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ORIGINAL PAPER

Nonconvulsive status epilepticus in Neurological ICU patients

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Abstract

INTRODUCTION: Nonconvulsive status epilepticus (NCSE) is a condition involving seizures without convulsions; it is usually characterized by altered consciousness and behavioral and vegetative abnormalities. Owing to the nonspecific symptoms, NCSE is often overlooked, especially in neurological intensive care unit (NICU) patients. Therefore, we investigated the etiology, clinical features, electroencephalographic (EEG) changes, treatment options, and outcomes of NCSE in NICU patients with altered consciousness.

METHODS: This study retrospectively collected the data of 20 patients with altered consciousness in the NICU. NCSE diagnoses were established by the treating neurologist who had been trained to recognize nonspecific clinical signs and recognize complex EEG changes.

RESULTS: We identified 20 patients (43.95±20.70 years) with clinical signs and EEG findings consistent with NCSE; 9 were female. All the patients suffered from altered consciousness. Five patients had established epilepsy. NCSE was attributed to acute pathological conditions. The underlying cause of NCSE was intracranial infection in 6 patients (30%), cerebrovascular disease in 5 patients (25%), irregular use of epilepsy drugs in 2 patients (10%), immune-related inflammation in 1 patient (5%), other infections in 4 patients (20%), and unknown cause in 2 patients (10%). Fifteen patients had diffused, and five patients had temporal focal EEG abnormalities. Six of 20 NCSE cases (30%) resulted in death. All the patients, except for the patients who died, received anticonvulsant therapy and their altered conscious state was promptly altered.

CONCLUSION: The clinical symptoms of NCSE without convulsions are often obscure and difficult to detect. NCSE can cause serious consequences and even death. Therefore, for patients with a high clinical suspicion of NCSE, continuous EEG monitoring is needed to quickly identify this condition and promptly start treat them.

Abbreviations:

NCSE	- Nonconvulsive status epilepticus
ICU	- Intensive care unit
NICU	- Neurological intensive care unit
EEG	- Electroencephalogram
AEDs	- Antiepileptic drugs
SE	- Status epilepticus
STESS	- Status epilepticus severity score
GCSE	- General convulsive status epilepticus
GTCSs	- Generalized tonic-clonic seizures
ILAE	- International League Against Epilepsy

INTRODUCTION

Status epilepticus (SE) is a major neurological condition characterized by perpetuating or recurrent seizures for a certain period. SE can be divided into general convulsive SE (GCSE), which is easily recognized, and the severity is well established, and nonconvulsive SE (NCSE), which is characterized by some degree of altered consciousness as well as behavioral and vegetative abnormalities (Meierkord & Holtkamp, 2007; Sutter *et al.* 2016). NCSE constitutes approximately 20% of all SE cases in patients in general hospitals (Claassen *et al.* 2004; Dunne *et al.* 1987; Zhang *et al.* 2021), and approximately 47% of all SE cases in patients in intensive care units (ICUs)(Laccheo *et al.* 2015; Nusbaum & Gupta, 2019). Among patients who were comatose but had no clinical signs of seizures, electroencephalogram (EEG) monitoring was able to diagnose NCSE in 8% of SE patients in an ICU (Lattanzi *et al.* 2021). Although the incidence of NCSE in the ICU is high, the symptoms, especially in patients with altered consciousness, are nonspecific, so it is frequently mis diagnosed. A seizure longer than 30 minutes associated with prolonged epileptiform discharges on EEG is indicative of NCSE (Pan *et al.* 2021), but the Neurocritical Care Society has proposed shortening the 30 minutes period to 5 minutes. The International League Against Epilepsy (ILAE) task force has proposed a new definition of NCSE: a repetitive or prolonged electrographic seizure without any motor manifestations lasting longer than 5minutes (Trinka *et al.* 2015).

