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Non-Convulsive Status Epilepticus : Challenges & Conundrums

ABSTRACT

Non-convulsive Status Epilepticus (NCSE) is a type of status epilepticus with subtle or no motor phenomena. Its manifestations are protean varying from subtle behavior change in ambulatory patients to confusion or coma in the critically ill ICU patient. An electroencephalogram (EEG) is mandatory for a definitive diagnosis. However, EEG patterns are often ambiguous and hence may warrant long recordings and expert interpretation. Within the intensive care setting, the diagnostic challenge is in delineating non-epileptic conditions such as posthypoxic, metabolic, or septic encephalopathies from NCSE. The etiology of NCSE is varied ranging from acute NCSE in a variety of acute brain injuries and systemic illnesses to epileptic encephalopathies in persons with prior epilepsy. The etiology and clinical form of NCSE are strong predictors for response to treatment and overall prognosis. Accordingly, therapeutic strategies vary from minimal to aggressive approaches guided by the underlying etiology and treatment responses.

Key words: Status epilepticus, nonconvulsive, Subtle status

INTRODUCTION

Non-convulsive seizures are epileptic seizures that have subtle or no clinical motor phenomena in a patient with impaired consciousness. Non-convulsive status epilepticus (NCSE), a subtype of status epilepticus (SE), is an enigmatic condition with protean manifestations. Outside the intensive care unit (ICU) and hospital setting, the clinical features of this disorder may be very discrete and are sometimes hard to differentiate from normal behavior. NCSE is seen a third of patients presenting with altered mental status to the emergency department.[1] NCS is also being increasingly recognized in obtunded patients in the ICU. It is identified in 10–25% of patients with acute brain injury and is associated with worse outcomes.[2] However, NCSE is commonly missed both in the emergency room and in the ICU, because of its pleomorphic presentation, often in the setting of other serious illnesses. The electroencephalogram (EEG) constitutes the cornerstone of a diagnosis of NCSE, but the EEG patterns in NCSE may be ambiguous and confusing, warranting long recordings, electrophysiological expertise, and clinical correlation,[3] especially in obtunded or confused critically ill patients in the ICU. Treatment strategies in NCSE are also controversial. While there is consensus that NCS and NCSE need treatment, the urgency and intensity of treatment is still unclear. The varied presentations, etiologies, and prognosis of the conditions under this broad umbrella of NCSE have made it difficult to provide clear treatment guidelines. Thus, NCSE represents one of the great challenges in neurology because of its frequently missed diagnosis, equivocal EEG patterns, controversies regarding classification and diagnostic criteria, approaches to treatment and potential sequelae.[4-8]

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DEFINITION

NCSE denotes an enduring epileptic condition with reduced or altered consciousness ranging from confusion to coma, behavioral and vegetative abnormalities, or merely subjective symptoms such as auras, but without major convulsive movements.[9]

Classically, SE was defined as a "a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition."[10] The latest version of SE classification[11] groups SE based on semiology (apart from etiology, EEG correlates and age) as SE with and without motor phenomena. The group with motor phenomena has a subgroup with convulsive activity. This leaves a broad umbrella of conditions that would qualify for NCSE. The newly proposed ILAE definition of SE is broad 2015 [Box 1] and clearly defines two time points operationally for convulsive status based on clinical and experimental evidence: t1 of 5 min beyond which the seizure is considered "prolonged" and t2 of 30 min, beyond which there is risk

of long term sequelae.[11] However, similar data for NCS is lacking.[12,13] The 2015 ILAE definitions acknowledge that there are different forms of NCSE, likely warranting different temporal criteria and, by implication, different intensities of treatment. The ILAE time, "t1" is set at 10 min for absence SE and focal unaware seizure status (CPSE)[14] but is completely speculative for other forms of NCSE. Thus, NCSE refers to a group of highly heterogeneous clinical conditions, lasting beyond 10–30 min, in which continuous or recurrent electrographic seizure activity results in non-convulsive clinical features.[11]

CLASSIFICATION OF NONCONVULSIVE STATUS EPILEPTICUS

Logically, there are many forms of focal seizures without convulsions or other dramatic motor presentations, depending on where in the brain they start and develop. These may be classified according to electrographic evidence of focal or generalized cortical seizure activity. NCS and status may be further categorized by etiology and level of consciousness, both of which have been demonstrated to have prognostic weight.[15,16]

The classical forms of NCSE are described in patients with prior epilepsy, and are largely based on the type of EEG activity. They include typical and atypical absence SE (ASE), simple partial SE, and complex partial SE. These patients are often confused but ambulant and do not have other acute systemic illness.

