliminate terms with clinical connotations, such as triphasic waves, which implies a metabolic encephalopathy. Once standardised, the new terminology will ease the task of multicentre research projects in looking for the diagnostic significance of each pattern.

There seems to be agreement that the overall picture of the electroencephalographic discharge and its evolution in time and space is helpful in differentiating the electroencephalography of encephalopathies from that of NCSE. A clear development with a build-up of rhythmic activity or generalised spike-wave discharges at 3 Hz or faster and decremental features with flat periods associated with clinical seizure activity strongly indicate NCSE.[76] It should be noted that a simple electroencephalographic response to benzodiazepines is reported with most patterns and is therefore of minor value in the differential diagnosis, whereas a positive electroclinical response may be of diagnostic value. The current work on these issues carried out by the American Clinical Neurophysiology Society subcommittee[75] is an important step in the right direction.

Suspect clinical features of NCSE

It is not possible to do an electroencephalogram on each and every patient presenting with an unexplained change in behaviour or mental state. Husain and colleagues' study[77] is of great practical use in view of those clinical features highly suggestive of NCSE and therefore helpful in deciding when to do an emergency electroencephalogram.[77] Ocular movement abnormalities and remote risk factors for seizures such as stroke, neoplasia, dementia, and previous neurosurgery have a very high combined sensitivity for NCSE.

Pathophysiology

A recent review by Chen and Wasterlain[5] summarises the current concepts of basic mechanisms underlying the development and maintenance of status epilepticus.

Therefore, we focus on differences in pathophysiological processes underlying absence status epilepticus and localisation-associated NCSE. Current considerations are based on the assumption that the mechanisms resulting in absence or localisation-associated NCSE are comparable, although certainly not identical, to those mechanisms underlying absence or partial seizures.

The neuronal networks that generate absence seizures are completely different from those underlying partial seizures. Thalamocortical neuronal populations are crucial in absence status epilepticus,[78] and neuronal networks within the hippocampal formation and adjacent limbic and neocortical structures, including parietal and occipital regions, are relevant in simple and CPSE.[79] There are also notable differences in neurotransmitter changes. The synchronisation of thalamocortical discharges that occurs during absence status epilepticus depends on GABAergic processes located in the nucleus reticularis thalami.[80] By contrast, the generation and maintenance of limbic status epilepticus involve activation of NMDA and other glutamate receptors.[81] Such differences may also explain possible consequences of either form of status epilepticus. The development of excitotoxicity has been reported during limbic status epilepticus but not in absence status epilepticus.[79]

Neuronal and clinical consequences

Outcome assessment after NCSE is hampered by the difficulty in separating the effects of continuing seizure activity from those of an underlying cause and from complications occurring in the clinical course, including effects of treatment. Not surprisingly, NCSE in pre-existing epilepsy has a substantially better prognosis than NCSE caused by acute neurological or systemic disorders.[82]

Does NCSE have deleterious neuronal and clinical consequences at all? Experimental animal studies may give some insight into pathophysiological mechanisms. Meldrum and colleagues[83] induced GCSE with bicuculline in baboons for 1·5–5 h and this caused neuronal damage in cerebellar, hippocampal, and neocortical structures. If convulsions were avoided by complete muscle relaxation, neuronal cell loss was less severe but not completely prevented, which indicates the deleterious effects of continuing epileptic activity itself.[84] Self-sustaining status epilepticus induced by electrical stimulation of limbic structures in rats results in a phenomenological spectrum ranging from continuous partial to continuous GCSE.[85] In animals with partial motor status epilepticus, neuronal damage and development of chronic epilepsy was substantially less severe, but still present. In experimental animals with NCSE, induced with pilocarpine, neuronal loss in the motor cortex and in the dentate gyrus was reported, and 2 months later, behavioural analysis showed motor deficits and disturbances in social behaviour.[86] Such consequences may be explained by the excitotoxicity as reported in experimental animal models of limbic status epilepticus.[87]

In summary, animal data on status epilepticus indicate that the severity of functional and structural consequences on the brain depends on the extent of convulsive activity. However, non-convulsive epileptic activity has the potential to damage neurons as well.

