Non-convulsive status epilepticus in adults – an overview

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Summary

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Status epilepticus (SE) is the most frequent neurological emergency requiring admission on the intensive care unit (ICU). The classification of status epilepticus may be dichotomised into the "convulsive" and the "non-convulsive" form. Whereas the diagnosis of generalised convulsive status epilepticus (GCSE) is easily made in view of the evident manifestation, the diagnosis of non-convulsive status epilepticus (NCSE) may become very difficult according to its non-spectacular and protean presentation. Non-convulsive status epilepticus is a common cause of altered mental status and delirium; and a substantial number of comatose patients in the intensive care unit may suffer from NCSE. The most important part of making a diagnosis of NCSE is to think of it at all. The definite diagnosis of NCSE is dependent on electroencephalographic (EEG) confirmation. Repetitive or, optimally, continuous EEG recording may help to closely monitor seizure activity and to guide the therapy in order to protect the patient from under- and/or over-treatment. The interpretation of EEG recordings of NCSE may become challenging because of numerous artifacts caused by the patient, caregivers and devices, and because of trace elements of ambiguous significance and of waveforms mimicking epileptic activity.

Non-convulsive status epilepticus was historically subdivided into the groups of complex-partial status epilepticus (focal; CPSE) and absence status (generalised; AS). Most recently, a classification

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proposed by the International League Against Epilepsy (ILAE) has subdivided focal NCSE into aura continua (non-convulsive simple partial SE with maintained consciousness) and into dyscognitive SE (with impaired consciousness) of

abbreviations	
AED	antiepileptic drug
AS	absence status
BD	benzodiazepines
CISE	critical illness status epilepticus
CPR	cardiopulmonary resuscitation
CPSE	complex-partial status epilepticus
CSE	convulsive status epilepticus
CSF	cerebrospinal fluid
CT	computer tomography
CYP450	cytochrome P 450
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
EEG	electroencephalography
GCSE	generalised convulsive status epilepticus
HIV	human immunodeficiency virus
ICU	intensive care unit
IGE	idiopathic generalised epilepsy
LEV	levetiracetam
LZP	lorazepam
MDL	midazolam
MRI	magnetic resonance imaging
MSE	myoclonic status epilepticus
NCSE	non-convulsive status epilepticus
PET	positron emission tomography
PHT	phenytoin
PLED	periodic lateralised epileptiform discharges
RSE	refractory status epilepticus
SE	status epilepticus
SGSE	secondarily generalised status epilepticus
SPECT	single-photon emission computer tomography
TPW	triphasic waves
VPA	valproic acid

mesial temporal or neocortical origin. Several patients with focal NCSE or AS were known for pre-existing epilepsy. In addition, other types of NCSE have been reported, like "subtle" SE where convulsions in patients with GCSE clinically stop, but the continuous epileptic activity electroencephalographically still persists. Another variant belongs to those patients with critical illness where the serious disorder and/or medications may trigger an acute, prolonged and all too often very-hard-to-treat epileptic condition ("critical illness SE" [CISE]). The majority of these patients will never have had seizures before. Of note, none of the currently proposed classifications has gained broad acceptance and official approval.

Since the need for immediate and intensive treatment of GCSE is beyond debate, the insidiously calm presentation of NCSE may mislead to a much less aggressive therapeutic approach. However, experimental and clinical data suggest that continuous epileptic activity in the brain during NCSE associated with consecutive (glutamatergic) hyperexcitation triggers neurotoxicity and proapoptotic mechanisms which eventually may lead to irreversible brain damage and the onset of a chronic epileptic disorder or to an irreversible neurological deficit. Thus, recent national and international guidelines and reviews recommend immediate and intensive treatment for NCSE as well as for GCSE. With a few exceptions, the first drug is an intravenous benzodiazepine, mainly lorazepam; intravenous phenytoin or valproate should be started without delay. Persistence of NCSE after administration of these two classes of drugs heralds refractory SE (RSE) where single or combinations of drugs in anaesthetic dosages requiring intubation and enteral antiepileptics may be added except for the cases of AS or an underlying terminal disease. The outcome of NCSE is mainly determined by the type, duration, cause and the severity of concomitant diseases.

Keywords: non-convulsive status epilepticus; intensive care unit; diagnosis; electroencephalography; treatment; benzodiazepines

Introduction

Status epilepticus (SE) is the most common neurological emergency requiring treatment in the intensive care unit (ICU). After the first depiction almost 3000 years ago, SE has only gained increased attention since a few decades because of the improved availability of neurophysiological techniques, the better understanding of the mechanisms of seizure propagation and termination,

the advances in intensive care medicine and the growing number of antiepileptic drugs available for treatment. From an operational and clinical viewpoint, SE is divided into two main entities, convulsive SE (CSE) and non-convulsive SE (NCSE). Convulsive SE includes the focal and generalised (GCSE) forms, while NCSE encompasses all other non-convulsive forms of prolonged, not self-limited focal and generalised epileptic manifestations. While a widely accepted definition of GCSE exists, such a definition for NCSE is still lacking. The uncertainties in NCSE considerably augment with respect to the yet unresolved issues of types representing NCSE, the almost unknown epidemiology, the immense number of causes, the difficulties to determine the prognosis and, especially, to the debates about best treatment [1]. Although guidelines approved by specialty boards and neurological societies exist, they lack high-level evidence due to the almost absence of high-quality (level of evidence class I- or II-) studies. Thus, several important issues regarding NCSE urgently need further investigation: How to improve awareness of NCSE? Which clinical signs point to the presence of NCSE? Is there a valid score to build? Which is the best treatment? What is the role of the newer antiepileptic drugs? The value of steroids or other immunotherapeutics in the treatment of NCSE is still unclear, but increasing, mainly experimental, evidence points to an important contribution in RSE. On the more pathophysiological level, the crucial question "Does non-convulsive status epilepticus damage the brain?" is still waiting for a conclusive answer. Basic and clinical research on the mechanisms and treatment of NCSE may enormously profit from the formation of a worldwide and interdisciplinary network. The present article tries to address these issues in the light of the current literature; it has to be considered as a momentarily valuable, but not definitively evident and conclusive statement.

History

The term "status epilepticus" was introduced in 1824 by Calmeil as the French expression "état de mal" when he was writing his thesis on the experiences he had made at the Salpêtrière and Charenton Asylum [2]. While the ancient Greek-Roman medicine assumed that epilepsy and seizures may be an impressive but not lethal disease, the probably very first account of SE and its serious prognosis can even earlier be found on the Neo-Babylonian Akkadian cuneiform in the 25/26 Sakikku (718–612 BC) [3]. Almost half a

century after Cameil, the term "status epilepticus" appeared for the first time in a textbook of clinical medicine when Bazire translated Trousseau's book "Leçons en Médecine Clinique" [4]. At that time, it became clear that there were different types of SE, the obvious form with convulsions as well as the more "silent" variants of the "dreamy state" or the "fugue épileptique" or the prepsychotic "twilight states", well depicted by the eminent French (Charcot, Bourneville, Trousseau) and British (Jackson, Gowers) neurologists. The advent of clinical electroencephalography (EEG) [5] allowed for better differentiation of the clinically almost indistinguishable states of purely postictal alterations and non-convulsive status epilepticus. The typical EEG picture of absence status (AS) was discovered by Lennox and co-workers [6]. The occurrence of long-lasting, continuous neurological signs as a result of epileptic activity recorded by EEG was presented in a hallmark paper by Scott and Masland in 1953 [7]. Penfield and Jasper reported the existence of continuous somato-sensory SE for which they coined the term "aura continua" [8]. Landolt emphasised the usefulness of EEG for the discrimination between AS and complex-partial SE (CPSE) which clinically often are barely to distinguish [9]. Karbowski having organised a symposium on psychomotor status (i.e. CPSE from temporal origin) in 1979 compiled 36 already published and eight own cases, all supported by EEG, in the conference monograph [10]. The Xth Marseille Colloquium on Epilepsy held in 1962 was the first conference devoted to classify the various forms of SE. However, there were "as many forms of SE as types of seizures exist" as Gastaut stated, and the classification was only published 8 years later and received almost no attention [11]. Despite the Santa Monica Meeting on SE in 1980 [12], SE was not included in the still valid "Classification of Epilepsy and Epileptic Syndromes" of the International League Against Epilepsy (ILAE) of 1989 [13]. The most recent attempts of a classification of SE have come from the ILAE and the Cleveland Clinic Group [14, 15], and, with special regard to NCSE, from Shorvon [16, 17].

This lack of a broadly accepted classification is the more unsatisfying, as it impedes research efforts for better epidemiological treatment and prognostic data, and as it obscures prognosis and stronger evidence for the treatment of particularly NCSE.

Definition

There is no accepted definition of NCSE. One carefully elaborated definition recently proposed by Shorvon states: "Non-convulsive status epilepticus is a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in non-convulsive clinical symptoms." [16, 17] These clinical symptoms mainly include focal deficits like aphasia and amnesia, an impairment of consciousness or an altered behaviour ranging from stupor and coma to delirium and frantic psychosis. Occasionally, automatisms or subtle facial, periorbicular, abdominal and limb twitches, tonic eye deviation or spontaneous (mostly horizontal) nystagmus-like movements, and extensor response(s) of the big toe(s) may be present [18].

How long is prolonged? Thirty minutes were the historically determined duration of GCSE [19]; however, this view has been challenged after the hallmark Veterans Affairs-study published in 1998, evaluating the best first-line treatment of GCSE [20], by Lowenstein et al. who proposed a substantially shorter duration of five minutes [21]. This proposal was adopted by several groups and incorporated into national guidelines, like the Swiss one [22]. In the case of NCSE, the situation is much more equivocal as an expert panel first recommended 60 minutes [19], whereas Jordan six years later proposed 15 to 30 minutes [23] and the most recent comprehensive overview has reiterated a duration of 30 minutes [24]. The author favours a much shorter duration of five minutes identical to the one used in GCSE. This opinion relies on two pivotal facts: first, from the brain's perspective, it does not make a big difference whether a motor neuron or a non-motor neuron is exposed to prolonged continuous epileptic discharges – both neurons risk to be damaged by excitotoxic mechanisms leading to neuronal death and impaired neurological function. Second, sound data supports the observation that 80% of seizures last less than one minute and more than 90% are terminated within two minutes, i.e., self-terminating seizures persisting for five minutes or more may be very rare and indicate that the usually self-restricting, inherent antiepileptic mechanisms were insufficient and fail to stop the epileptic activity [25–27]. It is also important to underscore that the shorter the time of diagnosis and the start of treatment of NCSE are, the faster NCSE can be stopped and the better its outcome may be. Conversely, delayed diagnosis and therapy of NCSE may result in a vicious circle of progressive brain damage and increasing resistance to the antiepileptic drugs applied which all together then may prolong the duration of NCSE and impair its treatment and prognosis [28–36].

Types, clinical and electroencephalographic manifestations of NCSE

In general, NCSE in adults is subdivided into the two main groups of focal and generalised NCSE, where simple-partial SE (SPSE) and CPSE, and AS are the principal types, respectively [37]. The most recent proposal of classification has been created by a group of foremost experts in the field of epilepsy on behalf of the ILAE [14]. However, this group too was unable to unanimously settle with their own proposal what may reflect the difficulties encountered in establishing a useful and correct classification of seizure, epilepsy and status epilepticus. The group introduced the term "aura continua" globally encompassing all forms of non-convulsive SPSE where maintained consciousness is a prerequisite. Thereby, they left the more restricted definition of "aura continua" of Penfield who assigned only the forms with continuous somatosensory sensations to "aura continua". The ILAE also replaced CPSE by the term "dyscognitive" SE making an additional subdivision into those forms attributed to derive from the "mesial temporal" and those from the "neocortical" brain areas. Both forms essentially require impaired consciousness. While the forms originating from the mesial temporal lobe regions may be summarised as "limbic status" manifesting with limbic sensations, the manifestations of the neocortical forms reflect the region of origin involved – in the case of aphasia, for example, the inferior frontal lobe or the superior temporal gyrus.

With respect to the advent of advanced life support and the astounding progress of (critical care)

medicine the author of this review would like to introduce a third group of subtypes of NCSE concerning seriously affected patients in intensive care units (ICU). This group will be called "critical illness SE" (CISE) and more extensively delineated below. An overview of the different types of NCSE is given in figure 1.