Over the past two decades, extensive use of prolonged bedside EEGs has identified electrographic seizures in increasing numbers of obtunded critically ill patients. While these may occasionally be superimposed on epilepsy syndromes, more often they arise *de novo* during acute and serious medical neurologic or traumatic illnesses.[17-19] This type of NCSE (now termed Comatose NCSE) is likely the most common types of NCSE found by continuous EEG (CEEG) monitoring of critically ill patients in ICUs.[20,21]

Various studies,[15,16,22] have demonstrated distinct differences in these two groups with respect to onset age, epilepsy history, clinical presentation, episode duration and mortality to support a broad classification of NCSE in clinical practice[11] into a

i) Classical form, termed NCSE proper or ambulatory NCSE in ambulant patients with prior epilepsy and
ii) Comatose NCSE in critically ill comatose patients in ICU with seizures on CEEG monitoring.

A. Ambulatory or proper NCSE

Ambulator NCSE includes a variety of forms in non-comatose patients and presents clinically with a wide spectrum of behavioral manifestations, ranging from barely noticeable symptoms, to confusion or mutism. Based on EEG findings, these patients can be grouped as:

1. Generalized NCSE or ASE
2. Partial, focal or localization-related NCSE.

1. Absence status epilepticus (ASE)

ASE occurs in up to 25% of patients with idiopathic generalized epilepsy (IGE)[23,24] and may be subdivided into four categories: [25]

i. Typical ASE (or petit mal SE);
ii. Atypical ASE (or spike-wave stupor);
iii. Situation-related ASE and;
iv. ASE with focal features

Typical ASE usually occurs in children and adolescents with IGE but is seen in adults and elderly where epileptic seizures persist after adolescence.[23,26,27] Rarely, it may be the first clinical presentation of IGE in adulthood,[28,29] and elderly.[27] The EEG shows continuous, regular generalized spike-wave at 3–4 Hz with a frontal maximum, and may later become slower and poorly formed and discontinuous.[30] The clinical hallmark is the abrupt change in the level of consciousness in the patient. The most patients are not comatose but are lethargic and confused, with decreased spontaneity and slow speech, at times associated with automatisms or subtle myoclonic, atonic, or autonomic phenomena.[25]

Atypical ASE occurs in patients with symptomatic generalized epilepsy, particularly in patients with Lennox-Gastaut syndrome, myoclonic-astatic epilepsy (Doose syndrome); severe myoclonic epilepsy of infancy (Dravet syndrome), myoclonic absences, Angelman syndrome, Rett syndrome and ring chromosome 20 syndrome.[31-33] The EEG shows a generalized continuous waxing and waning 2–3.5 Hz spike and wave discharge lasting for over half of the record. Clinically, a worsening of the already compromised baseline neurological state may be observed, without a clear onset and offset of the ictal condition, unlike typical ASE. Establishing NCSE in a patient with underlying epileptic encephalopathy is particularly challenging,[34] and the recent EEG criteria address this special issue.[35]

Situation-related generalized ASE usually occurs in non-epileptic adults or elderly subjects and is precipitated by drugs, toxic, metabolic disturbances, or electroconvulsive therapy.[15,36,37] Several drugs associated with ASE (Cock 2015 include recreational drugs (especially amphetamines, ecstasy and cocaine), psychotropic drugs (tricyclic antidepressants, bupropion), antihistaminics and analgesics (diphenhydramine, tramadol) and antibiotics isoniazid, quinolones and some cephalosporins), chemotherapy (cisplatin) and immunotherapy agents. Medication related triggers often occur in the setting of severe medical illness, especially renal dysfunction.[38,39] Antiepileptic drugs vigabatrin, tiagabine, and the Sodium channel drugs (CBZ, OXCBZ PHT LTG) can themselves trigger ASE.[40]

ASE with focal features occurs in subjects with localization-related epilepsy, most often of extratemporal (frontal) origin in whom a phenomenon of secondary bilateral synchrony on EEG causes bilateral or generalized epileptiform discharges mimicking, a true ASE.[25]

2. *Partial Status Epilepticus*

Complex partial SE (Focal SE with impaired awareness)

Originally, it considered synonymous with Temporal lobe SE or "psychomotor status." Focal SE is now recognized from extratemporal regions as well. The impairment of awareness can be quite severe with partial or complete amnesia for the episode. Oroalimentary and manual automatisms and vegetative signs (pallor, mydriasis, and salivation) may be prominent but not universal. In patients with prior epilepsy, some of the clinical features including motor phenomena mimic individual seizures.