Translation of these experimental findings to human NCSE should be made with caution. Status epilepticus in animal models is typically associated with extensive continuous excitatory seizure activity, whereas NCSE in human beings is generally interrupted by periods of less severe activity. Duration and frequency of epileptic activity correlates with the extent of neuronal damage[88] and therefore experimental status epilepticus cannot indiscriminately be compared with the human disorder.

Neuronal consequences of NCSE in human beings can be assessed methodologically in post-mortem autopsies or in vivo with neuroimaging. Commonly, NCSE is a disorder that does not result in death, unless the underlying causative medical disorder is lethal. Because in such cases allocation of the origin of neuronal cell loss is not always certain, there are currently no reliable reports on structural consequences of NCSE as shown by histology.

Structural neuroimaging has also been used to look for cerebral consequences of status epilepticus. One patient with temporal lobe epilepsy was reported to have developed hippocampal atrophy after CPSE.[89] This report differs from another MRI volumetry study that assessed nine patients up to 12 months after GCSE and there was no atrophy in limbic structures.[90]

Neuron-specific enolase, which probably indicates some form of neuronal damage, was increased in one study after CPSE.[91] This, however, does not necessarily indicate any clinical deficits.

NCSE in patients with pre-existing epilepsy allows assessment of isolated clinical effects of continuing epileptic activity. Outcome is reported to be good to excellent for both CPSE[9,19,69] and absence status epilepticus, either in patients with idiopathic generalised epilepsies[19] or in patients with de novo late-onset absence status.[23] Advanced analysis of neuropsychological functions in patients with pre-existing epilepsy, and at least one episode of CPSE, showed an excellent intellectual prognosis in adults.[92] Shneker and Fountain[82] compared mortality in 100 patients with NCSE on the basis of cause regardless of subtype. Patients with NCSE due to pre-existing epilepsy had a low mortality (3%), whereas patients with NCSE due to acute medical disorders had a mortality of 27% indicating the overall importance of cause on outcome. Complications due to the causative medical disorder, due to treatment, and perhaps due to persistence of seizure activity seem to be the basis for the high mortality of more than 50% in elderly critically ill patients with NCSE.[93] An accumulation of these complications is usually encountered in patients in a coma with status epilepticus. These patients have a very poor prognosis and mortality ranges between 47%[25] and

60%.[94] This range, however, is similar to that of patients in a coma without epileptiform electroencephalographic features ranging between 54%[25] and 66%.[94] In the Veterans Affairs Cooperation Study on the treatment of status epilepticus,[72] outcome of subtle status epilepticus was significantly worse than that of overt GCSE, and mortality rates were 65% and 27%, respectively.

In summary, available human data so far indicate that most clinical forms of NCSE, with the exception of subtle status epilepticus, are benign in terms of morbidity and mortality. Poor outcome may be attributed to cause and associated complications. However, this does not mean that treatment decisions should only be based on the expected outcome. Clearly, the risk of severe physical injuries and other complications that patients may have during NCSE, particularly if consciousness is impaired, have to be considered.

Pharmacological management

Treatment of NCSE depends on the type and the cause. As most clinical forms of NCSE, with the exception of subtle status epilepticus and in contrast to GCSE, are not associated with acute systemic and chronic neurological complications, we suggest a less aggressive pharmacological management. Regarding subtle status epilepticus, recommendations for initial treatment are based on one randomised controlled trial.[72] The therapeutic approach for the other subtypes relies only on retrospective and empirical data.