The primary generalised NCSE may occur as typical or atypical AS, where the former is present in adults with a known history of idiopathic generalised epilepsy (IGE). The onset of typical AS is almost always precipitated by a medication error, malcompliance or provocative factors, like fever and infection or sleep disturbances; clinically the patients show a confusional state, but often were able to perform complex activities of daily living. Duration can last from half an hour up to weeks [38–40]. The EEG shows the classical generalised 3/sec spike-wave pattern; the interictal background activity is normal. Atypical AS in adults may manifest either in patients with complex epileptic syndromes or "de novo" in patients without history of epilepsy. Clinical differentiation of atypical from typical AS may be difficult; however, the presence of additional subtle signs like eyelid myocloni, perioral automatisms has been proposed to rather point to atypical AS. Some authors suggest that the level of impaired consciousness and the deficits in performing complex tasks may be more pronounced [24]. The EEG shows less regular spike-wave activity of 2.5–4 Hz and the interictal background activity is slow [41]. The "de novo" AS in adults results from benzodiazepine withdrawal in the majority of cases, but it may also occur without any precipitating factor [42]. The EEG is characterised by spike-wave activity of markedly unstable frequency ranging from 0.5 to 4 Hz (fig. 2).

The clinical manifestations of aura continua are as various as there are distinct focal neurological non-convulsive deficits. Aura continua manifests with the typical "plus" symptoms of the involved cortical area and its adjacent tissues in the form of somatosensory perceptions, illusions or hallucinations. The quality of the experience is determined by the localisation of the epileptic focus, for instance, aura continua originating in the temporal lobe manifests by gustatory, olfactory, auditory or rising epigastric sensations, while somatosensory and visual illusions or hallucinations point to a parieto-(temporo-)occipital focus. The unspectacular appearance of aura continua may have led to only a few of publications; nevertheless, these forms of NCSE may be by far more frequently present in clinical practice. Other rare manifestations of aura continua include the opercular type with pharyngeal myoclonus and anarthria [43], the inhibitory

Figure 1 Types of non-convulsive status epilepticus.

The three main groups are the (primary) generalised (red), the focal (blue) and the group of acutely and severely affected patients with markedly impaired consciousness (green).
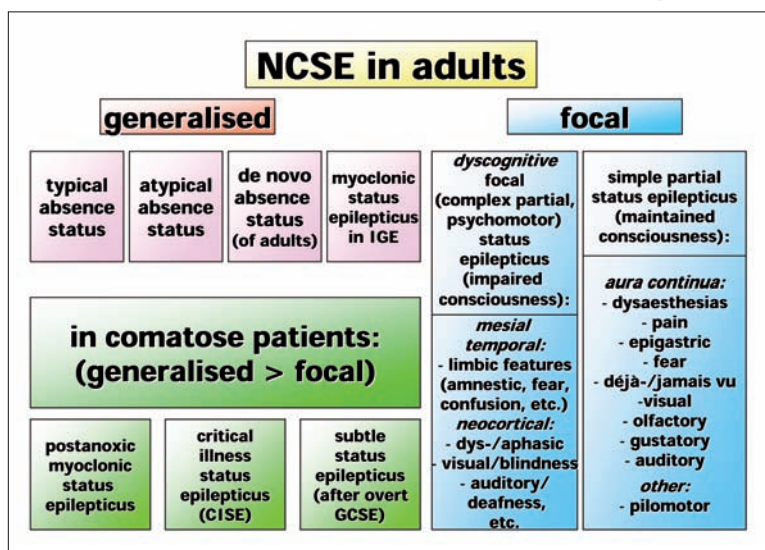
(paretic, aphasic and amaurotic), emetic, pilomotor and the gelastic types [44–50]. The surface EEG shows focal slowing with repetitive, regular and/or irregular spike-wave discharges of various frequencies (fig. 3 and 4).

Patients with cognitive, purely amnesic limbic or isolated fear SE were at the borderline between aura continua and dyscognitive SE of the mesial temporal supgroup according to the ILAE classification [51–55]. The surface EEG often eludes

Figure 2   EEG in absence status.

35-year-old computer engineer, having acute phases of confusion, but during them is able to drive a car. No intake of medication nor illicit drugs. Emergency EEG about 5 hours after start of confusional state. Patient walks around and talks intelligibly, however, he was unable to add 5 + 7. Note the aperiodic, but almost continuously generalised epileptic spikes and spike-wave discharges (1–2.5 Hz), pronounced over the frontal regions (fig. 2a). After administration of 5 mg lorazepam, the epileptic activity disappears and is replaced by an almost normal background alpha activity (fig. 2b).

a

b
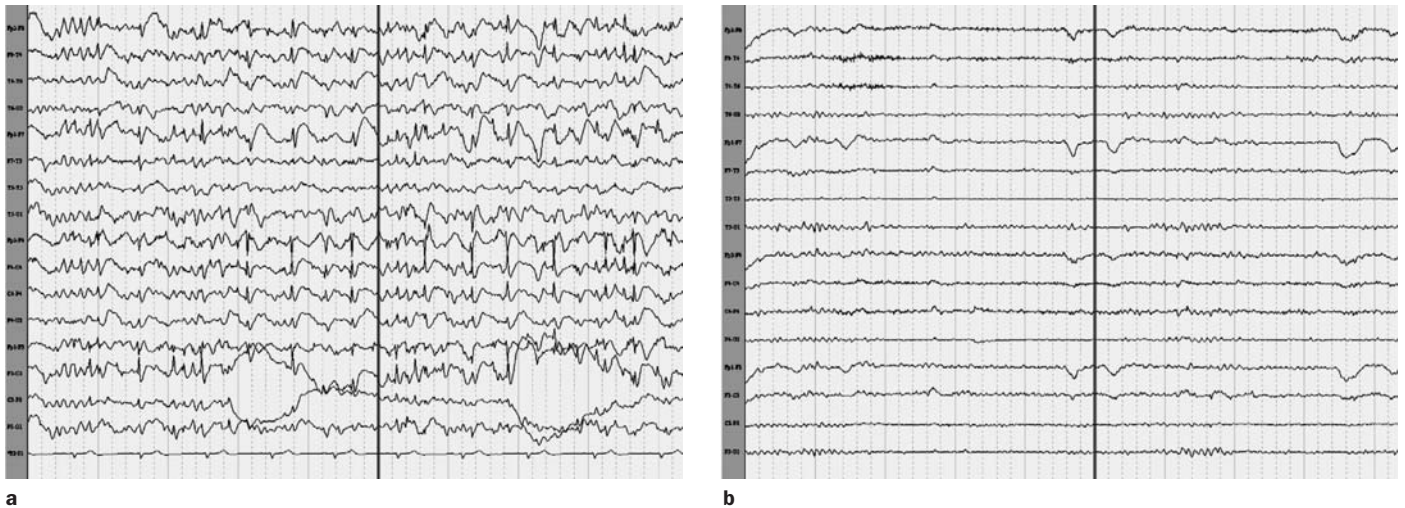
**Figure 3**   Aura continua with tonic spasms of the right leg.

38-year-old business man, operated for parietal meningeoma six months ago. Levetiracetam tapered to 500 mg/d. Start of feelings of "something is wrong in my head" followed by permanent spasms and short subtle myocloni of the left leg two days before admission. The EEG shows right parieto-central almost continuous beta activity typical of tonic seizures, intermingled with small spike-like discharges with phase reversal over electrode C4, the motor cortex region of the left leg.

Figure 4   Aura continua with repetitive adversive seizures.

82-year-old woman without pre-existing medical history presenting with speech arrest and prolonged adversive head version to the left. EEG showing slightly irregular/aperiodic spike-wave discharges mainly on the right lateral brain regions with extension to closer to the midline interrupted by short episodes of rhythmic delta waves (fig. 4a–c). This pattern may resemble periodic lateralised epileptiform discharges (PLEDs), but is sometimes slightly irregular (aperiodic) and – together with the clearly ictal semiology – was viewed to reflect epileptic activity which responded well to the application of lorazepam (fig. 4d). Repetitive brain imaging and CSF examinations did not reveal a causative process and the dyscognitive status epilepticus was considered to be of kryptogenic origin.

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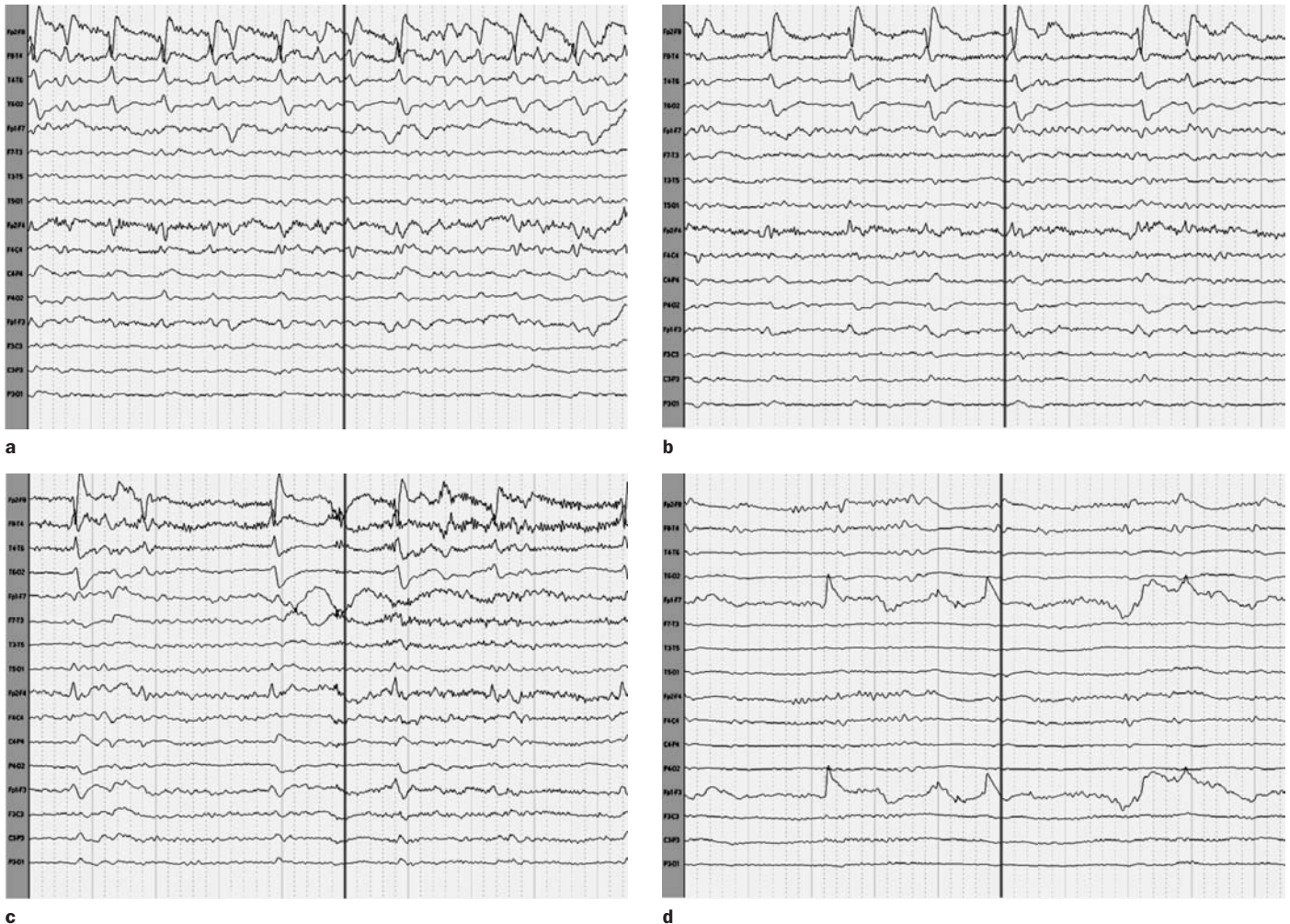
Figure 5   Symptomatic dyscognitive status epilepticus.