NCSE may occur in noncomatose or comatose patients: it was first described in noncomatose patients with epilepsy but is becoming increasingly recognized in comatose patients. The ILAE task force proposed a new classification of NCSE: NCSE with coma and NCSE without coma. NCSE without coma is commonly classified as generalized, focal or unknown (focal or generalized cannot be determined). Generalized NCSE consists of typical absence, atypical absence and myoclonic absence status. Focal NCSE can be divided into NCSE without impairment of consciousness, NCSE with aphasic status and NCSE impaired consciousness. NCSE with coma can be further categorized according to lateralized discharges and generalized epileptiform discharges (Trinka *et al.* 2015; Trinka & Kälviäinen, 2017). The detection of NCSE depends considerably on an initial suspicion of the condition and EEG verification of ongoing epileptic activity. The use of continuous EEG monitoring has been shown to increase the successful diagnosis of NCSE, especially in comatose patients. Although the diagnosis, treatment of NCSE remains controversial, a good outcome depends on early and appropriate treatment (Bravo *et al.* 2021).

In this study, we present our experience with the diagnosis of NCSE in NICU patients with altered consciousness and discuss the etiology, clinical features, EEG findings, therapeutic approaches and prognosis.

MATERIALS AND METHODS

All methods were carried out in accordance with relevant guidelines and regulations or the Declaration of Helsinki.

Patient population

This study retrospectively collected the data of patients in our NICU during the period from January 2019 to January 2021. All patients showed an acute and unexplained decreased level of consciousness. All patients were in compliance with the International League Against Epilepsy (ILAE) proposed a unified terminology and classification system based on the EEG standard for NCSE (Beniczky *et al.* 2013): (1) patients without known epilepsy-related encephalopathy, with epileptiform discharges (EDs)≤2.5 Hz or >2.5 Hz or rhythmic theta/delta activity (>0.5 Hz) and one of the following: clinical symptoms and EEG improvement after intravenous antiepileptic drug (AED) administration, subtle clinical seizures or typical spatiotemporal changes in the above EEG types; (2) patients with clear epileptic encephalopathy; compared with the baseline EEG, the amplitude or frequency is increased on the basis of the above EEG, and the clinical symptoms or EEG are improved after intravenous AEDs administration (The above two diagnostic criteria do not apply to children). The patients who presented with GCSE were excluded, and patients with NCSE following anoxic brain tumors or intracranial surgery were excluded. The diagnoses were established by the treating neurologist who had been trained to recognize nonspecific clinical signs and recognize complex EEG changes.

Study analysis

The electronic medical records were reviewed for demographic and clinical characteristics, including age, sex, seizure history, history of stroke, clinical features, EEG changes, treatments and outcomes. We identified the in-hospital mortality related to the status epilepticus severity score (STESS).

RESULT

Clinical characteristics

We identified 20 patients with clinical signs and electroencephalography records consistent with NCSE;