Typical absence status epilepticus and late-onset de novo absence status epilepticus are commonly treated successfully by intravenous administration of 10 mg diazepam or 4 mg lorazepam.[8,23,95] If seizures continue for more than 10 min after this treatment, these doses can be repeated. Eventually, bolus administration of intravenous valproic acid at 25–45 mg/kg (6 mg/kg per min) or phenobarbital at 20 mg/kg (50 mg/kg per min) is recommended. In patients with recurrent episodes of absence status epilepticus who are institutionalised or home cared, buccal, nasal, oral, or rectal administration of benzodiazepines might be a reasonable alternative.[96–98] Absence status epilepticus caused by paradoxical effects of antiepileptic drugs, such as phenytoin or carbamazepine, may be refractory to initial benzodiazepines, and seizure control was attained in all eight reported cases 24–48 h after discontinuation of the proconvulsant antiepileptics.[95] However, in this disorder response to benzodiazepines, and even spontaneous cessation of absence status epilepticus, has been reported.[57] Although in typical absence status epilepticus, recurrence of epileptic activity is not uncommon,[8] late-onset absence status epilepticus rarely reccurs, even in patients not taking antiepileptic drugs.[23] Atypical absence status epilepticus may not respond to benzodiazepines, and additional phenobarbital or valproic acid may be required.

The response to initial drugs in SPSE and CPSE depends on whether the disorder occurs in patients with pre-existing epilepsy or in patients with de novo status epilepticus presumably due to acute or progressive systemic or CNS disorders. In patients with a history of frontal or temporal lobe epilepsy, partial forms of status epilepticus may spontaneously terminate or rapidly respond to intravenous administration of 10 mg diazepam or 4 mg lorazepam. These doses are repeated in the case of persistence or recurrence of epileptic activity. If necessary, additional phenytoin (15–18 mg/kg) or equivalent dosage of fosphenytoin is recommended.[18] Though recurrence of CPSE is not unusual,[9] benzodizapines and fosphenytoin usually illicit a response. By contrast, de novo SPSE and CPSE are commonly refractory towards first-line treatment, and therefore subsequent intravenous phenobarbital at 20 mg/kg or valproic acid at 25–45 mg/kg should be administered.

Owing to favourable clinical outcome in patients with NCSE, caution should be taken with further treatment with intravenous anaesthetics.[50,99] Aggressive pharmacological treatment seems to have a greater risk on morbidity and mortality[100] than continuing non-convulsive seizure activity.[101] A European survey indicated that neurologists are more reluctant to administer anaesthetics in CPSE than in GCSE.[102] Alternatively, phenobarbital or valproic acid, if not already given as first-line or second-line treatment, should be tried first.[103] Furthermore, enteral topiramate and levetiracetam may be successful in this disorder,[104–106] and the latter is now available for intravenous administration. If CPSE cannot be terminated, generalised anaesthesia should be considered in the rare patients who are young and do not have additional medical problems, but treatment should be tailored for each patient. In these younger patients, anaesthetics such as midazolam (0·2 mg/kg bolus, 0·1–0·4 mg/kg per h infusion), propofol (2 mg/kg bolus, 5–10 mg/kg per h infusion), thiopental (2–3 mg/kg mg bolus, 3–5 mg/kg per h infusion), or pentobarbital (10–20 mg/kg bolus, 1–3 mg/kg per h infusion) can be given.[107] In these patients, there has been recurrence of seizure activity in more than 50% of cases,[108] and for this difficult-to-treat and prognostically poor variant we have coined the term "malignant" status epilepticus.[109]

Treatment of NCSE in coma is also tailored to its subtype. Subtle status epilepticus that developed from overt GCSE was studied in a randomised controlled trial with 134 patients.[72] Intravenous 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) stopped status epilepticus in only 8–24% of patients, and success rates were not significantly different in the study groups. The response rate in early overt GCSE was 44–65%, and the dramatic loss in efficacy of the predominantly GABAergic substances can be explained by modification of the $GABA_A$ receptor due to continued seizure activity.[110] Refractory subtle status epilepticus should be treated with intravenous anaesthetics, as described above, without further delay.[107]

Search strategy and selection criteria

References for this Review were identified through searches of PubMed from 1966 to January 2007 with the terms "status epilepticus" in combination with "absence", "complex partial", "non-convulsive", "simple partial", "subtle", and "coma", "animal data", "experimental", "outcome", "treatment", and "trial". Articles were also identified through searches of the references of articles and the authors' own files. Only papers in English were reviewed, except for historical references that were written in French. Case reports were considered if they contained outstanding new data otherwise not available. Abstracts and reports from meetings were included only if they presented new relevant information. The final list reflects papers relevant to the topics covered in the Review.