74-year-old retired high-school teacher suddenly experiencing sensorimotor aphasia, stupor and right-upper-sided eye deviation. EEG showed continuous periodic abortive spike-wave discharges, i.e. PLED, over the left hemisphere with predominance in the parieto-temporo-occipital region and also extending to the contralateral right side (fig. 5a). Administration of lorazepam immediately led to abolition of stupor, exe deviation and global aphasia; however, profound sensory (Wernicke's) aphasia persisted (fig. 5b). Eventually, diffusely expansive glioblastoma multiforme originating from the left parieto-occipital territory was found.


a

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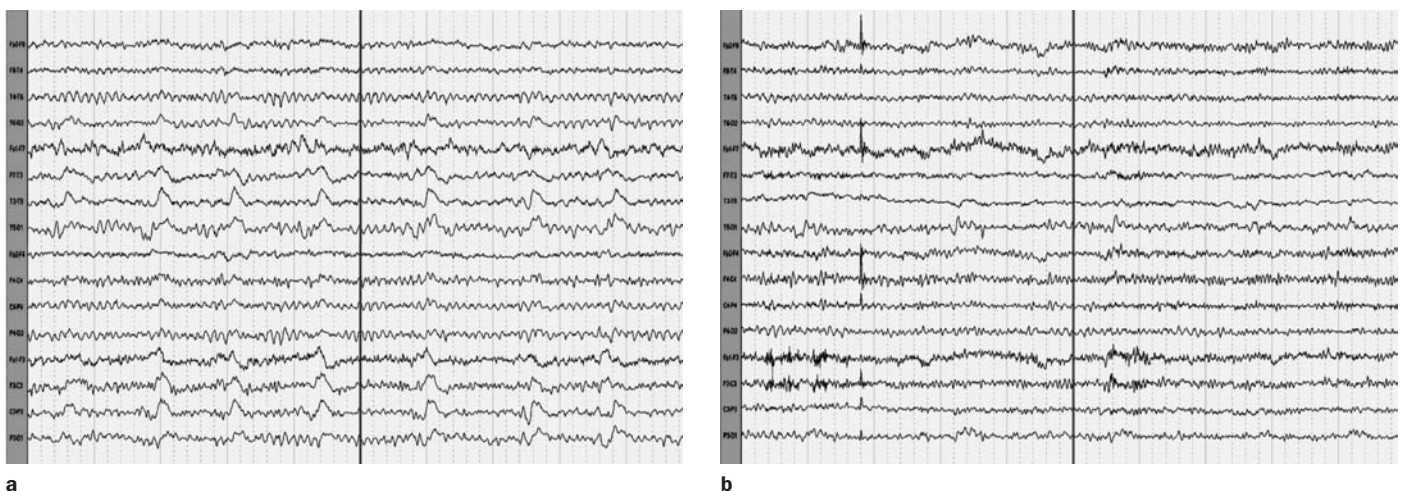
recognition because of the localisation of the focus in the deeply "covered" limbic structures [53] or the ictal activity is represented by rhythmic mid-temporal high-amplitude delta waves [56].

Dyscognitive SE (formerly CPSE) belongs to the group of focal NCSE in which an impairment up to the complete loss of consciousness is mandatory [14, 57]. In addition to the key cognitive and

Figure 6 Subtle status epilepticus / symptomatic dyscognitive status epilepticus.

55-year-old man suffering from pneumococcal sepsis with meningo-encephalitis, undergoing repetitive tonic-clonic generalised seizures, but later showed periodic episodes of tonic head version to the left. Continuous EEG shows short phases of slow low-amplitude theta-delta activity (fig. 6a) with series of repetitive seizures starting from the right temporo-central region with low-amplitude high-(beta) frequency discharges typical of initiation of tonic seizures (fig. 6b). This activity evolves into higher-amplitude slower epileptic discharges over the next ca 90 sec (fig. 6c–e) with attenuation over the next ca 80 sec (fig. 6e–h) when a new seizure starts from the right parietal region (fig. 6h–l). The patient did not regain consciousness within the seizures. These episodes were considered to represent "subtle" SE. The patient was aggressively treated with midazolam anaesthesia, intravenous phenytoin and levetiracetam and high-dose topiramate by nasogastric tube and recovered well.
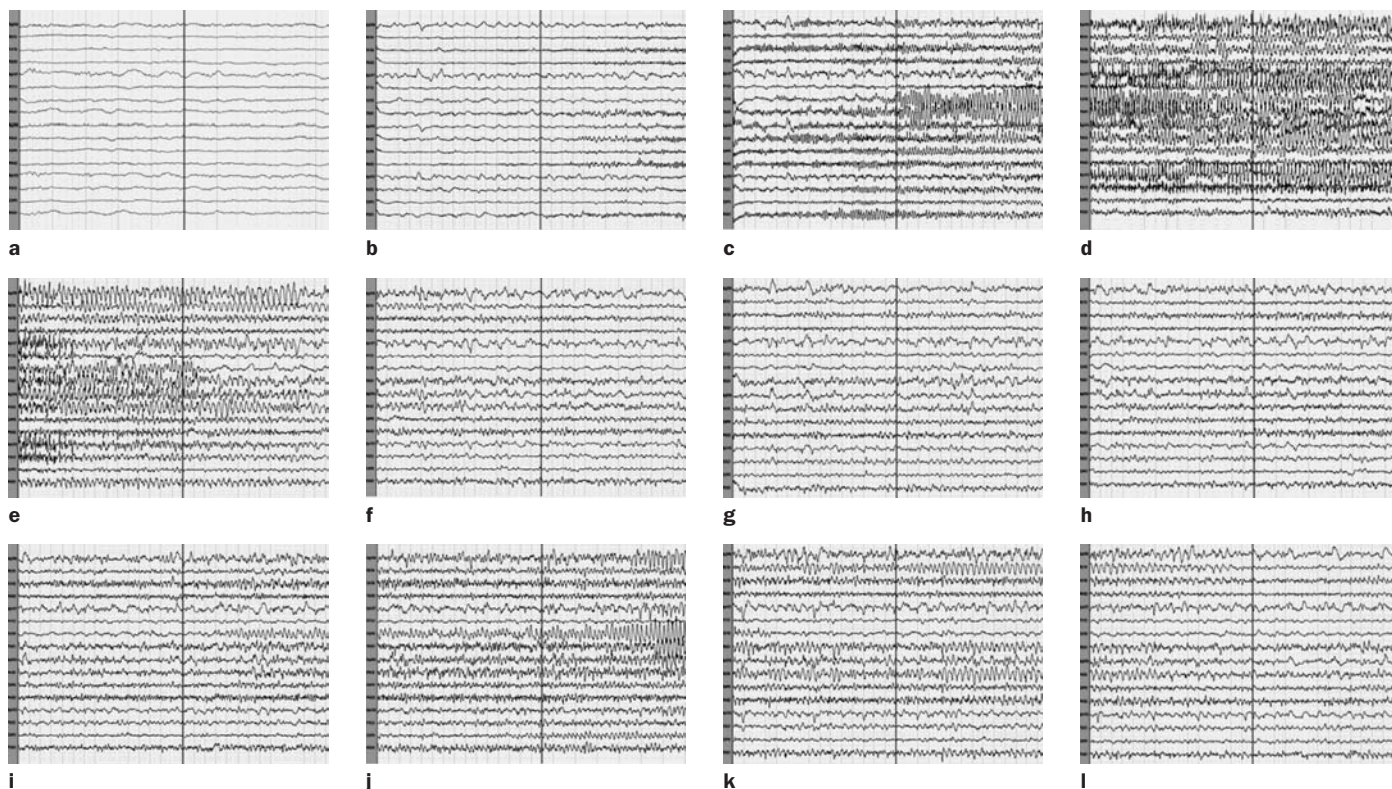
Figure 7 Drug-induced generalised critical illness status epilepticus.

89-year-old man admitted to another hospital for abdominal pain. Sigmoid diverticulitis was suspected and treated with the 4th-generation cephalosporine cefepime. The patient slowly became comatose and he was referred to the tertiary care centre. Head CT and CSF were normal. The EEG showed almost absent background activity replaced by generalised partially rhythmic delta activity mixed with a few multifocal epileptic spikes (fig. 7a). After administration of 1 mg midazolam, the patient immediately regained consciousness and started to talk relentlessly; theta background activity reappeared (fig. 7b). Some days later he returned home in a good condition.
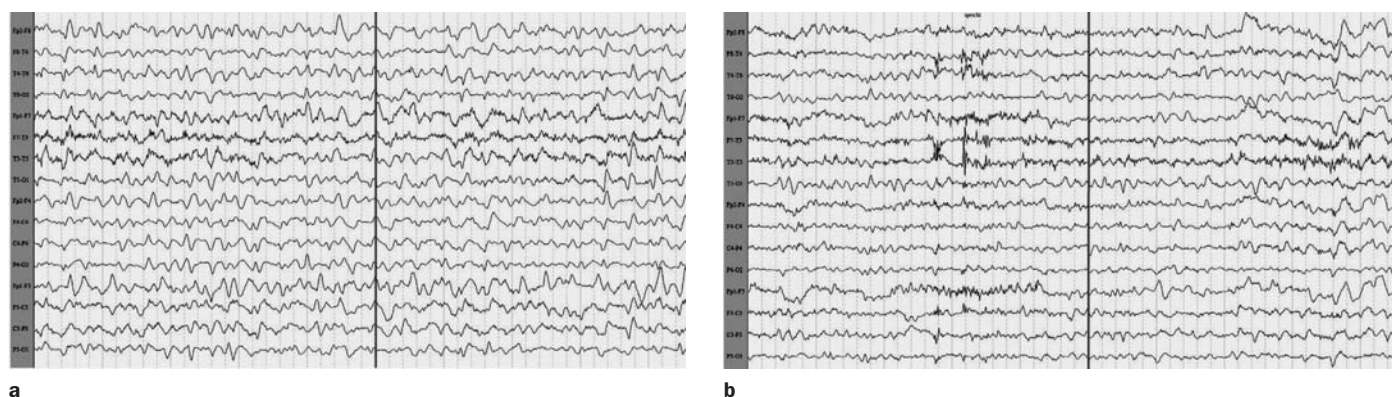
behavioural changes, some subtle clinical signs like discrete nystagmus, automatisms, muscle twitching, (unilateral) mydriasis or extensor response upon plantar stimulation may be present. Dyscognitive SE usually originates from the temporal and less frequently from the frontal lobes [58–61], rarely it originates from the parietal or occipital lobes. The long-lasting episodes of dyscognitive SE often

Figure 8A Triphasic waves or epileptic discharges? Stimulus-sensitive triphasic waves.

57-year-old woman with subarachnoid haemorrhage (Fischer Grade IV) and clipping of aneurysms of the left anterior and medial cerebral artery. The patient remained at GCS 4–6 without sedation. The EEG revealed a biphasic curve pattern with slowed background activity and focal slowing in the delta/subdelta range in the left frontal region (fig. 8A-a) which spontaneously or after acoustic stimulation (fig. 8A-b) changed into high-amplitude serial triphasic waves (fig. 8A-c).


a   b   c
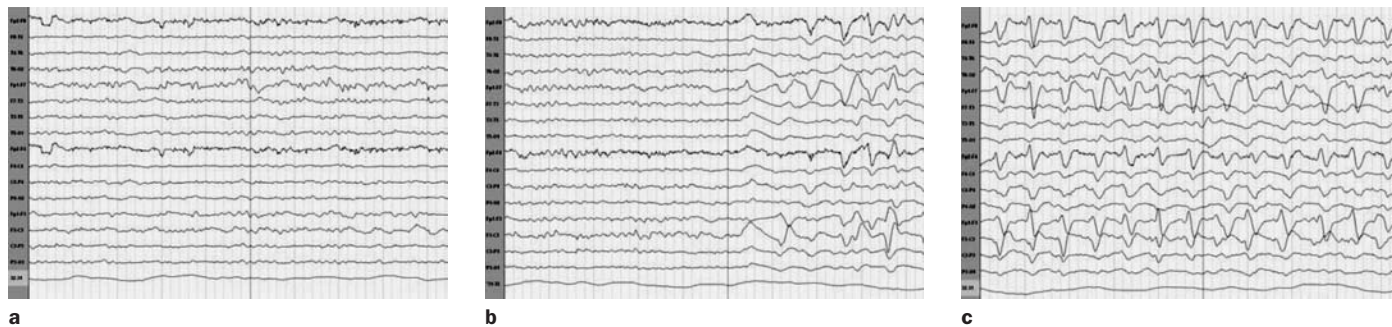
Figure 8B Triphasic waves are sensitive to benzodiazepines.

45-year-old woman with end-stage metastatic leiomyosarcoma of stomach undergoing chemotherapy with high-dose ifosfamide. The patient was comatose. The EEG showed almost continuous generalised, frontally accentuated triphasic waves and a few multifocal epileptic spikes (fig. 8B-a). These triphasic waves were markedly reduced in amplitude after administration of 5 mg of lorazepam (fig. 8B-b).