Frontal CPSE deserves special attention, as the behaviors can mimic psychiatric illness. Scalp EEG may not demonstrate clear ictal activity that confuses the picture further.[41] Positron emission tomography using [18F] fluorodeoxyglucose may lead to the correct diagnosis in such cases.[42] Frontal CPSE may also be mistaken for absence SE for reasons discussed above.

Response to treatment in Focal NCSE with impaired awareness is less robust with a greater chance of recurrence compared to typical absence status

Simple partial NCSE (Focal SE with preserved awareness)

Simple partial SE is rare and consists of seizures that produce no alteration in consciousness. It is more frequent with neocortical rather than limbic epilepsy.[4] The clinical symptoms may include fear, or visceral sensations such as nausea, hallucinatons and reversible blindness, negative motor phenomena such as aphasia and focal paresis. Diagnosis is primarily based on clinical findings as conventional scalp EEG is frequently ambiguous or normal.

B. Comatose NCSE

The term comatose NCSE is used to designate a state of coma accompanied by continuous or periodic epileptiform discharges on the EEG with or without minor motor activity.[16] The most frequent types of seizures in comatose patients are NCSzs,[43] but the inclusion of deep coma stages with epileptiform EEG discharges under the NCSE umbrella has led to a major conceptional enlargement of the generic term NCSE, with several highly controversial consequences.[44] The obtundation in patients with comatose SE is always confounded by a variety of reasons including the underlying cause and by medications such as anesthetics, muscle relaxants, and anticonvulsant drugs. Furthermore, the EEG demonstrates periodic patterns and rhythmic discharges that generally are not pathognomonic for NCSE, but relevantly contribute to the diagnostic confusion.[45] The clinically important questions that arise are whether i) the comatose state is a result of electrical seizures, ii) the ongoing electrical seizures worsen the overall prognosis and therefore, iii) whether they warrant treatment. Comatose NCSE in critically ill patients have been associated with high rates of mortality, permanent neurological injury and prolonged hospital stay and a diagnosis of comatose NCSE often forbodes a dismal prognosis.[21,46]

C. Subtle NCSE

Between 12% and 53% of subjects with convulsive SE subsequently evolve to a state of electrographic SE without motors signs, and this has been termed Subtle SE and is one type of NCSE that warrants aggressive treatment.[47] The clinical hallmarks of subtle SE include a persistent comatose state without prominent motor features. However, discrete ("subtle") muscle twitching may be present. The EEG mostly shows generalized periodic discharges, but lateralized and regional discharges may also occur. Although the term was originally used in a wider sense to also include post ictal encephalopathy,[48] current concepts allow the diagnosis of subtle SE only in the presence of EEG changes along with evidence of previous overt epileptic seizures or SE.[16]

ETIOLOGY AND RISK FACTORS

NCSs and NCSE may occur in virtually any condition that may affect, directly or indirectly, the homeostasis of the supratentorial brain [Table 1]. However, outcomes of NCSE are driven largely by the etiology, mortality is higher in patients with acute etiologies (27%) than in patients with epilepsy (3%) or cryptogenic (13%) NCSE.[49]

NCSE in chronic pathologies

About 50% of SE occurs in the setting of prior epilepsy,[50] and NCSE is similarly associated, estimated to have a prevalence of 6% in JME[51] and 15% in[24] cases of IGE with typical absences. Usually, the trigger is a change or omission of AED, or concurrent medications that lower AED levels. Other chronic pathologies include slowly progressive intracranial tumour and encephalomalacia on brain imaging in Laccheo 2015.[21]

Atypical ASE and can be triggered in a variety of prior symptomatic generalized epilepsies and may be difficult to diagnose in patients who have baseline cognitive impairment (see section above).

NCSE in acute pathologies

Subtle SE

A third of patients with convulsive status develop NCSE following transformation of f GCSE to NCSE, referred

Table 1: Causes of non-conuvlsive status epilepticus

Causes of non-conuvlsive status epilepticus
• Head trauma
• Cerebrovascular accident
• Ischemic stroke
• Venous stroke
• Intracerebral hemorrhage
• Subarachnoid hemorrhage
• Encephalitis
• Infectious: Viral: HSV, HIV, Neurosyphilis
• Autoimmune
• Paraneoplastic
• Slow viral: CJD
• Medications
• Overdose
• Antibiotics: Cephalosporins, Penicillins, Quinolones, Imipenem
• Methotrexate, Tiagabine, Lithium, Pseudoephedrine, Tramadol, Chloroquine, Ifosfamide, Baclofen, Cyclosporine
• Withdrawal
• Benzodiazepines, Opioids, Baclofen
• Genetic/developmental (PREVIOUS EPILEPSY)
• Mitochondrial disorders: MELAs,
• Lafora body disease
• Lennox Gastaut syndrome
• Ring chromosome 20
• Cortical dysplasia

to as subtle NCSE.[20] Subtle NCSE is common, but the diagnosis may be delayed or missed because the altered level of consciousness can mimic postictal encephalopathy or delirium,[52] leading to increased mortality.[14]