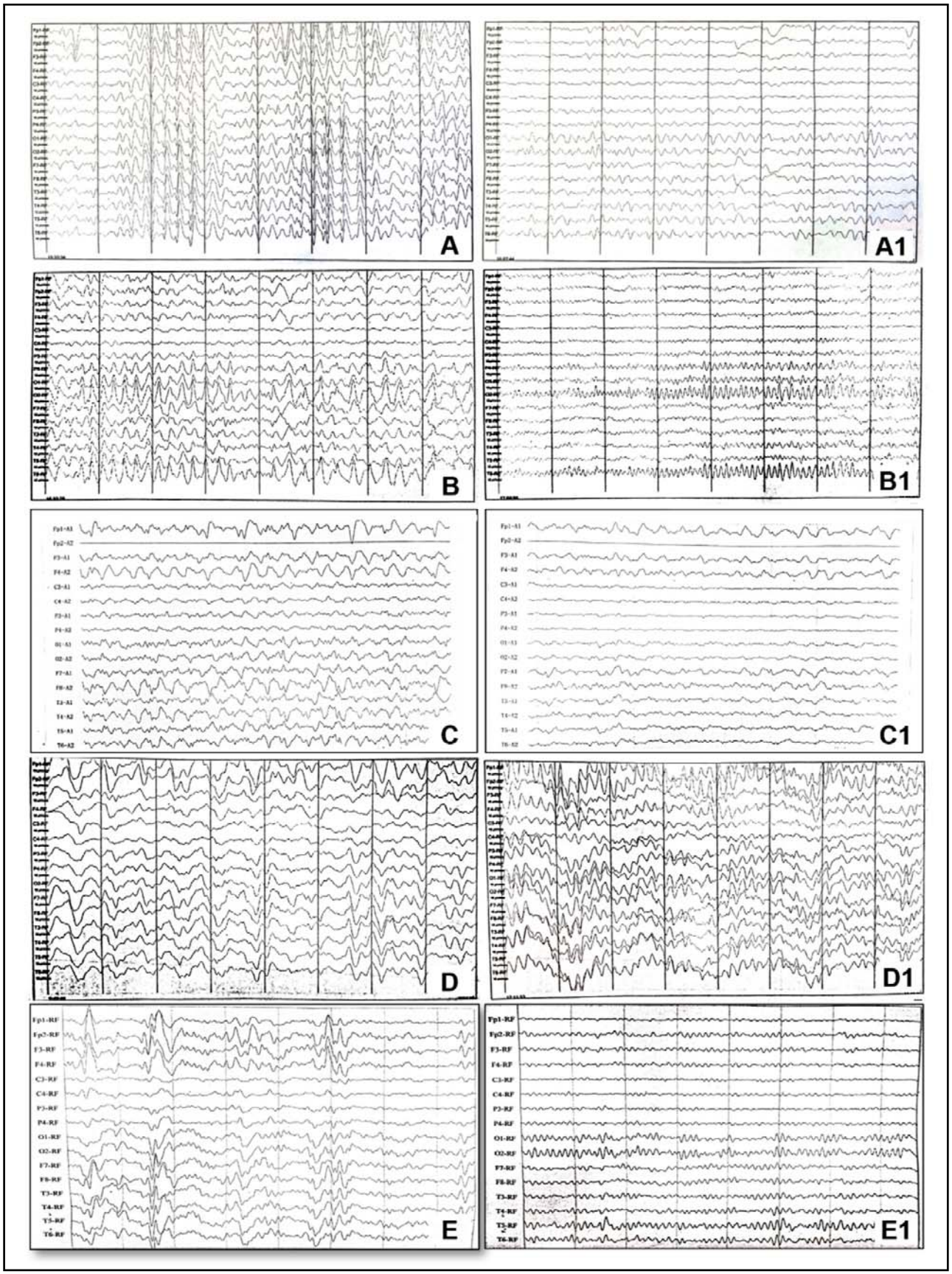

Fig. 1. EEG of NCSE patients before and after intravenous injection of AED.
EEG of patients with NCSE. (A-E) EEG of five NCSE patients showed that widespread rhythmic sharp waves or delta waves discharges. (A1-E1) After 35 minutes of intravenous injection of AEDs, the clinical symptoms and EEG of 5 patients were improved. NCSE: Nonconvulsive status epilepticus; EEG: Electroencephalogram; AED: Intravenous Antiepileptic Drug.

Tab. 1. Baseline clinical characteristics of the NCSE patients with altered consciousness (n=20)

Patients (n=20)	
Age (years)	43.95±20.7
Female-no. (%)	9 (45)
Male-no. (%) Specific etiology	11 (55)
Intracranial infection-no. (%)	6(30)
Cerebrovascular disease-no. (%)	5(25)
Irregular use of epilepsy drugs-no. (%)	2(10)
Immune-related inflammation-no. (%)	1(5)
Other infection-no. (%)	4(20)
Unknown cause-no. (%)	2(10)
EEG changes	
Lateralized discharges-no. (%)	5(25)
Generalized epileptiform discharges-no. (%)	15(75)
Past medical history	
Epilepsy-no. (%)	5(25)
Stroke-no. (%)	4(20)
Cognitive dysfunction-no. (%)	3(15)
Diabetes-no. (%)	3(15)
Hypertensive disease-no. (%)	5(25)
Coronary arteriosclerotic heart disease-no. (%)	1(5)
Auricular fibrillation-no. (%)	2(10)
Level of consciousness disturbance	
Somnolence-no. (%)	8(40)
Stupor-no. (%)	3(15)
Coma-no. (%)	7(35)
Vegetative state-no. (%)	1(5)
Confusion-no. (%)	1(5)

NCSE: Nonconvulsive status epilepticus;
EEG: Electroencephalogram.

there were 11 males and 9 females. The mean age was 43.95 years (range 23.25- 64.65 years). All the patients suffered from altered consciousness. Five patients had established epilepsy (Table 1).