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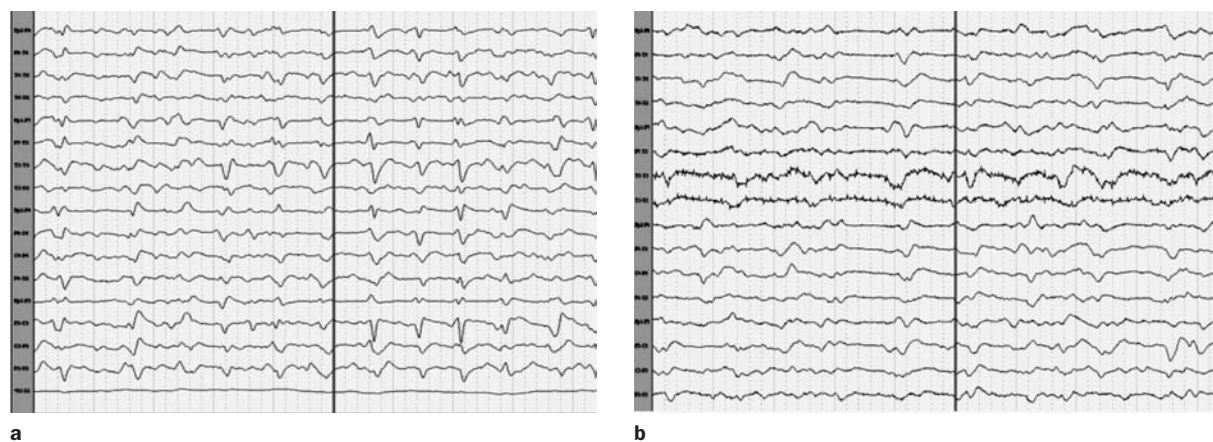
Figure 8C Triphasic waves resulting from accumulation of opioids – response to the opioid antagonist naloxone.

74-year-old man undergoing pancreatojejunostomy for pancreatic cancer. Postoperatively, he had multiorgan failure. Analgetic management included fentanyl. The patient did not regain consciousness and NCSE was suspected. The EEG revealed permanent rhythmically generalised, frontally accentuated triphasic waves mixed with some multifocal epileptic discharges (fig. 8C-a); the triphasic waves almost completely disappeared after administration of naloxone while the epileptic discharges persisted (fig. 8C-b).


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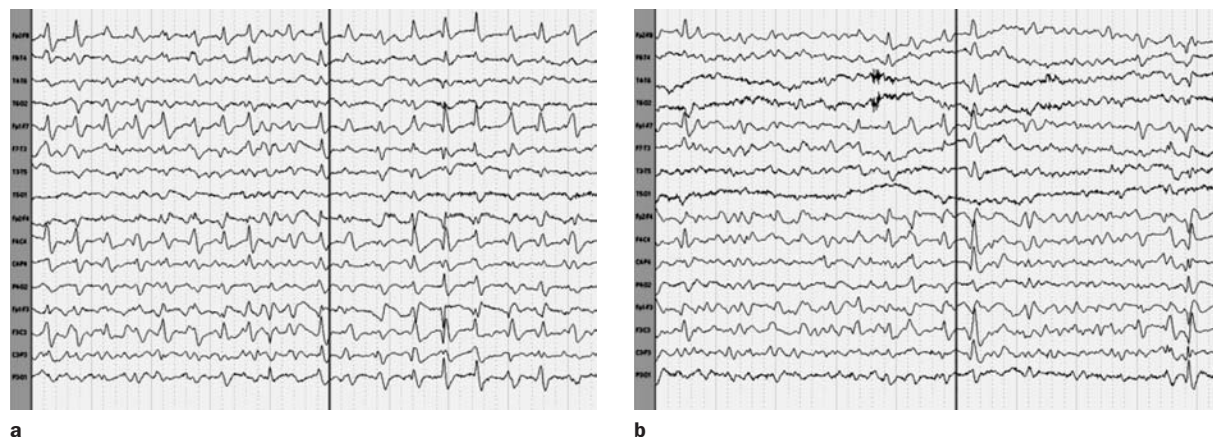
are also called "psychomotor status", emphasising the "strange" coincidence of severely impaired consciousness and altered behaviour together with an almost perfectly preserved functioning of the

Figure 9 Postanoxic myoclonic status epilepticus – differentiation from generalised convulsive status epilepticus.

79-year-old man undergoing aortocoronary bypass surgery. Some hours later on the same day he had cardiac arrest and was electromechanically resuscitated during 10 minutes. He had repetitive subtle generalised myoclonic seizures. The EEG revealed a slow low-amplitude background activity (fig. 9a) alternatively changing with generalised epileptic spike-wave discharges of 1 Hz (fig. 9b) which ceased after the administration of lorazepam and resulting in a diffusely spreading, non-reactive, frontally accentuated theta activity, a so-called theta coma often seen in postanoxic encephalopathy (fig. 9c). The patient did not regain consciousness and died 13 days later from septic pneumonia.
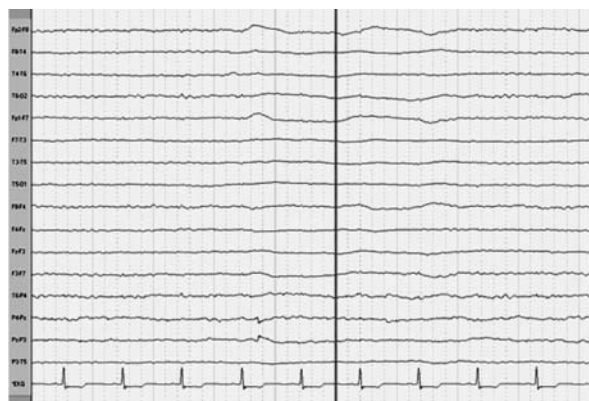
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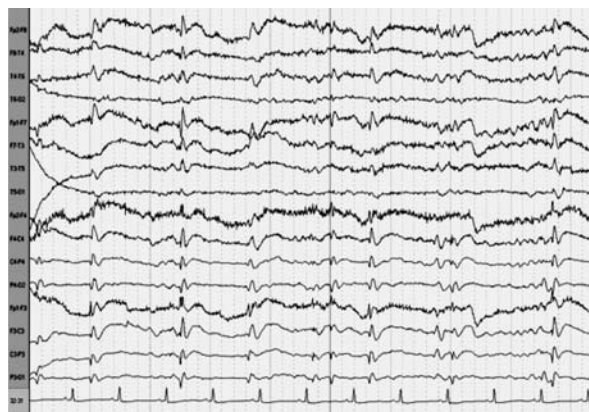
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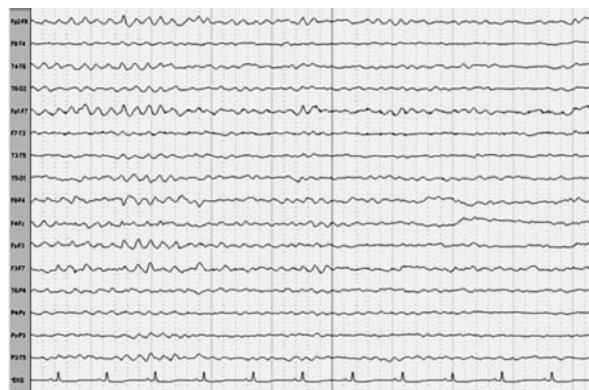
c

motor system allowing for extensive and often seemingly purposeful activities. It is well understandable that these episodes often were believed to be of "psychogenic" origin by the lay people already a long time ago [62]. In fact, the differentiation of this type of dyscognitive SE from non-epileptic conditions without EEG and by pure clinical means may become challenging even for the skilled epileptologist [63, 64]. The differentiation of NCSE from non-epileptic psychogenic pseudostatus is very important since the treatment of pseudostatus as SE may put these patients at life-threatening risks [65, 66]. Furthermore, it may become especially difficult to diagnose dyscognitive SE in elderly patients in whom it is as frequent as of 40% [67–69]. Typical psychiatric manifestations of dyscognitive SE include delirium [67, 70, 71], stupor or catatonia [72, 73], mental slowing [74], cognitive decline [75], aggressive behaviour [76] and psychotic depression [77]. When spreading to the neocortical areas of the temporal lobes, auditory or visual hallucinations may occur [78, 79]. The EEG of dyscognitive SE is characterised by irregular or regular focal spikes or spike-wave activity similar to the one observed in aura continua; however, the ictal activity in dyscognitive SE tends to involve a larger area which increases the likelihood to detect it by surface EEG (fig. 5) [80, 81].

In this context, the significance of "periodic lateralised epilepti*form* discharges" (PLED), as they are present in figures 4a and b and figure 5a, should be discussed. The EEG pattern of PLED was first described by Chatrian et al. [82] and denotes periodic lateralised spike(-wave)-like activity of about 0.5–1.5 Hz which may occur after a variety of cerebral events like tumours, bleedings and ischaemic strokes. They often persist for weeks and months and may poorly respond to antiepileptic treatment; the authors already doubted their true epileptic nature by choosing the term "epilepti*form*". However, he also occasionally observed PLED of epileptic nature. Pohlmann-Eden et al. in their seminal review proposed that PLED may not represent a specific single entity of pathological EEG activity, but a continuum ranging from rather benign epileptiform activity to clear-cut continuous ictal activity, i.e. SE [83]. This view was supported by later studies which stated that PLED following GCSE or serial epileptic seizures have to be considered as an ictal pattern; these PLED also responded to antiepileptic treatment [84]. The study of Assal et al. by using SPECT elegantly showed that PLED following SE or repetitive seizures were coupled with hypermetabolism which switched to hypo-/(normo-)metabolism as

soon as PLED ceased, again pointing to PLED as an ictal pattern [85].

The last group includes the "critical illness SE" (CISE) where patients experience NCSE because of (multi-)organ failure and/or often complex polypharmacotherapy [18]. The most frequent type observed clinically and electroencephalographically resembles dyscognitive SE with often secondary generalisation. The background activity in the EEG is usually very slow, and serial epileptic seizures without interictal recovery of the patient (instead of continuous epileptic activity) might be observed (fig. 6). Some of the CISE were induced by drugs, notably those targeting the CNS, but also antibiotics, like carbopenems, chinolones

(gyrase inhibitors) and most prominently, the fourth-generation cephalosporine cefepime [86–88]. These CISE mostly show a generalised ictal pattern with a very polymorphous background slowing, rhythmic delta activity and multifocal or generalised spike-wave activity. The EEG may also display triphasic waves (TPW) (fig. 7) which may become very rhythmic and sharply contoured, mimicking spike-wave activity of (NC)SE. However, these TPW were not ictal, but reflect encephalopathy [81, 89]. Although first described in the context of hepatic encephalopathy [90, 91], TPW may occur in any other type of encephalopathy, like renal, postanoxic and drug-induced (cytostatic drugs, opiates) encephalopathy. Importantly, TPW

Figure 10 Postanoxic myoclonic status epilepticus with subclinical seizures.

81-year-old man undergoing cardiac arrest and cardiopulmonary resuscitation. He was treated with midazolam anaesthesia for 3 days, but did not awake after stopping anaesthesia. The EEG showed a non-reactive, very low amplitude (sensitivity of 2 µV/mm) fast beta activity of 20–25 Hz (fig. 10a). This background activity was interrupted by extensive bursts of generalised myocloni, most probably originating from the reticular brain-stem region ("reticular myoclonus") (fig. 10b). But there were also generalised seizures with evolving delta activity, sometimes intermingled with the myoclonic bursts (fig. 10c–f). This activity eventually responded to anaesthesia with propofol and midazolam (fig. 10g). Nevertheless, the patient died 2 days later of non-epileptic complications.