NCSE in critical illness

CEEG recordings of adults in the ICU estimate the overall rate of NCSE at about 10–20%[53] and this increases to about 30% in critically ill patients[18] this includes patients with acute brain injuries, but it is rarely the admission diagnosis, as patients develop NCSE after the inception of the critical illness.[54]

Traumatic brain injury

About 10% of patients with TBI have NCS based on CEEG recordings,[55,56] and these are linked to elevated intracranial pressure and cerebral metabolic distress, that may t lead to additional brain damage[57,58] and worse outcome.[59]

Cerebrovascular insult

Ischemic stroke

NCS are more common than convulsive seizures in the 9% of patients who have seizures after an acute ischemic stroke.[60,61] Ischemic stroke constitutes 20% of all causes of NCSE among comatose patients in the ICU[17] and about 18% of patients with intracerebral hemorrhage have NCSE on CEEG.[62,63]

Subarachnoid hemorrhage

NCS and NCSE were diagnosed in 7–18% of patients of SAH,[53,54,64,65] and was associated with older age and higher mortality. NCSE beyond the 5th day after SAH was associated with 100 % mortality,[64] supporting the need for rigorous treatment of NCSE that follows SAH. However the role of prophylactic AEDs is unclear.[65]

Encephalitis

Both infectious and noninfectious causes of encephalitis are well established causes of SE including NCSE, with seizures (often non convulsive) being associated with autoimmune encephalitis in 78% of patients.[66] Autoimmune and paraneoplastic encephalitis accounted for 40% of a case series of new onset refractory SE,[67] but systematic data on the incidence of NCS and NCSE in encephalitis is lacking.

Hypoxic ischemic encephalopathy

NCS and SE, occurs in up to 30% of patients who remain comatose after surviving cardiorespiratory arrest (CRA).[68] In most of these patients, the brain injury is severe and largely irreversible and usually associated with extremely poor outcomes, independent of the NCSE[69] and it is unclear whether treatment with AEDs improves the catastrophic prognosis.[70,71]

Favorable outcomes may be expected in a small subgroup (viz age <65 years, conversion to a shockable rhythm and prehospital return of spontaneous circulation during resuscitation.[72] Reactive pupils and motor reflexes and 3 days after CRA[73] and a reactive EEG background significantly improve prognosis.[74-76]

The epileptic nature of postanoxic myoclonus is still a matter of debate.[77] Acute post hypoxic myoclonus may have cortical or subcortical mechanisms[78], but early post anoxic myoclonus within 24 h is a predictor of poor outcome,[79] Cchronic post hypoxic myoclonus on the other hand is often stimulus sensitive and has a lear cortical basis.[80]

Medications and drugs

A variety of drugs including a range of antibiotics[81] have been implicated for an increased seizure risk, especially with underlying renal dysfunction, brain lesions or epilepsy. Antiepileptic drugs such as tiagabine and an overdose of carbamazepine or lamotrigine may also trigger ASE.[38] Other drugs have been implicated include baclofen, opioids and its antagonists, anticancer drugs, methotrexate as well as withdrawal of antiseizure medications such as benzodiazepines [Table 1].

DIAGNOSIS OF NCSE

NCSE can manifest with a number of different symptoms, altered mental status being the most common, occurring in 82% of patients. Among these, the specific manifestation was confusion in 49%, coma in 22%, lethargy in 21%, and memory loss in 8%.[82] A rapid and unexpected emergence of any of these symptoms in the absence of another plausible explanation should raise a suspicion of NCSE. On the other hand, a number of conditions may resemble NCSE

clinically but are not associated with periodic or rhythmic EEG abnormalities. These include prolonged migraine auras, transient global amnesia, transient ischemic attacks, sleep walking and somnambulism, and psychiatric disturbances such as stupor or dissociative disorders.[83]

Hence, a bedside EEG should be ordered in any situation where the altered behavior is abrupt in onset and unexplained [Box 1].

In ambulatory patients, when NCSE is clinically suspected and EEG recording is not feasible, 2 mg intravenous lorazepam may be administered for diagnostic purposes. A clear clinical response to benzodiazepines indicates a diagnosis of NCSE. This is also true for the rare cases of NCSE with negative surface EEG [Box 2].