If epileptiform electroencephalographic discharges occur in patients in a coma, due to an underlying medical disorder such as global hypoxia, anticonvulsant treatment may be less aggressive because clinical outcome in these patients is similarly poor to those without such electroencephalographic features.[25,94]

Conclusion

NCSE is a disorder comprising a broad clinical spectrum that requires charactersitic electroencephalographic changes to confirm the correct diagnosis. The diagnosis of epilepsy in general is a clinical one, which is why a diagnosis of status epilepticus should not be based on electroencephalographic features alone.

Morbidity and mortality depend on the underlying cause, and in general, most clinical forms of NCSE seem to be less harmful than status epilepticus with generalised convulsive phenomenology. Treatment approaches should aim to rapidly terminate NCSE to prevent patients from having serious injuries, particularly if consciousness is impaired. However, outcome data suggest that in refractory cases, with the exception of subtle status epilepticus, a less aggressive management is recommended. Future clinical research should focus on randomised controlled treatment trials that rely on strict definitions and diagnostic criteria for NCSE and its subtypes.

Authors' contributions

Both authors contributed equally to the research for and the preparation of this Review. Both authors have seen and approved the final version. HM did the literature seach on definition, clinical forms, and aetiology. MH did the search on epidemiology, consequences, and management. Both authors did additional searches on related topics and prepared the first drafts of their search topics. All sections were intensively discussed by both authors who also prepared further versions of the text together and the final version of the manuscript.

Conflicts of interest

We have no conflicts of interest.

Acknowledgments

This Review is dedicated to Dr Katharina Buchheim (May 17, 1965–December 1, 2005), who made significant contributions to the field and whose career was prematurely curtailed.