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g
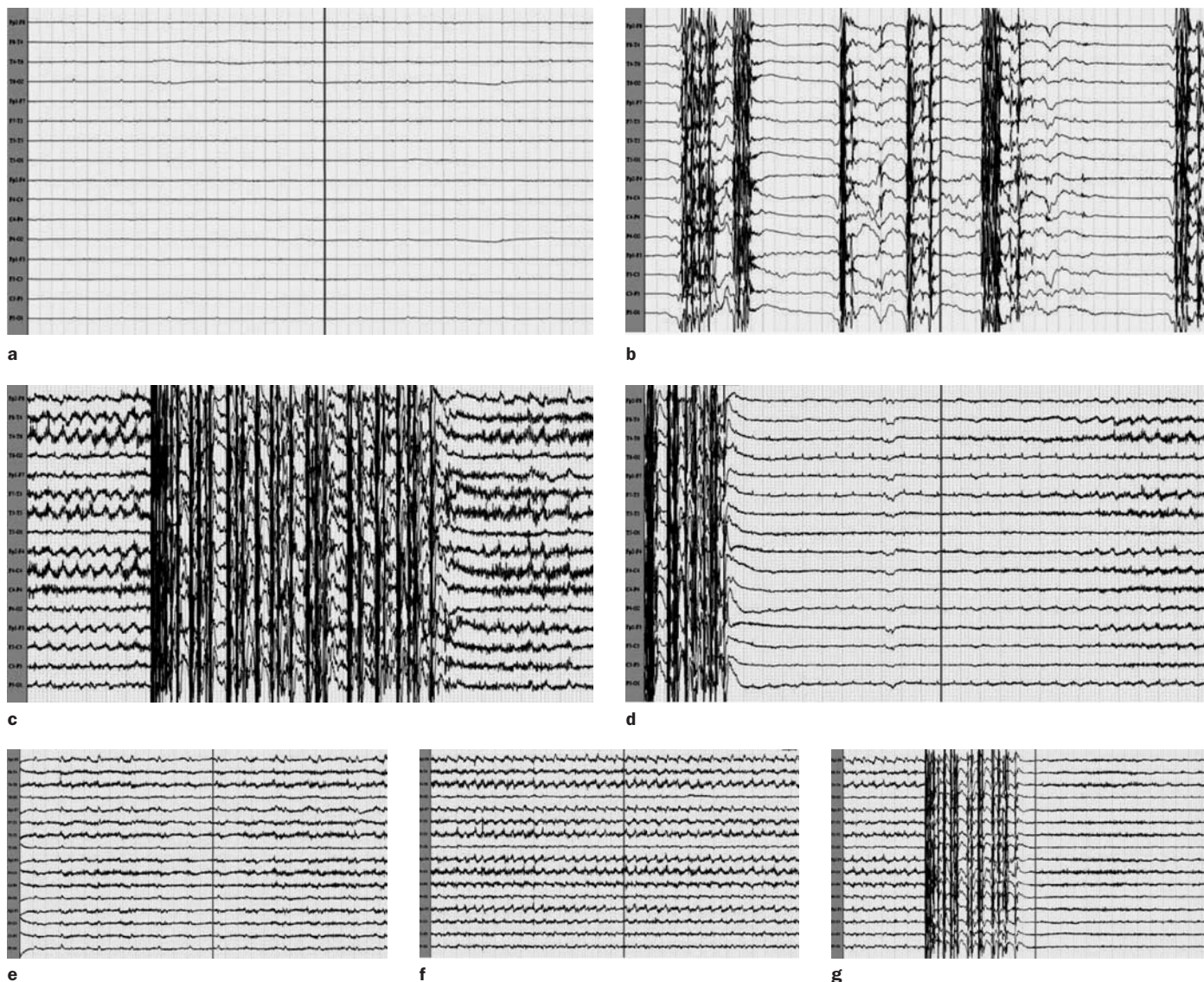
may disappear after administration of benzodiazepines (fig. 8a and 8b) (or naloxone in the case of opiate-overdose [fig. 8c]) [92, 93]. Thus, the response of this EEG pattern to benzodiazepines does not help to distinguish TPW from ictal spike-wave activity. A more detailed analysis for the differentiation of NCSE from TPW is given by a recent study by Boulanger et al. [94].

Figure 11 Generalised subtle myoclonic status epilepticus.

64-year-old woman undergoing cardiopulmonary resuscitation after ventricular fibrillation. She remained comatose and had bilateral eyelid myoclonus, tonic left upper gaze deviation and irregular body myocloni. The EEG revealed generalised (slightly a-)periodic epileptiform discharges (GPED) which – together with the subtle ictal semiology – were considered to be of epileptic nature (fig. 11a). The initial response to intravenous midazolam led to the suppression of the epileptic discharges (fig. 11b). However, the generalised epileptic discharges reappeared some hours later (fig. 11c) and neither high-dose midazolam nor propofol did abort this activity and barbiturates could not be administered because of the cardiac frailty. The patient died 3 days later.

Another subtype is called "subtle" SE, denoting those cases of NCSE which smoothly develop from preceding overt GCSE, a concept built upon the experimental work of Treiman et al. [29] and clinically supported by DeLorenzo and colleagues [95].

The third subtype encompasses the postanoxic myoclonic SE (MSE) where patients experience bursts, clusters or continuous, focal or generalised, symmetric, rhythmic myocloni [96, 97]. Clinically and electrographically this state may be sometimes difficult to separate from the putatively non-epileptic, often symmetric reticular myoclonus [98]. Occasionally, stimulus-sensitive focal or generalised subtle myocloni associated with epileptic discharges in the EEG can be observed in patients after cardiopulmonary resuscitation (CPR); evolution from severely suppressed background activity into an ictal pattern and attenuation following administration of i/v midazolam represent seizure activity and not a purely encephalopathic pattern (fig. 9). Alternating reticular brain-stem and epileptic cortical activity can occasionally be recorded in EEG of patients after CPR (fig. 10). Subtle generalised MSE initially may respond to midazolam, but can become increasingly resistant to further treatment (fig. 11).

Several authors do not consider postanoxic myoclonic SE as a form of NCSE because its treatment very often clinically does not improve the general serious condition of the patient. However, continuous clinical and electrographical postanoxic (subtle) myoclonic epileptic activity *is* SE, irrespective of the lack of substantial response to treatment. This resistance to therapy may rather reflect the very severe global brain damage in these patients making recovery implausible (cf. also paragraph on prognosis).

Epidemiology

Sound epidemiological data about the incidence of NCSE and its subtypes are not available yet because of the lack of an accepted definition and as a result from using different criteria including and excluding some forms of NCSE. Additionally, it is likely that the protean, often unspectacular and calm presentation of NCSE is frequently missed, leading to a substantially underestimated incidence of NCSE when compared to GCSE with its self-evident clinical manifestation. There are five large population-based studies and an overview about the incidence of SE in general [99–104]. Their data are summarised in table 1a and 1b after being pooled and weighted according to their size; information about the incidence of specifically NCSE

Table 1a   Incidence of NCSE: synopsis of five population-based studies on the epidemiology of status epilepticus.

types of status epilepticus	Bologna (I)[a, e] (Vignatelli 2003) (n = 336.876) <4% non-whites	Marburg (D)[a, e] (Knake 2001) (n = 743.285) <4% non-whites	Geneva (CH)[a] (Coeytaux 2000) (n = 1.735.420) 4% non-whites	Rochester, MN (USA)[b] (Hesdorffer 1998) (n = ~544.215) 4% non-whites	Richmond, VA (USA)[a] (DeLorenzo 1996) (n = 202.774) *57% non-whites*
absence status	2.0	6.0	3.5	0.6 (3.3)[d]	1.0
CPSE	16.0	43.3	26.7	7.1[c] (38.9)[d]	3.0 (?)*
subtle	–	–	1.2	–	–
myoclonic	16.0	–	–	1.9 (10.4)[d]	2.0
(others)	7.0	4.0	6.4	1.2 (6.5)[d]	1.0
GCSE	9.0	14.0	33.1	4.6 (25.1)[d]	29
SGSE	41.0	19.3	13.9	2.9 (15.8)[d]	43 (?)*
other	9.0	13.4	15.2	–	21 (?)
total[b]	10.7	17.1	10.3	18.3	50
gender: ♂/♀[b]	9.7/11.5	26.1/13.7	12.1/7.8	23.2/13.1	not available

[a]   Values in per cent.

[b]   Incidences per 100 000.

[c]   Classification "partial" only, no further subdivision into "simple" or "complex".

[d]   *A substantial proportion of CPSE may be included in the category "partial, secondarily generalised".*

[e]   Adults > age 20 only.

*   Some cases of NCSE probably included in the group of SGSE.

and its subtypes is extracted as much as possible. The incidence of NCSE may be 6/100 000, representing about 40% of all SE; however, when looking at this proportion in a tertiary care centre where critically ill patients are more frequent, it may be markedly increased. About 8% of all comatose patients in a tertiary-care-centre ICU had NCSE [105]. It is important to use the EEG as an additional tool to examine patients in coma of unknown origin and know the various patterns of EEG changes associated with coma of both NCSE and metabolic encephalopathy, respectively [81, 89]. About two thirds of NCSE are dyscognitive SE. The incidence of NCSE in males is twice that of females.

Table 1b   Incidence of different types of NCSE according to the results of population-based studies on the epidemiology of status epilepticus.

	all studies percentual [%]	all studies, population-weighted percentual [%]	absolute per 100 000 p.	
non-convulsive forms				
absence status	3.16	3.71	0.531	
CPSE	25.58	29.67	4.219	
myoclonic	5.68	3.22	0.510	
subtle	0.24	0.58	0.060	
others	4.98	5.66	0.745	
total	39.64	42.84	6.065	39.80%
convulsive forms				
GCSE	22.04	25.38	3.647	
SGSE	26.60	19.54	3.559	
others	11.72	11.48	2.340	
total	60.36	56.40	9.173	60.20%
total	100.00	99.24	15.238	100.00%

Causes

Two general conditions have to be considered when looking at the causes of NCSE: first, NCSE in those patients with known epilepsy and, second, in those patients with no history of epilepsy.

The main reasons for NCSE in epileptic patients are changes in AED levels. They include lowering of levels by purposeful or inadvertent reduction of AED dosages, or by non-compliance [106]. Toxic levels of AED too may cause NCSE [107]. Almost all AED may provoke worsening of seizures or even of an epileptic syndrome in some patients [108]. The AED tiagabine, inhibiting the re-uptake of GABA from the synaptic cleft by blocking the GABA transporter-1, may induce NCSE by interference with the pre- and postsynaptic $GABA_{A/B}$ receptors and other mechanisms modulating transmitter release [109, 110]. Antiepileptic drug levels impaired by co-administration of other enzyme-inducing drugs may also facilitate the onset of NCSE. Other reasons may be inappropriate AED selection, for example, carbamazepine or phenytoin (PHT) for an IGE syndrome [111, 112]. Ex-

ternal factors, like fever, drugs, sleep shifts and deprivation, photic stimulation and hormonal changes also may trigger NCSE in epileptic patients [32].

Structural and metabolic-toxic changes are the principal causes of NCSE in patients without a history of epilepsy. Non-convulsive status epileptici resulting from structural alterations include acute events like intracranial haemorrhages, traumatic brain injuries and ischaemic strokes [113–116]. Subacutely, primary brain tumours and metastases may provoke NCSE [117–119]. Infections, like herpes encephalitis, neurosyphilis and Creutzfeldt-Jakob disease, may be associated with NCSE [120–122]. Chronically progressing conditions causing seizures encompass all the different forms of neurodegenerative disorders, like Alzheimer's disease, frontotemporal dementia spectrum, cerebral amyloid angiopathy, etc. [123, 124]. Several metabolic conditions may be associated with NCSE as an epileptic reaction to the changed cerebral physiological environment. Both hypoglycaemic and hyperglycaemic states may be associated with NCSE [125, 126]. Hyperthyroidism and hypothyroidism are causes of NCSE; while the first is known in thyrotoxic crisis [127], the latter occurs in myxoedema [128] or steroid-responsive encephalopathy associated with autoimmune thyroiditis (the former "Hashimoto encephalopathy") where NCSE occurs with a frequency of 10 to 15% [129–133]. Disturbances of sodium, potassium and calcium homoeostasis may be associated with NCSE [37, 78, 134–136]. Hypomagnesaemia induced by therapies with cis-platin, amphothericin B and so on can cause NCSE [137]. Numerous other (illicit and approved) drugs are known to lower seizure threshold (table 2). The most important drug causing NCSE is alcohol withdrawal and only very rarely alcohol intoxication [138]. It is of special interest to the neurologist that – beyond drugs like antibiotics, anticancer and immunosuppressive drugs – some antipsychotic drugs, antidepressants and some antiepileptic drugs (tiagabine, vigabatrine, gabapentin, carbamazepine, phenytoin) may cause NCSE [139]. This list would be incomplete if increasing age as "risk factor" for NCSE was not mentioned [140, 141]; an epidemiological study in the Hong Kong population showed a 3- to 8-fold increase in the incidence of SE [142].