Box 1: Suspect non-convulsive status epilepticus and perform electroencephalogram if any of these clinical scenarios

i. Obtundation following generalized convulsions or GCSE
ii. Subtle signs such as twitching, blinking, and nystagmus in a stuporous patient
iii. Unexplained stupor or confusion, especially in the elderly or critically ill
iv. Altered mental status in the elderly, particularly after benzodiazepine withdrawal
v. "Stroke plus" when the sensorium appears disproportionately poor.

Box 2: Benzodiazepine trial in suspected NCSE

Why?
- Patients who are obtunded and EEG facilities not available
- Diagnostic uncertainty regarding rhythmic/periodic EEG patterns in patients with neurological presentation suggestive of NCSE.

Where?
- In a medical/ICU setting with physiological observations (oxygen saturations, hemodynamic parameters), with suitable resuscitation facilities.
- Real time EEG recording preferred.

What?
- Small incremental doses of a fast acting benzodiazepine agent that will not accumulate
- Intravenous midazolam preferred
- Start with 1 mg intravenously and repeat at intervals of several minutes with reassessment of the patient condition
- Maximum total dose of 10 mg intravenous midazolam or 0.2 mg/kg (Jirsch and Hirsch Clin Neurophysiol 2007).

When to stop the trial?
- Clear clinical improvement and/or resolution of EEG appearance
- Respiratory or hemodynamic compromise
- Maximum dose administered (midazolam 0.2 mg/kg).

How to interpret the trial?
- Positive Benzodiazepine trial
  - o Definite NCSE: If the clinical impairment and ictal EEG pattern resolve
  - o Possible NCSE: If the EEG improves but the clinical state of the patient does not.
- Negative benzodiazepine trial
  - o Does not rule out NCSE. Consider a rapid infusion of second line ASM agent under the above monitoring conditions.

NCSE: Non-convulsive status epilepticus, EEG: Electroencephalogram

Electroencephalography in NCSE

Continuous EEG monitoring

Since seizures are often brief and intermittent a single 20–30 min EEG is likely to miss the diagnosis of NCS, and longer continuous recordings are required.[84-86] The widespread use of portable, digital machines has facilitated longer bedside EEG records, improving the recognition of subclinical seizures and NCSE in encephalopathic critically ill patients.[21]

CEEG recording in the ICU provides increasing yield over first 48 h.[18] CEEG is recommended for at least 24 h, as this is likely to identify 80–95% of patients with NCS, and should be started as soon as is feasible.[87] Where CEEG is not readily available, repeated "spot (30 min)" EEGs over 24 h can be a reasonable substitute.[88] Absence of epileptiform discharges in the initial 2 h recording reduces the yield of a longer recording to <5%,[89] and hence, the initial EEG findings may be used to select patients for longer recordings.[90,91] These data, however, fail to clarify whether the interventions that follow have any effects on outcome.[92]

Interpretation of CEEG: The ictal interictal continuum

The interpretation of CEEG recordings in comatose patients requires expertise, as patterns can be indeterminate and confusing, especially because clinical correlates are lacking. Post hypoxic encephalopathy and metabolic and septic encephalopathies and rare neurodegenerative disorders such as Creutzfeldt Jakob disease cause obtundation in sensorium with EEG showing periodic and fluctuating patterns of various morphologies with varying degrees of suppression of the background rhythms. Many of these EEG patterns mimic NCSE but in fact represent severe encephalopathy[93] and may lead to an overdiagnosis if based only on the EEG record.[94]

Efforts to define and classify EEG patterns and correlate them to clinical states have been ongoing[95,96] and the most widely accepted currently are the Salzburg criteria[35] [Figure 1]. These criteria have been validated[97] and incorporated into the latest version of American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology.[98]

Some EEG patterns are now clearly recognizable as ictal, and a few other classical coma patterns as clearly non ictal viz alpha theta or delta coma, low voltage rhythm and burst suppression,' Ambiguous patterns, with generalized or lateralised periodic discharges [Figure 2], are found in a third of patients on CEEG[99,100] and these constitute a spectrum, now known as the ''ictal-interictal continuum."[101] In these cases, at least one of the additional criteria is needed to diagnose NCSE (a) subtle clinical ictal phenomena, (b) typical spatiotemporal evolution, or (c) response to antiepileptic drug treatment.