References

1 Lennox WG. The treatment of epilepsy. *Med Clin N Amer* 1945; **29:** 1114–28.
2 Gastaut H, Roger J, Roger A. Sur la signification de certaines fugues epileptiques: etats de mal temporal. *Rev Neurol* 1956; **94:** 298–301.
3 Niedermeyer E, Khalifeh R. Petit mal status ("spike-wave stupor"): an electro-clinical appraisal. *Epilepsia* 1965; **6:** 250–62.
4 Treiman DM, DeGiorgio CMA, Salisbury SM, Wickboldt CL. Subtle generalized convulsive status epilepticus. *Epilepsia* 1984; **25:** 653.
5 Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol* 2006; **5:** 246–56.
6 Mayeux R, Lueders H. Complex partial status epilepticus: case report and proposal for diagnostic criteria. *Neurology* 1978; **28:** 957–61.
7 Treiman DM, Delgado-Escueta AV. Complex partial status epilepticus. *Adv Neurol* 1983; **34:** 69–81.
8 Tomson T, Lindbom U, Nilsson BY. Nonconvulsive status epilepticus in adults: thirty-two consecutive patients from a general hospital population. *Epilepsia* 1992; **33:** 829–35.
9 Cockerell OC, Walker MC, Sander JW, Shorvon SD. Complex partial status epilepticus: a recurrent problem. *J Neurol Neurosurg Psychiatry* 1994; **57:** 835–37.
10 Niedermeyer E, Ribeiro M. Considerations of nonconvulsive status epilepticus. *Clin Electroencephalogr* 2000; **31:** 192–95.
11 Celesia GG. Modern concepts of status epilepticus. *JAMA* 1976; **235:** 1571–74.
12 Knake S, Rosenow F, Vescovi M, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. *Epilepsia* 2001; **42:** 714–18.
13 Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. *Neurology* 1998; **50:** 735–41.
14 DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996; **46:** 1029–35.
15 Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 2000; **55:** 693–97.
16 Vignatelli L, Tonon C, D'Alessandro R. Incidence and short-term prognosis of status epilepticus in adults in Bologna, Italy. *Epilepsia* 2003; **44:** 964–68.
17 Shorvon S. Status epilepticus: its clinical features and treatment in children and adults. Cambridge: University Press, 1994.
18 Tomson T, Svanborg E, Wedlund JE. Nonconvulsive status epilepticus: high incidence of complex partial status. *Epilepsia* 1986; **27:** 276–85.
19 Scholtes FB, Renier WO, Meinardi H. Non-convulsive status epilepticus: causes, treatment, and outcome in 65 patients. *J Neurol Neurosurg Psychiatry* 1996; **61:** 93–95.
20 Lennox WG. Epilepsy and related disorders. Boston, MA: Little Brown and Company, 1960.
21 Livingston S, Torres I, Paulli LL, Rider RV. Petit mal epilepsy. Results of a prolonged follow-up study of 117 patients. *JAMA* 1965; **194:** 227–32.
22 Sheth RD, Drazkowski JF, Sirven JI, et al. Protracted ictal confusion in elderly patients. *Arch Neurol* 2006; **63:** 529–32.
23 Thomas P, Beaumanoir A, Genton P, et al. 'De novo' absence status of late onset: report of 11 cases. *Neurology* 1992; **42:** 104–10.
24 Scholtes FB, Renier WO, Meinardi H. Simple partial status epilepticus: causes, treatment, and outcome in 47 patients. *J Neurol Neurosurg Psychiatry* 1996; **61:** 90–92.
25 Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology* 2000; **54:** 340–45.
26 Holtkamp M, Buchheim K, Siegmund H, Meierkord H. Optical imaging reveals reduced seizure spread and propagation velocities in aged rat brain in vitro. *Neurobiol Aging* 2003; **24:** 345–53.
27 DeToledo JC. Changing presentation of seizures with aging: clinical and etiological factors. *Gerontology* 1999; **45:** 329–35.
28 Penberthy LT, Towne A, Garnett LK, et al. Estimating the economic burden of status epilepticus to the health care system. *Seizure* 2005; **14:** 46–51.
29 Hunter RA. Status epilepticus; history, incidence and problems. *Epilepsia* 1959; **1:** 162–88.

30 Seshia SS, McLachlan RS. Aura continua. *Epilepsia* 2005; **46:** 454–55.

31 Haffey S, McKernan A, Pang K. Non-convulsive status epilepticus: a profile of patients diagnosed within a tertiary referral centre. *J Neurol Neurosurg Psychiatry* 2004; **75:** 1043–44.

32 Dunne JW, Summers QA, Stewart-Wynne EG. Non-convulsive status epilepticus: a prospective study in an adult general hospital. *Q J Med* 1987; **62:** 117–26.

33 Licht EA, Fujikawa DG. Nonconvulsive status epilepticus with frontal features: quantitating severity of subclinical epileptiform discharges provides a marker for treatment efficacy, recurrence and outcome. *Epilepsy Res* 2002; **51:** 13–21.

34 Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; **22:** 489–501.

35 Gastaut H. A propos d'une classification symptomatologique des états de mal épileptiques. In: Gastaut H, Roger J, Lob H, eds. Les états de mal épileptiques. Paris: Masson, 1967: 1–8.

36 Rona S, Rosenow F, Arnold S et al. A semiological classification of status epilepticus. *Epileptic Disord* 2005; **7:** 5–12.

37 Shorvon S. The classification of status epilepticus. *Epileptic Disord* 2005; **7:** 1–3.

38 Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res* 1990; **5:** 49–60.

39 Wieser HG. Temporal lobe or psychomotor status epilepticus. A case report. *Electroencephalogr Clin Neurophysiol* 1980; **48:** 558–72.