Diagnosis and differential diagnosis

The diagnosis of NCSE relies on the combination of the patient's history, the clinical signs and the EEG. Sometimes, the clinical and electroencephalographic response to the administration of benzodiazepines may help to confirm the diagnosis. The broad range of clinical signs and symptoms were mentioned in the section on the different types of NCSE. Their protean, often unspectacular manifestations make it very difficult to diagnose NCSE on clinical grounds alone. Nevertheless, a remote condition facilitating the onset of an epileptic disorder, severely impaired consciousness and spontaneous eye movements (i.e. horizontal nystagmus) were significantly associated with the presence of NCSE [143]. A history of epilepsy may facilitate to think of NCSE; absence of such a history will not exclude the presence of NCSE in patients, since NCSE may often be the first manifestation of an epileptic condition in patients admitted to hospitals [30, 144, 145]. However, NCSE does not exclusively start in ICUs or hospitals, but also at home, in psychiatric institutions, in nursing homes and asylums.

According to Jordan, the following conditions warrant further evaluation regarding a possible diagnosis of NCSE [23]:
– episodes of blank staring, automatisms, aphasia or perseverations of actions;
– unexplained onset of impaired consciousness, especially if its level fluctuates;
– fluctuating aphasia without structural lesion explaining the aphasic deficit;
– impaired consciousness or mentation associated with minimal clinical signs, like eyelid, facial or truncal subtle myoclonus, horizontal nystagmus and spontaneous extensor position of one or both big toes;
– prolonged postictal state or postictal unawareness of longer duration than 15 to 30 minutes;
– protracted state of reduced alertness after brain surgery or any other surgery where cerebral functions are at risk.

To confirm the diagnosis of NCSE warrants the exclusion of other diagnoses. The differential diagnosis of NCSE encompasses acute stroke, inflammation (like limbic or paraneoplastic encephalitis), infection (like herpes simplex encephalitis), primary brain tumours and metastases in the nonmotor areas, "pure" psychiatric causes of delirium, stupor and delusions or hallucinations, and non-epileptic, psychogenic pseudostatus. Several approved and illicit drugs as well as metabolic and electrolyte alterations may produce neurological and behavioural states resembling NCSE without detectable ictal activity in the concurrently recorded EEG.

To conclude, the most important step in the diagnosis of NCSE is "to think of it at all!" [18]. In addition, the value of 24-hour availability of EEG

cannot be overestimated if NCSE is clinically suspected, but warrants definitive confirmation. The various EEG patterns of NCSE and its confounders were already presented in the "types of NCSE" section of this article; more detailed information is displayed in several excellent reviews elsewhere [37, 41, 56, 81, 89, 146].

The diagnostic value of other paraclinical examinations may depend on the very specific context. Thus, analysis of cerebrospinal fluid may help to diagnose an underlying CNS infection; unspecifically and as a bystander phenomenon, there may be pleocytosis of up to about 30 cells and slightly elevated protein levels in the CSF of non-infectious NCSE [147]. An increase of neuron-specific enolase upon NCSE was suggested [148–150]. The various imaging modalities may be of lesser value in the emergency diagnosis of NCSE, but may reveal valuable localisatory, structural (CT, MRI, DTI), pathophysiological (DWI, SPECT) and

Table 2 Drugs causing non-convulsive status epilepticus.

approved medications

CNS active drugs

neuroleptics
   especially: clozapine
   chlorpromazine
   olanzapine

lithium

antidepressants
   tricyclic (-"pramins")
   tetracyclic (maprotilin, mianserin)
   not (or even anticonvulsant): SSRI

stimulants
   theophylline
   appetite moderators
   (methylphenidate; effect not definitely determined)
   mid- and high-dose opiates
   flumazenil
   benzodiazepine withdrawal

antiepileptic drugs

tiagabine

vigabatrine

carbamazepine

phenytoin

antibiotics

penicillin (derivatives)
   penicillin G
   mezlocillin
   piperacillin

calvulanic acid

cephalosporins
   cefepime
   ceftazidime

gyrase inhibitors
   ciprofloxacin
   ofloxacin
   enoxacin
   exception: norfloxcain (does not cross the BBB)

carbopenems
   imipenem
   meropenem

anticancer drugs

ifosfamide

busulphane

immunosuppressants

cyclosporine

mycophenolate mofetil

tacrolimus

intravenous contrast mediums

antiarrhythmics

illicit drugs

tranquillisers/sedatives

benzodiazepine withdrawal

barbiturate withdrawal

opiates

mid to high doses of all opiates
   (low doses probably anticonvulsive)
   morphine
   heroin
   buprenorphine
   (hydr-)oxycodon

stimulants

cocaine

amphetamine

designer amphetamines
   paramethoxyamphetamine (PMA)
   paramethoxymethamphetamine (PMMA)
   (benzyl-)piperazines

alcohol

withdrawal

(excessively high intake)

Abbreviations:
BBB: blood-brain barrier; SSRI: selective serotonine
re-uptake inhibitors.

Figure 12 Pathophysiological aspects and sequelae of non-convulsive status epilepticus.
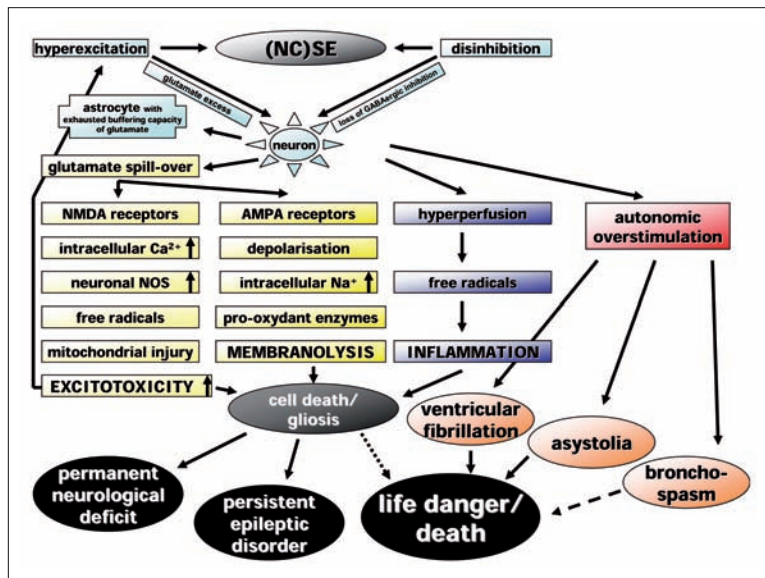
metabolic (PET) information about the involved brain areas, especially when used in a combined, complementary manner [151–154]. The readily availability, the ease of acquisition and the important information displayed in acute stroke placed DWI among the most performed imaging modalities, increasingly also in an emergency setting. In the context of NCSE, it is of note that hyperintense DWI changes (with or without reduced ADC maps) may also be observed. However, the hyperintensities in NCSE are very often less bright, show a very cortical pattern, often not exactly respecting a perfusion territory typical of a specific cerebral artery and they may disappear within 5 to 7 days – in contrast to the ischaemic DWI hyperintensities persisiting for 2 to 6 weeks [155–158].

Pathophysiological aspects

Pathophysiological aspects of NCSE are similar to those observed in the convulsive forms of SE on the cellular and local network (neuronal/astroglial) level, but they may be different on the level of the brain and the whole body [31, 159, 160].

Neurons, astroglial cells and small local networks affected by continuous epileptic activity of GCSE and almost all forms of NCSE (except for AS) display a cascade of electrochemical events triggered by the synchronous hyperexcitability. This hyperexcitability may result from a direct increase of excitatory mechanisms or a reduction of the local inhibitory network (i.e. disinhibition), or both of them. Hyperexcitability usually is linked with an excessive glutamatergic spillover of neu-

rons which also exceeds the capacity of glutamate-reuptake ("buffering") by astroglial cells. Toxic amounts of extracellular glutamate overstimulate glutamate receptors and induce a disruption of the extra-/intracellular Ca^{2+}-homoeostasis with accumulation of cytotoxic intraneuronal Ca^{2+}-concentrations. Excess of the second messenger Ca^{2+}-ion paralyses or overdrives numerous downstream metabolic processes vital for the neurons and may induce acute cell death or apoptosis [161]. The high energy demands of the hyperexcited neurons exhaust the pool of energy sources of the brain which is almost exclusively dependent on glucose. Energy failure leads to a loss of function of the Na^+/K^+-ATPase which is followed by a breakdown of the ionic transmembraneous homoeostasis and by subsequent concomitant water influx into the neurons and astroglial cells, cell swelling and death. As another consequence, toxic metabolites, nitric oxide formed upon activation of the neuronal and inducible forms of NO synthase, and radicals may accumulate intra- and extracellularly, and further act as cytotoxic substances, especially to cell membranes, or as chemoattractants for inflammatory cells. Eventually, there may be local destruction of functional brain tissue and gliosis with loss of function leading to persistent neurological deficits or the onset or aggravation of an epileptic disorder.

On the level of the whole body, GCSE has the additional consequence of exhaustive motor activity which will lead to profound metabolic changes such as lactic acidosis, hyperthermia and sympathetic overdrive in the phase of decompensation [162, 163]. When persisting, these factors may create an immediate life-threatening condition. In contrast, NCSE will not induce whole-body energy exhaustion with its metabolic sequelae because of the lack of excessive motor activity, but it is essential to note that continuous epileptic activity in non-motor brain regions, like in the temporal lobes or the insular and opercular cortex, may directly overstimulate autonomic sympathetic and parasympathetic centres which in turn may induce life-threatening autonomic hyper- or hypoactivity, most importantly ventricular arrhythmias or asystolia and bronchospasm [164]. An overview of these mechanisms is schematically drawn in figure 12.

Prognosis

The prognosis of a disorder in general refers to the outcome with regard to survival or death (i.e. mortality), to deficits, disabilities or handicaps, and to the response to treatment. Prognosis is essential

Figure 13 Prognosis of different forms of non-convulsive status epilepticus according to the impact of the underlying condition.
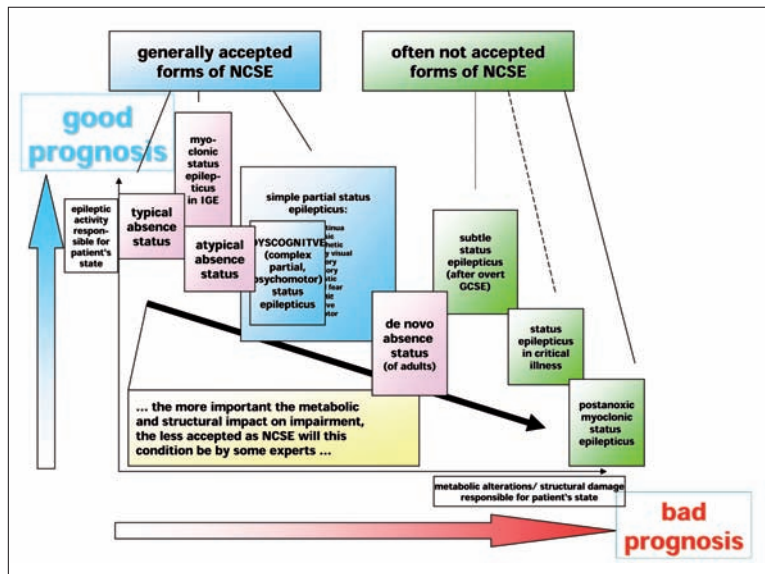
to determine the need, the immediacy and the intensity of the treatment; it also serves to handle the questions and expectations of the patients and their relatives.

Overall mortality of SE in general ranges within 10–33% in the population-based epidemiological studies [165]. Short-term mortality was 19% in a large population-based study irrespective of the type of SE; however, the data were collected from 1965 to 1984, at a time when treatment and ICU care of SE were not at the level of nowadays standards [166]. The long-term mortality over the first 10 years after SE in the same population was 40% and thus threefold higher than that of the matched general population [167]. Older patients with NCSE also share a higher mortality than those without [142]. Mortality of specifically NCSE has been 19% in a more recent study; mortality was significantly associated with symptomatic NCSE [168]; accordingly, an earlier study observed a much higher mortality of 57% in patients with exclusively symptomatic NCSE on an ICU [169]. Additionally, the prognosis of NCSE may not only include the issues of mortality and response to treatment, but also those of the mid- and long-term sequelae, like the likelihood of recurrence of NCSE and the onset of epilepsy after NCSE [136]. Recent data suggest that the risk of recurrence of (NC)SE ranges from 30 to 100% depending on the underlying cause of NCSE [170]. About 40% of patients will experience an unprovoked seizure within 10 years after one or repetitive episodes of (NC)SE [171].