Diagnostic value of benzodiazepines in NCSE diagnosis: Challenges and limitations

Intravenous administration of benzodiazepines with both improvement of the clinical state and the EEG is a strong argument in favor of NCSE and is also recommended as

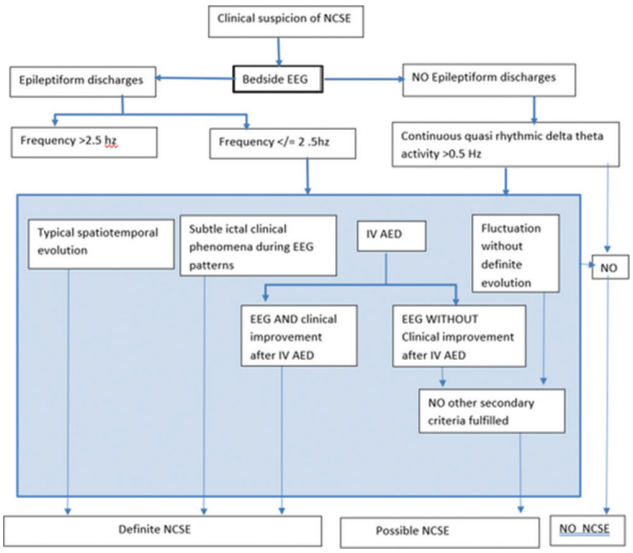

Figure 1: Salzburg EEG criteria for NCSE. NCSE: Non-convulsive status epilepticus, EEG: Electroencephalogram. (Adapted from Leitinger *et al*. Lancet Neurology 2016;15:1054-62)

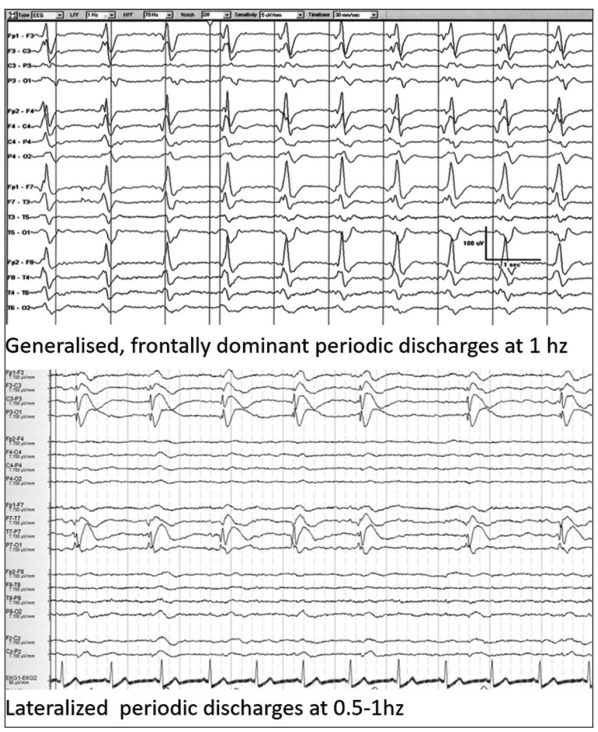

Figure 2: Ambiguous EEG patterns: The ictal interictal continnum. EEG Patterns in these two figures will need further evaluation for fluctuations in frequency and morphology, clinical correlations and response to IV benzodiazepine before establishing a diagnosis of non convulsive status epilepticus. Refer to Salzburg EEG criteria (Benickzy S 2013)

a purely clinical diagnostic test when EEG is unavailable [Box 2]. While this is useful in "proper NCSE," its value in other generalized periodic patterns such as triphasic waves of hepatic encephalopathy, Creutzfeld Jakob Disease and Epileptic encephalopathies, where the EEG may improve without corresponding improvement in the clinical behavior Johnson *et al*. 2017,[102] Gelisse *et al*. 2019[103] is questionable. Moreover, many of these patterns disappear spontaneously in sleep.

EEG in coma after HIE

Especially in patients with severe cerebral hypoxia, a particularly confusing scenario is the presence clinical myoclonus in the first few days with EEG burst suppression patterns of various degrees that mimic NCSE., available data do not indicate that pharmacological treatment of either the EEG alterations or early posthypoxic myoclonus has any positive impact on the patient's prognosis.[17,79] Administration of anticonvulsants in such cases appears to be just EEG cosmetics.[94] It important to note that while less myoclonus may be relief for nurses and family members, the comatose patient himself does not have any benefit from such treatment.