40 Andermann F, Robb JP. Absence status: a reappraisal following review of thirty-eight patients. *Epilepsia* 1972; **13:** 177–87.

41 Primavera A, Gianelli MV, Bandini F. Aphasic status epilepticus in multiple sclerosis. *Eur Neurol* 1996; **36:** 374–77.

42 Wells CR, Labar DR, Solomon GE. Aphasia as the sole manifestation of simple partial status epilepticus. *Epilepsia* 1992; **33:** 84–87.

43 Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Boston MA: Little Brown and Company, 1954.

44 Wieser HG, Hailemariam S, Regard M, Landis T. Unilateral limbic epileptic status activity: stereo EEG, behavioral, and cognitive data. *Epilepsia* 1985; **26:** 19–29.

45 Manford M, Shorvon SD. Prolonged sensory or visceral symptoms: an under-diagnosed form of non-convulsive focal (simple partial) status epilepticus. *J Neurol Neurosurg Psychiatry* 1992; **55:** 714–16.

46 Lugaresi E, Pazzaglia P, Tassinari CA. Differentiation of "Absence Status" and "Temporal Lobe Status". *Epilepsia* 1971; **12:** 77–87.

47 Walker MC, Smith SJ, Sisodiya SM, Shorvon SD. Case of simple partial status epilepticus in occipital lobe epilepsy misdiagnosed as migraine: clinical, electrophysiological, and magnetic resonance imaging characteristics. *Epilepsia* 1995; **36:** 1233–36.

48 Bauer G, Dobesberger J, Bauer R et al. Prefrontal disturbances as the sole manifestation of simple partial nonconvulsive status epilepticus. *Epilepsy Behav* 2006; **8:** 331–35.

49 Engel J, Jr., Ludwig BI, Fetell M. Prolonged partial complex status epilepticus: EEG and behavioral observations. *Neurology* 1978; **28:** 863–69.

50 Drislane FW. Presentation, Evaluation, and Treatment of Nonconvulsive Status Epilepticus. *Epilepsy Behav* 2000; **1:** 301–14.

51 Fincham RW, Yamada T, Schottelius DD et al. Electroencephalographic absence status with minimal behavior change. *Arch Neurol* 1979; **36:** 176–78.

52 Cascino GD. Nonconvulsive status epilepticus in adults and children. *Epilepsia* 1993; **34** (suppl 1)**:** S21–S28.

53 Baykan B, Gokyigit A, Gurses C, Eraksoy M. Recurrent absence status epilepticus: clinical and EEG characteristics. *Seizure* 2002; **11:** 310–19.

54 Berkovic SF, Andermann F, Guberman A, et al. Valproate prevents the recurrence of absence status. *Neurology* 1989; **39:** 1294–97.

55 Granner MA, Lee SI. Nonconvulsive status epilepticus: EEG analysis in a large series. *Epilepsia* 1994; **35:** 42–47.

56 Kimura S, Kobayashi T. Two patients with juvenile myoclonic epilepsy and nonconvulsive status epilepticus. *Epilepsia* 1996; **37:** 275–79.

57 Thomas P, Valton L, Genton P. Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy. *Brain* 2006; **129:** 1281–92.

58 Markand ON. Pearls, perils, and pitfalls in the use of the electroencephalogram. *Semin Neurol* 2003; **23:** 7–46.

59 Roger J, Lob H, Tassinari CA. Status epilepticus. In: Magnus O, Lorentz de Haas AM, eds. Handbook of clinical neurology: The epilepsies. Amsterdam: North Holland Publishing Company, 1974: 145–99.

60 Fernandez-Torre JL. De novo absence status of late onset following withdrawal of lorazepam: a case report. *Seizure* 2001; **10:** 433–37.

61 Thomas P, Lebrun C, Chatel M. De novo absence status epilepticus as a benzodiazepine withdrawal syndrome. *Epilepsia* 1993; **34:** 355–58.