For several reasons the prognosis of NCSE is one of its most equivocal and debated topics [172–174]. First, there is no broadly accepted definition which leads to the inclusion and/or exclusion of some forms of NCSE depending on the specific criteria of the investigators in these studies which in turn may have weakened the strength of the results and made it difficult to compare these studies. Second, it is important to respect the variety and heterogeneity of types of NCSE which render it impossible to make a universal prognosis for NCSE [175]. Third, it has become clear that any prognosis in any form of NCSE has to be considered within the specific context of the presence of underlying (causative) or concomitant (non-causative) disorders [1, 37, 174]. Fourth, the prognosis of NCSE is influenced by the time until adequate treatment will have been installed, i.e., delayed diagnosis and therapy will impact the outcome in a negative way [35, 37]. Fifth, there is increasing doubt as to whether the vast amount of experimental animal data on (NC)SE in fact strongly relates to NCSE in humans [176]. Many of these data were derived from specific animal models, often at different developmental stages or periods of postnatal life. The uncertainty of the reliability of the results of these studies was best reflected in one issue of *Progress in Brain Research* by addressing the yet unresolved question "Do seizures damage the brain?" [177]. In recent years, however, there has been increasing evidence from pathological and imaging data that all types of NCSE except for AS may damage the brain [178–183].

Keeping these issues in mind, the prognosis of the different types of NCSE will be discussed according to the classification shown in figure 1. Additionally, it seems helpful to place these types of NCSE into a Cartesian graph where the x-axis denotes non-epileptic factors increasingly responsible for the patient's state and prognosis, and where the y-axis assigns increasing importance to the epileptic activity determining the patient's global state and prognosis (fig. 13). Thus, it becomes clear that in the case of AS (left top) the epileptic activity is almost completely responsible for the patient's state, while, at the other end (right bottom), the epileptic activity in postanoxic MSE may contribute only little to the patient's global state of almost always deep coma. However, a recent study has shown that the occurrence of MSE in patients after cerebral anoxia represents an independent poor-outcome predictor, emphasising that MSE might be more than an innocent bystander of hypoxic brain damage [184]. Nevertheless, it follows that the prognosis of AS is closely linked to the response to antiepileptic treatment, whereas the prognosis of MSE is mainly dependent on the severity of global brain damage and the failure of other vital organs, and less on the result of the

antiepileptic treatment. Accordingly, the prognosis of CISE is mainly determined by the prognosis and response to treatment of the underlying critical illness.

As an approximate rule, the types of NCSE where the epileptic activity largely contributes to the patient's impairment share a better prognosis than those forms where patients suffer from critical illness. This fact has been corroborated by a simple clinical score for the prognosis of SE in adults, using consciousness, type of SE, age and history of seizures as items. The patients with the highest scores corresponding to the poorest prognosis were those without history of seizures, age over 65, NCSE and coma [185]. Absence status has an excellent prognosis with respect to response to treatment and outcome [37]. An exception might be de novo AS in adults caused by withdrawal of benzodiazepines; here, the prognosis is influenced by the interference of benzodiazepine addiction. The prognosis of atypical AS also is good, especially when atypical AS occurs de novo in non-epileptic patients; however, it has often to be considered with respect to an underlying more severe idiopathic generalised epileptic syndrome which per se may be associated with a more serious outcome. Aura continua often shares a good prognosis, but this is again dependent on the cause of aura continua and concomitant diseases; aura continua difficult to control may be caused by malformations, astroglial tumours, (residual) intracerebral haematomas or mitochondrial diseases. The prognosis of dyscognitive SE is good in general, but also determined by the presence or absence of structural lesions and concomitant disorders. The prognosis is much more serious in most forms of CISE because of the underlying disorder; however, the NCSE plays an important contributory role to the course of the disease as it may additionally worsen the global outcome of the patient. Subtle SE also shares a serious prognosis with respect to the long-lasting persisting epileptic activity which impairs response to treatment (inducing the vicious circle described earlier) which may increase the likelihood of irreversible brain damage. The worst prognosis must be attributed to postanoxic MSE, where about 80% of patients die and the surviving almost never return to a conscious life remaining in the permanent vegetative state. This outcome reflects the catastrophic brain damage caused by anoxia; MSE has to be considered not as a main causative factor, but as an indicator and epiphenomenon reflecting the disinhibitive state after abolition of inhibitory mechanisms of the brain and the global cerebral spillover with hyperexcitatory transmitters and excitotoxic metabolites [184, 186–188].

Treatment

The treatment of NCSE basically follows the same principles as do therapeutic algorithms for GCSE, although there is an appalling lack of studies specifically devoted to the optimal treatment of NCSE which would fulfil the criteria of evidence classes I or II. Again, this absence of data may result from the absence of an accepted definition of NCSE, from its heterogeneity and the divergent opinions even of experts whether NCSE might damage the brain or not implicating a more or less aggressive treatment strategy [1, 172, 173]. Nevertheless, more recent reviews and guidelines emphasise the need for immediate, resolute and type-adapted treatment of NCSE [18, 22, 24, 33, 189]. It is important to note that the most studies providing data discussed below were predominantly carried out in patients with GCSE and not in patients with NCSE. However, their evidence may also apply to the patients having NCSE, at least not until novel specific data will provide different results. As mentioned in the previous paragraph, the antiepileptic treatment becomes the more important, the more the epileptic activity per se contributes to the patient's state, whereas in the symptomatic forms of NCSE like CISE the successful therapy of the underlying and concomitant non-epileptic disorders will mainly determine prognosis and outcome of the patient.

Once NCSE has been diagnosed, the patient should be checked and stabilised for the basic vital parameters. Then, thiamine 250 mg should be given intravenously before any glucose-containing fluids or higher concentrated glucose solutions for correction of hypoglycaemia will have been administered; this schedule is especially recommended in the case of suspected alcohol addiction or malnutrition, but may be performed in all patients with NCSE with regard to its harm-sparing potential and the low risk of adverse effects.

The initiation of the antiepileptic treatment without delay is one of the most important factors in the therapy of NCSE: the longer NCSE persists, the more difficult it is to be terminated.

The immediate administration of intravenous benzodiazepines (BD) is the unequivocal, evidence-based first step for the efficient treatment of NCSE; caregivers hereby should be prepared to ventilate the patient if respiratory depression will occur. The most frequently used BD are diazepam, lorazepam (LZP), midazolam (MDL) and clonazepam (only in Europe where an i/v-formulation is available). Although these substances share the same basic mode of action, they differ in many pharmacokinetic and pharmacodynamic aspects [190–192].

The most used BD diazepam is highly lipophilic, enters the brain very quickly and binds to the GABA$_A$ receptor. However, it then rapidly dissociates from this receptor subsequently equilibring with fat tissue. This may explain the often observed recurrence ("breakthrough") of (NC)SE after administration of diazepam. If additional doses of diazepam are given, the patient is at risk to be overdosed as soon as a new equilibrium level is reached and the diazepam accumulated in the fat tissue redistributes to the brain and its receptors [193]. This phenomenon and the fact that diazepam undergoes complex metabolism generating more than 40 active metabolites make this substance very demanding to handle and achieve predictable levels and effects [190, 191]. Thus – and against widely common practice – diazepam is no longer the BD of choice in SE.

The less lipophilic BD LZP which is not metabolised to further active compounds accordingly has become the BD of choice for the first-line treatment of (NC)SE [194]. Lorazepam additionally leads to less respiratory depression [195] when compared to other BD and – most important for a sustained antiepileptic effect and the avoidance of recurrence of SE – it seems to bind in a semicovalent manner at the GABA$_A$ receptor site extending its effect up to about 24 hours despite falling blood levels [196–199]. The dominant role of LZP in the treatment of (NC)SE was definitively established by the hallmark multicentre prospective double-blind Veterans Affairs-Study published in the *New England Journal of Medicine* in 1998, comparing four different first-line regimens (phenytoin [PHT], diazepam followed by PHT, phenobarbital and LZP) where LZP showed to be significantly superior to PHT, but not to the other drugs; it was, however, easier to handle [20]. The pre-hospital use of LZP for the treatment of serial seizures or SE was safe and efficient in a large study in adults 3 years later. Unexpectedly (but calming), respiratory problems were significantly more frequent in the placebo group; it also seemed likely that LZP was superior to diazepam in terms of efficacy [200]. Unfortunately, lorazepam is still not approved by the Swiss authorities (Swissmedic) for the use in SE.

Midazolam (MDL) is a very rapidly acting BD with a short half-time [190, 191]; therefore, stable antiepileptic effect needs repetitive or continuous administration [201–203]. It also has markedly sedative and stronger respiratory depressive properties which make it less suitable for first-line treatment of SE, but it is widely used for the treatment of refractory SE (RSE, cf. below). Nevertheless, for pharmacological reasons and in the specific ICU environment, the ultra-fast antiepileptic activity of MDL may be exploited by first-line administration of a bolus of 1 to 5 mg to induce the very immediate effect, while at the same time also lorazepam 2–8 mg is given which will start to exert its sustained effect just at the decline phase of MDL. Midazolam can also be safely administered intramuscularly and may be preferred in those SE where i/v access is not available or its installation at risk [203, 204].

Clonazepam may have a profile similar to that of LZP and is widely used in French-speaking countries; however, sound studies are lacking probably because of no available intravenous formulation in some Anglo-American countries [205–207].

While BD are being given as first-line treatment, the patient should undergo laboratory exams including haematological and chemical parameters as well as checking for thyroid hormone status, infectious diseases (especially herpes encephalitis) and an extensive drug screen because several "club drugs" like amphetamine and its ("designer-")derivatives (paroxymethamphetamine [PMA], paramethoxymethamphetamine [PMMA], [benzyl-]piperazines and cocaine) may provoke NCSE [208–214].

Since BD are not the mid- or long-term treatment of epileptic disorders and these medications impair the patient's awareness, memory and consciousness which may impede the judgement of the patient's neurological state in the course of the disease, the concomitant administration of a "classic" AED should be put ahead. Actually, there are three different compounds with an intravenous formulation available on the market: PHT, valproic acid (VPA) and levetiracetam (LEV), but only PHT is approved for the treatment of (NC)SE in Switzerland.

Phenytoin was the first antiepileptic drug beyond the sedatives BD and barbiturates to be administered intravenously. The feasibility, safety and efficacy of i/v PHT was demonstrated in the early 1950s, however, not in studies which would satisfy standards of nowadays [215, 216]. The only study yielding Class-I evidence for i/v PHT in GCSE was the already cited VA study; it showed that PHT alone was significantly inferior to lorazepam to stop SE, but it was efficient when given together with i/v diazepam [20]. The use of the i/v formulation of the drug implicates to keep several cautions in mind: the solution has to be stabilised at a high, very basic pH, which necessitates a central line and a infusion rate of no more than 50 mg per minute. The substance by itself and the additives of the i/v formulation may induce serious cardiac and local cutaneous ("purple-glove syn-

drome") adverse effects [217–219]. In addition, phenytoin is highly protein bound and metabolised by the cytochrome P 450 (CYP450) system, mainly the 2C9 and 2C19 variants, which produces several pharmacokinetic and -dynamic interactions, especially to be observed when coumarins, dexamethasone, cytostatic drugs, other AED or some antibiotics were co-administered [220–224]. The non-linear pharmacokinetics of PHT bear a high risk of toxic levels; their close monitoring is essential. The prodrug fosphenytoin is stabilised at a physiological pH and free of cardiotoxic additives which allows for a much faster infusion rate and also for intramuscular administration [225], but there is no advantage in terms of faster reaching the therapeutic level because the prodrug has to be metabolised by plasma phosphatases into phenytoin [226, 227]. These properties, together with an about 10 times higher price than PHT, resulted in a lack of approval in almost all European countries, Switzerland included [228, 229].