On the other hand, EEG can provide prognostic information in hypoxic–ischemic encephalopathy after CRA.[104] Seizures are detected in up to 40% of CRA survivors in a coma, and have been associated with adverse outcomes.[105,106] EEG patterns, such as burst-suppression, nonreactive background activity, or isoelectric EEG recordings are indicators of an unfavourable prognosis.[107] Although prognostication of poor outcome seems reliable, predictions for good prognosis still remain inaccurate.[105]

Imaging in NCSE

Imaging is mandatory when investigating focal SE, particularly at first presentation, to exclude a structural cause. Often there is a higher likelihood of identifying a remote symptomatic cause. On the other hand, patients with absence SE would be expected to have normal conventional neuroimaging. Transient changes on DWI and T2-FLAIR sequences are seen in up to half the patient with SE.[108] However, signal changes in the cortex may be falsely localising and may also involve the thalamus and pulvinar ipsilateral to the epileptiform activity. Leptomeningeal enhancement, luxury perfusion on MR angiography and diminished focal cortical veins on susceptibility weighted imaging may be noted in hyperperfused ictal regions.[109,110] Arterial Spin Labeling shows high CBF in the cortical epileptogenic zone, the ipsilateral pulvinar, and the contralateral cerebellum. A major challenge with these MRI findings is that we do not know how long the signal change persists after the cessation of SE: perfusion normalizes from seconds to minutes after the end of the episode, whereas signal changes on DWI and T2/FLAIR may require up to several weeks to resolve.[108]

Functional imaging studies such as the PET and SPECT may show abnormalities which indicate an unstable neuronal metabolic situation. This may, at best, support the diagnosis

of NCSE in challenging cases (such as focal SE) where scalp EEG lacks the sensitivity to secure the diagnosis.[111] The diagnostic role of the more sophisticated imaging techniques is still unclear.

MANAGEMENT OF NCSE

Unlike Convulsive SE which has standardized, rigorous treatment algorithms, treatment strategies for NCSE remain diverse and controversial due to the differing prognoses for the subtypes of NCSE.[4]

For patients with prior IGE, brain damage is not a primary concern. The goal of treatment is to return the patient to a functional state; hence, treatment approaches may be conservative. By contrast, NCSE related to acute cerebral damage is likely to be a marker of the severity of brain injury, rather than the phenomenon responsible for poor outcome. The majority of critically ill patients die of their underlying comorbidities and the role of NCSE as an independent factor of mortality remains questionable. Likewise, to demonstrate permanent brain damage as result of seizure activity in itself is difficult in the context of catastrophic events such as cerebral hypoxia, brain hemorrhage or trauma. In view of this, the aggression with which NCS must be treated in these settings is unclear.[112]

Several reviews inform choice and stratification of treatments for the broader spectrum of SE[113-115] but few specifically explore the treatment of NCSE[116,117] and NCSs.[118,119]

Most of the evidence for pharmacotherapy is derived from subgroup analyses of larger studies in SE.[120,121] The limited comparative studies on ASMs in NCSE have not consistently established the efficacy of a particular ASM,[122,123] traditional or new, but there is some evidence for the use of lacosamide.[124,125]

Considering the limited evidence regarding specifc seizure pharmacotherapy for NCSs/NCSE, the general principles of care are outlined below

Prinicples of management of NCSE

1. Suspect NCSE and establish correct diagnosis of type of SE and its precise etiology.
2. Use adequate doses of benzodiazepine in the early stages, initial doses are far too frequently inadequate.
3. Start treatment with parenteral medications with a view to speedily control the seizures. The rapid initiation of the drug in adequate doses is more important than the specific choice of drug. The presence of liver or renal dysfunction does not merit adjustments in the loading dose.
4. Choice of drug should be based on the type of seizures (focal versus generalized) and the spectrum of active comorbidities in the patient (viz liver or renal failure, cardiac arrhythmias, etc.). ASMs are deployed in a tiered fashion with intravenous nonsedating ones as the first and may be also second choice before moving to sedating drugs and oral medications.
5. When possible CEEG should be used to titrate therapy. The decision to use a sedating ASM and especially anesthetic agents should be guided not only by the EEG findings but also the overall clinical status, including airway protection, underlying etiology and general medical condition of the patient and possible overall prognosis.
6. When seizures are improving slowly in a patient with multiple medical issues and is not intubated, waiting several hours or even days for seizures to gradually reduce in frequency may be less problematic than loading more sedating medications.
7. A quick and thorough search for possible underlying medical systemic conditions that may have triggered the non-convulsive status is mandatory. Effective treatment will need that all these issues be addressed promptly. Immunotherapies for possible autoimmune causes may have to considered based on clinical suspicion alone, as tests results for these are often delayed and inconclusive.
8. NCSE after hypoxic-ischemic brain injury is considered an entity distinct from other acute forms of NCSE, as the underlying brain damage is largely irreversible and usually associated with an extremely poor outcome. CEEG during therapeutic hypothermia after CRA improved detection of seizures but the impact of early treatment is still controversial[126] Outcomesmay not improve with early seizure detection and treatment (Wijdicks 2002), but CEEG may assist in selection of patients for aggressive treatment and guide prognosis.[70]
9. Once seizures are controlled, sedating IV medications should be weaned first. Intermittent or continuous EEG may be required to ensure seizure freedom for at least 48–72 h. A couple of minor breakthrough seizures clinically or electrographically may not warrant re introduction of sedative IV medications.
10. The decision to wean other ASMs should be a measured one, based on the estimated risk of subsequent seizures, weaning the least effective medication first would be advisable. The process of weaning may have to be slow over several weeks or months, and documentation of the pattern of success with the ASMs would assist weaning in a rational order in the outpatient clinic.