62 Primavera A, Giberti L, Scotto P, Cocito L. Nonconvulsive status epilepticus as a cause of confusion in later life: a report of 5 cases. *Neuropsychobiology* 1994; **30:** 148–52.

63 Guberman A, Cantu-Reyna G, Stuss D, Broughton R. Nonconvulsive generalized status epilepticus: clinical features, neuropsychological testing, and long-term follow-up. *Neurology* 1986; **36:** 1284–91.

64 Armon C, Radtke RA, Friedman AH. Inhibitory simple partial (non-convulsive) status epilepticus after intracranial surgery. *J Neurol Neurosurg Psychiatry* 2000; **69:** 18–24.

65 Gloor P. Consciousness as a neurological concept in epileptology: a critical review. *Epilepsia* 1986; **27** (suppl 2)**:** S14–S26.

66 Kaplan PW. Nonconvulsive status epilepticus in the emergency room. *Epilepsia* 1996; **37:** 643–50.

67 Escueta AV, Boxley J, Stubbs N, et al. Prolonged twilight state and automatisms: a case report. *Neurology* 1974; **24:** 331–39.

68 Roberts MA, Humphrey PR. Prolonged complex partial status epilepticus: a case report. *J Neurol Neurosurg Psychiatry* 1988; **51:** 586–88.

69 Williamson PD, Spencer DD, Spencer SS et al. Complex partial status epilepticus: a depth-electrode study. *Ann Neurol* 1985; **18:** 647–54.

70 Thomas P, Zifkin B, Migneco O et al. Nonconvulsive status epilepticus of frontal origin. *Neurology* 1999; **52:** 1174–83.

71 Drislane FW, Schomer DL. Clinical implications of generalized electrographic status epilepticus. *Epilepsy Res* 1994; **19:** 111–21.

72 Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus: Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998; **339:** 792–98.

73 Shorvon S, Walker M. Status epilepticus in idiopathic generalized epilepsy. *Epilepsia* 2005; **46** (suppl 9)**:** 73–79.

74 Treiman DM. Generalized convulsive status epilepticus in the adult. *Epilepsia* 1993; **34** (suppl 1)**:** S2–11.

75 Hirsch LJ, Brenner RP, Drislane FW et al. 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* 2005; **22:** 128–35.

76 Treiman DM, Walker MC. Treatment of seizure emergencies: convulsive and non-convulsive status epilepticus. *Epilepsy Res* 2006; **68** (suppl 1)**:** S77–82.

77 Husain AM, Horn GJ, Jacobson MP. Non-convulsive status epilepticus: usefulness of clinical features in selecting patients for urgent EEG. *J Neurol Neurosurg Psychiatry* 2003; **74:** 189–91.

78 Quesney LF, Gloor P. Generalized penicillin epilepsy in the cat: correlation between electrophysiological data and distribution of 14C-penicillin in the brain. *Epilepsia* 1978; **19:** 35–45.

79 Hosford DA. Animal models of nonconvulsive status epilepticus. *J Clin Neurophysiol* 1999; **16:** 306–13.

80 Huguenard JR, Prince DA. Clonazepam suppresses GABAB-mediated inhibition in thalamic relay neurons through effects in nucleus reticularis. *J Neurophysiol* 1994; **71:** 2576–81.

81 Fountain NB, Lothman EW. Pathophysiology of status epilepticus. *J Clin Neurophysiol* 1995; **12:** 326–42.

82 Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology* 2003; **61:** 1066–73.

83 Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates; ischemic cell change and its relation to ictal physiological events. *Arch Neurol* 1973; **28:** 10–17.

84 Meldrum BS, Vigouroux RA, Brierley JB. Systemic factors and epileptic brain damage. Prolonged seizures in paralyzed, artificially ventilated baboons. *Arch Neurol* 1973; **29:** 82–87.