Intravenous valproic acid (VPA) has been available in central European countries for more than 20 years und may be an alternative to PHT in the treatment of SE [230–232]. Valproic acid has the broadest spectrum off all AED to date and does not induce marked impairment of consciousness. It is a weak to moderate inhibitor of the CYP450 system and, as a short-chain fatty acid, metabolised by beta-oxidation in the liver and renally eliminated after glucuronidation [233–238]. The substance leads to the production of ammonia (sometimes dramatically exacerbated by the presence of a mitochondrial urea-cycle enzyme defect like ornithyl-carbamoyl-transferase deficiency) which should be closely controlled after fast loading; levels of ammonia up to 70 μmol (normal 7–34) usually were well tolerated, whereas levels >90 μmol may lead to substantial obtundation which warrants for a dose reduction [239–241]. During i/v therapy for SE, levels of free (unbound) VPA should be monitored, because this fraction (normally 10–15%) rises overproportionally in the case of high doses and hypoalbuminaemia [242, 243] and may induce toxicity (sedation, elevated liver enzymes, low platelelet count, reversible parkinsonism, pancreatitis) [244–246]. The use of VPA in patients with intracranial bleedings is questionable because of the various effects of VPA on platelet number and function as well as on several clotting factors [247, 248]. But, in general, the safety of i/v VPA, even at high doses, fast infusion rates and in cardiac instable patients, was demonstrated in several studies [249–259]. However, prospective randomised well-(i.e. PHT-)controlled studies which had provided the Class-I evidence necessary to gain approval by regulatory boards (including Swissmedic) are still lacking. Nevertheless, some countries (Norway, Canada, Singapore) approved the drug on "summative, use-proven evidence"; i/v VPA was lately approved for the treatment of GCSE also in Germany after recommendations upon an extensive review of an expert panel [260]. A randomised double-blind pilot trial, using PHT or VPA as *first-line treatment before administration of benzodiazepines,* showed a trend to superiority of VPA against PHT; however, the study was underpowered and statistically flawed; thus, these results should be interpreted with caution and further studies are warranted [261, 262]. Most recently, a controlled randomised prospective trial comparing i/v VPA with i/v PHT (n = 50 in each group) after failure of BD has shown a significantly superior efficacy of VPA compared to PHT (p >0.05); the study also reiterated the importance of a treatment as soon as possible [263].

An intravenous formulation of levetiracetam (LEV) has recently been introduced, but has not gained approval for SE yet. This drug has a very favourable pharmacokinetic and -dynamic profile with no known interaction with any drug and only very few adverse effects (mainly slight somnolence and behavioural alterations which play no role in the acute treatment of SE) [264–266]. Levetiracetam has a substantial first-dose effect [267] and its fast i/v-application in healthy volunteers is safe and leads to high drug levels [268, 269]. After an experimental study had performed and shown an important anticonvulsant effect in SE [270], small studies used LEV as a third- or fourth-line treatment in refractory SE, often also given by nasogastric tube [271–275]. There are two reports of a few cases of NCSE probably induced by LEV, but these intriguing observations await further confirmation by other studies [276, 277].

The administration of LEV seems to be most favourable in critically ill, post-transplantation and HIV patients with (NC)SE on therapy with multiple drugs where the risk of significant adverse effects and interactions is especially high.

All the three substances discussed have the advantage that they can be switched 1:1 from the i/v-dose to oral administration without problems.

The success rate of the administration of one BD and an i/v AED (PHT/VPA/LEV) depends on the type of NCSE. It is almost 100% in all forms of AS and it is high in epileptic patients with aura continua or dyscognitive SE. The rate drops in patients with aura continua or dyscognitive SE resulting from structural lesions (tumours, haemorrhages) or in patients with CISE due to multiorgan failure. It

Figure 14 Therapy algorithm of non-convulsive status epilepticus.
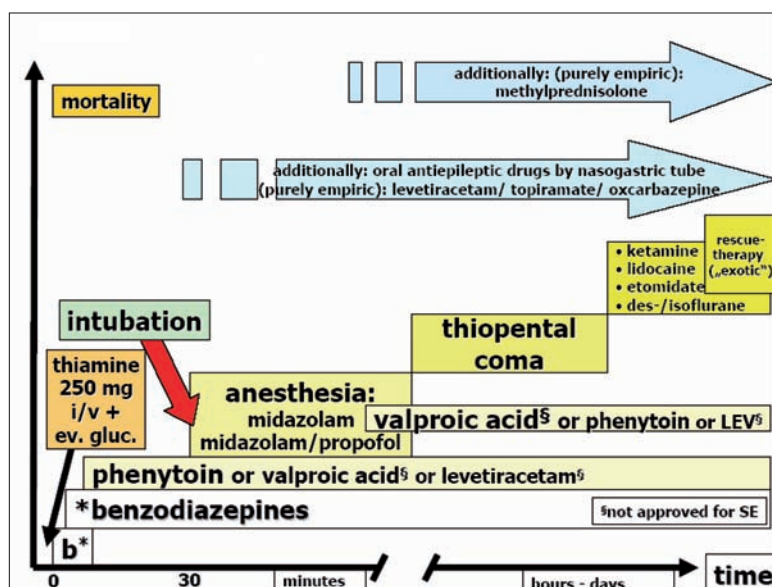
is lowest in patients with subtle SE and especially in postanoxic MSE [184, 185, 278].

Status epilepticus persisting after the administration of two AED is called refractory SE which occurs in about (20–)30% of all cases of SE [279–281]. It is treated by induction of anaesthesia after intubation of the patient with either midazolam, lorazepam, propofol and midazolam, or thiopental [282–298]. Studies evaluating these treatments are of small size and often not directly comparable because of different parameters used, especially electroencephalographic titration of depth of coma (suppression of epileptic activity vs burst suppression vs electrocerebral silence) [299–303]. A meta-analysis could not find a superiority of any of these treatments in terms of outcome [303].

Midazolam lowers blood pressure and undergoes tachyphylaxis because of alterations of the $GABA_A$ receptor subunit composition upon long-term stimulation like in SE [304]. It also bears the risk of accumulation accompanied by a very prolonged recovery from coma in patients with impaired renal function due to the pharmacologically active glucuronated metabolite α–1–OH-midazolam [305].

Propofol is a highly lipophilic, very short-acting anaesthetic which functions as an anticonvulsant at different sites ($GABA_A$ receptor, NMDA receptor, voltage-gated Ca^{2+}-channels) [294, 306–311]. When used as single anaesthetic compound, the substance may cause myocloni resembling seizures; however, this phenomenon is non-epileptic and most probably related to disinhibition of subcortical structures [312, 313]. To avoid the phenomenon or true "withdrawal" seizures, it is recommended to use propofol always combined with (a small dose of) a BD

[22]. Anaesthesia with propofol is associated with intake of 1200–1500 kcal of lipids due to the solvent based on soy oil. The drug should not be used longer than 5 days because it may cause the life-threatening "propofol-infusion syndrome" consisting of severe acidosis, liver failure and extensive rhabdomyolysis [314]. A pilot trial using propofol in 31 episodes of patients with refractory SE showed control of SE in two thirds of the patients without serious adverse effects [315].

When MDL and propofol fail, barbiturate coma with thiopental may be started. Barbiturates are very potent antiepileptic drugs and additionally downregulate global brain metabolism leading to a sort of "hibernating" brain state and, thus, reduce the risk of hyperexcitation and the accrual of toxic metabolites. However, they are markedly cardio-depressive and may induce severe hypotension. Barbiturate coma in SE is accompanied by a mortality of 30–50% [303]. Unfortunately, the barbiturate easiest to handle, pentobarbital, is no longer on the market in Europe. Thus, thiopental is the only available drug for this purpose; it is initially ultra-fast and -short acting because it is highly lipophilic, and it quickly crosses the blood-brain barrier, but it immediately accumulates also in the fatty tissues. From there, it will again equilibrate and redistribute to the brain structures. This eventually leads to very prolonged recovery from coma after stopping the drug [316, 317].

Other (additional) therapeutic options in RSE include the administration of all available i/v-AED (i.e. VPA and LEV, when PHT was first used) or enteral AED by nasogastric tube. Among those AED, high-dose topiramate was successfully used in small case series [318–320]. Lidocaine, ketamine, etomidate and clomethiazole were also "rescue" therapeutics [321–332], while others reported successful use of inhalative anaesthetics ("-fluranes") despite reports of a possible proconvulsant effect of some compounds of this class [333–338].

Intravenous steroids may become another therapeutic alternative in RSE because there is increasing evidence that continuous epileptic activity stimulates the production of proinflammatory mediators like cytokines (especially interleukin-1β [339]) and helps to sustain epileptic activity. Steroids also are effective in some paediatric epilepsy syndromes, like infantile spasms, Landau-Kleffner syndrome and Rasmussen encephalitis [340–342]. The reported clinical experience in adult patients is small, but some cases with RSE responded to treatment with steroids [343, 344].

To summarise, a treatment algorithm of NCSE is proposed in figure 14 and dosages of the drugs discussed in this section are shown in table 3.

Table 3 Drug dosing for non-convulsive status epilepticus.

drug	dosing		
A. first-line			
lorazepam	<60 y	4 mg i/v	repeat once
	60–80 y	2 mg i/v	repeat 1–3 times
	>80 y	1 mg i/v	repeat up to 5 times
clonazepam	<60 y	1 mg i/v	repeat 1–2 times
	60–80 y	0.75 mg i/v	repeat 1–3 times
	>80 y	0.50 mg i/v	repeat up to 3 times
midazolam	<60 y	5 mg i/v	repeat several times, if necessary
	60–80 y	2 mg i/v	repeat several times, if necessary
	>80 y	1 mg i/v	repeat several times, if necessary
diazepam	<60 y	10 mg i/v	repeat 1–2 times
	60–80 y	5 mg i/v	repeat 1–3 times
	>80 y	2.5 mg i/v	repeat up to 5 times
B. second-line			
phenytoin			
loading		15–18 mg / kg body weight at 50 mg/min	
maintenance	<70 kg	150 mg i/v	every 12 h; start 6 h after loading
	70–90 kg	175 mg i/v	every 12 h; start 6 h after loading
	>90 kg	200 mg i/v	every 12 h; start 6 h after loading
valproic acid			
loading	<60 y	30–45 mg i/v / kg body weight in 30 min	
	60–80 y	20–30 mg i/v / kg body weight in 30 min	
	>80 y	15–25 mg i/v / kg body weight in 30 min	
maintenance		start the same dose as the loading dose *concomitantly over 24 h*	
levetiracetam			
loading	<60 y	25–30 mg i/v / kg body weight in 15 min	
	60–80 y	15–25 mg i/v / kg body weight in 15 min	
	>80 y	10–20 mg i/v / kg body weight in 15 min	
maintenance*	<60 y	1000–1500 mg every 12 h	
	60–80 y	750–1000 mg every 12 h	
	>80 y	500–750 mg every 12 h	
C. third-line			
midazolam		(100–) 300–600 (–4000) µg/min	
propofol		(100–) 300–600 (–1000) mg/hour (+ midazolam or lorazepam!)	
thiopenthal			
bolus		100–250 mg	repeat until seizures stop
maintenance		3–5 mg / kg body weight / hour	
D. additional ("fourth-line", "rescue") therapy			
i/v			
lidocaine			
loading dose		1.5–2.0 mg/ kg body weight	repeat once after 20–30 min
maintenance		3–4 mg/ kg body weight/ hour	

ketamine		
loading dose	0.7–2.0 mg/ kg body weight	
maintenance	2–6 mg/ kg body weight/ hour	
clomethiazole		
loading dose	5–12 mg/ kg body weight	
maintenance	0.6–4.0 mg/ kg body weight/ hour	
etomidate		
loading dose	0.25 mg/ kg body weight as bolus within 30 sec	
maintenance	0.02 mg/ kg body weight per minute as continuous infusion	
inhalative		
isoflurane		
loading	0.5 (–3.0)% of end-tidal volume	
maintenance	0.8–2.0% of end-tidal volume	
oral		
topiramate	100–400 mg	every 12 hours
oxcarbazepine	600–1200 mg	every 12 hours; monitor sodium!

* dose must be adapted if renal function is impaired

Conclusions

Non-convulsive status epilepticus is one of the most important neurological emergencies requiring rapid diagnosis, being confirmed by EEG and treated without delay and with appropriate aggressiveness. The often unspectacular and unspecific clinical manifestation of NCSE makes it important to "think of it at all" in any patient presenting with unexplained new onset of behavioural changes, impaired consciousness and/or focal, non-convulsive neurological deficits. Treatment of NCSE closely follows the rules of the other forms of SE.

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