In addition to the above general principles, treatment decisions are often driven by the specific type of NCSE and the level of consciousness of the patient.

Typical ASE

Typical ASE usually responds rapidly to intravenous benzodiazepines (IVBZPs). Valproate or levetiracetam is a good choice if IVBZPs are ineffective or contraindicated. De novo ASE is a situation-related NCSE, often triggered by drugs or drug withdrawal. Therefore, elimination of the trigger and transient AED therapy is usually sufficient.[40]

Atypical ASE

Atypical ASE in persons with Symptomatic Generalized Epilepsy can be challenging; expert advice should be sought, preferably at a dedicated epilepsy centre.

Focal SE

Unlike with typical Absence SE, response of focal SE to IVBZP is often delayed and recurrence occurs frequently. The challenges in treatment come when focal status persists despite IVBZPs and conventional AEDs. It is unclear if or when to use of anesthetic levels of medications in these relatively healthy patients. The results of treatment are driven by the underlying etiology and ability to treat the triggering event.

NCSE with coma (not preceded by convulsive SE)

NCSE with coma (not preceded by convulsive SE), requires a judicious and rapid stepwise pharmacotherapy approach with first- and second-line nonsedating ASMs used intravenously in full loading doses and rapid assessment of response; a parallel search and aggressive treatment of the underlying cause is recommended, including metabolic, septic autoimmune and paraneoplastic work up based on the clinical context. After two or more ASMs have failed, the decision to use anesthetic medications may be made based on patient demographics, etiology, and the general medical condition of the critically ill patient including airway and ventilation issues.

Subtle SE (NCSE after convulsive SE)

Subtle SE (NCSE after convulsive SE) usually warrants rapid and aggressive escalation to IV anesthetic drugs if second-line pharmacotherapy options fail, essentially a convulsive SE treatment protocol can be followed.

Super refractory and New Onset Refractory Status Epilepticus.

Failed first attempts at weaning of IV sedating medications in patients with convulsive SE, implies superrefractory SE and this would clinically resemble non-convulsive status with coma. Prolonged ICU stay on ventilator is fraught with inherent secondary complications of sepsis and multiorgan failure is unavoidable. Treatment choices narrow down and include anesthetic medications like ketamine, additional oral ASMs, Ketogenic diet, immunotherapies and in rare cases emergency epilepsy surgery, if the epileptic focus is clearly identified. Robust evidence for well informed choice in this regard are currently unavailable.[113,114]

PROGNOSIS IN NCSE

As NCSE encompasses a heterogenous group of disorders, it is associated with a corresponding variety of prognoses that are based on varying degrees of evidence. Some forms for example, SE with coma after CRA is associated with nearly 100% mortality. Although this may be largely attributable to the anoxia, an additive adverse effect of seizures or SE is implicated in the poor outcomes after head trauma.[57,58] Other studies indicate little long term impact of seizures *per se* on the final patient outcomes.[49,52] Recent evidence suggest that etiology is a strong predictor of the outcome and non-anoxic prolonged episodes of NCSE should be not considered a hopeless condition.[5,15]

CONCLUSION

Non-convulsive status is a group of heterogenuous clinical conditons with highly variable clinical presentations, etiology, clinical course, and outcomes. EEG is mandatory for confirming the diagnosis of NCSE. Present guidelines recommend continuous EEG monitoring in patients with convulsive seizures or SE who do not return to the neurofunctional baseline after initial treatment with AEDs, as also in patients with other neurological critical illnesses with unexplained altered levels of consciousness. With use of CEEG, we are beginning to define distinct subtypes of NCSE. The type of NCSE and the etiology are strong predictors of prognosis and thus should be used to guide treatment. Use of intravenous anesthetics for treatment of NCSE that is refractory to first-line and second-line treatment is still a matter of debate, and systematic trials that study treatment outcomes should help us answer this question. New-generation broad-spectrum AEDs with favourable safety profiles are being investigated and seem promising.

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