85 Brandt C, Glien M, Potschka H, et al. Epileptogenesis and neuropathology after different types of status epilepticus induced by prolonged electrical stimulation of the basolateral amygdala in rats. *Epilepsy Res* 2003; **55:** 83–103.

86 Krsek P, Mikulecka A, Druga R, et al. Long-term behavioral and morphological consequences of nonconvulsive status epilepticus in rats. *Epilepsy Behav* 2004; **5:** 180–91.

87 Meldrum BS. Concept of activity-induced cell death in epilepsy: historical and contemporary perspectives. *Prog Brain Res* 2002; **135:** 3–11.

88 Lowenstein DH, Shimosaka S, So YT, Simon RP. The relationship between electrographic seizure activity and neuronal injury. *Epilepsy Res* 1991; **10:** 49–54.

89 Bauer G, Gotwald T, Dobesberger J, et al. Transient and permanent magnetic resonance imaging abnormalities after complex partial status epilepticus. *Epilepsy Behav* 2006; **8:** 666–71.

90 Salmenpera T, Kalviainen R, Partanen K, et al. MRI volumetry of the hippocampus, amygdala, entorhinal cortex, and perirhinal cortex after status epilepticus. *Epilepsy Res* 2000; **40:** 155–70.

91 DeGiorgio CM, Heck CN, Rabinowicz AL, et al. Serum neuron-specific enolase in the major subtypes of status epilepticus. *Neurology* 1999; **52:** 746–49.

92 Adachi N, Kanemoto K, Muramatsu R, et al. Intellectual prognosis of status epilepticus in adult epilepsy patients: analysis with Wechsler Adult Intelligence Scale-revised. *Epilepsia* 2005; **46:** 1502–09.

93 Litt B, Wityk RJ, Hertz SH, et al. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* 1998; **39:** 1194–202.

94 Lowenstein DH, Aminoff MJ. Clinical and EEG features of status epilepticus in comatose patients. *Neurology* 1992; **42:** 100–04.

95 Osorio I, Reed RC, Peltzer JN. Refractory idiopathic absence status epilepticus: A probable paradoxical effect of phenytoin and carbamazepine. *Epilepsia* 2000; **41:** 887–94.

96 Dreifuss FE, Rosman NP, Cloyd JC et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998; **338:** 1869–75.

97 Collins M, Marin H, Rutecki P, Heller D. A protocol for status epilepticus in a long-term care facility using rectal diazepam (Diastat). *J Am Med Dir Assoc* 2001; **2:** 66–70.

98 Scott RC. Buccal midazolam as rescue therapy for acute seizures. *Lancet Neurol* 2005; **4:** 592–93.

99 Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: "the cure may be worse than the disease"). *Neurophysiol Clin* 2000; **30:** 377–82.

100 Ropper AH. Neurological und neurosurgical intensive care. Boston: Lippincott Williams & Wilkins, 2003.

101 Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. *J Clin Neurophysiol* 1999; **16:** 341–52.

102 Holtkamp M, Masuhr F, Harms L, et al. 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* 2003; **74:** 1095–99.

103 Limdi NA, Shimpi AV, Faught E et al. Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–55.

104 Rossetti AO, Bromfield EB. Determinants of success in the use of oral levetiracetam in status epilepticus. *Epilepsy Behav* 2006; **8:** 651–54.

105 Patel NC, Landan IR, Levin J, et al. The use of levetiracetam in refractory status epilepticus. *Seizure* 2006; **15:** 137–41.

106 Bensalem MK, Fakhoury TA. Topiramate and status epilepticus: report of three cases. *Epilepsy Behav* 2003; **4:** 757–60.

107 Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus. *Eur J Neurol* 2006; **13:** 445–50.

108 Claassen J, Hirsch LJ, Emerson RG, et al. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology* 2001; **57:** 1036–42.

109 Holtkamp M, Othman J, Buchheim K, et al. A "malignant" variant of status epilepticus. *Arch Neurol* 2005; **62:** 1428–31.

110 Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. *J Neurosci* 1997; **17:** 7532–40.