Etiology

NCSE was attributed to acute pathological conditions including cerebrovascular disease, intracranial infection, immune-related inflammation, etc. The underlying cause of NCSE was intracranial infection in 6 patients (30%), cerebrovascular disease in 5 patients (25%), irregular use of epilepsy drugs in 2 patients (10%), immune -related inflammation in 1 patient (5%), other infections in 4 patients (20%), and unknown cause in 2 patients (10%) (Table 1).

EEG changes

All patients showed an acute unexplained decreased level of consciousness. The clear-cut EEG criteria for NCSE modified from Kaplan (2007) by the International ILAE were used (2013). The EEG recordings of all patients (n=20) showed epileptic activity; 15 patients (75%) had bilateral, and 5 patients (25%) had lateralized epileptiform discharges. 10 patients (50%) had continuous generalized spike-wave/sharp-wave discharges or spike-slow-wave complexes/sharp-slow-wave complexes. 9 patients (45%) had generalized rhythmic delta or theta activity. It was usually difficult to interpret the EEG patterns mentioned above. An improvement in the EEG changes and clinical features with intravenous AEDs supported the diagnosis of NCSE, but it was not necessary for the diagnosis NCSE when patients had no response to AEDs (Table 1).

Treatment

All NCSE patients received intravenous diazepam during the acute phase. Intravenous injection of diazepam took effect for 1-3 minutes and quickly entered the central nervous system through blood flow (Product Information, 2021). After epilepsy control, oral AEDs (Sodium valproate, oxcarbazepine, levetiracetam, or any combination of these drugs) were used according to the patient's condition. As shown in figure 1, after 35 minutes of intravenous injection of diazepam, the clinical symptoms and EEG of 5 patients were improved.

Outcomes

6 patients (30%) with NCSE died during hospitalization; 1 patient (5%) died from HIV-associated encephalitis with unresolved SE, 2 patients (10%) died from basilar artery syndrome, 1 patient (5%) died from multiple organ dysfunction syndrome, 1 patient (5%) died from respiratory failure, and 1 patient (5%) died from the formation of cerebral hernia.11patients (55%) returned to a normal condition. 5 patients (25%) who had a previous history of epilepsy returned to normal status.

The STESS can predict the prognosis. A high STESS was predictive of increased mortality. Patients with STESSs of 1 to 3 presented low mortality; however, those with STESSs of 4-6 presented high mortality (Table 2).

DISCUSSION

We evaluated patients admitted to the NICU with unexplained altered consciousness for whom typical EEG findings were observed. These patients were finally confirmed with the challenging diagnosis of NCSE. In our study, we observed the most common causes of NCSE were intracranial infections and cerebrovascular diseases, which is in accordance with findings by Bravo *et al.* (Bravo *et al.* 2021). Our study found that all NCSE patients suffered from acute pathological

Tab. 2. STESSs and in-hospital mortality

STESS	1	2	3	4	5	6
Number of patients	0	3	11	3	0	3
Mortality	0	0	2	1	0	3
(%)	(0%)	(0%)	(18.18%)	(33.33%)	(0%)	(100%)

STESS: status epilepticus severity score

conditions, except for in the cases of irregular use of AEDs. Consistent with the results of epidemiological studies in Germany, it was more difficult to diagnose NCSE in patients without prior epilepsy than in patients with established epilepsy (Power *et al.* 2015).

Acute pathological conditions plus severely altered consciousness may indicate a poor prognosis in NCSE patients. At the same time, the severity of the disturbance of consciousness may be related to the prognosis (Lee *et al.* 2021), and refractory NCSE was associated with significantly more frequent complications and worse outcome (Dericioglu *et al.* 2021). NCSE has been associated with considerable mortality in critically ill patients (Claassen *et al.* 2004; Lee *et al.* 2021; Litt *et al.* 1998; Young *et al.* 1996). Underlying causes were the determinants for mortality (Power *et al.* 2015). In our study involving 20 patients, six (30%) of the patients with NCSE died during hospitalization; one died from HIV-associated encephalitis with unresolved SE, two died from basilar artery syndrome, one died from multiple organ dysfunction syndrome, one died from respiratory failure, and one died from the formation of cerebral hernia. NCSE is often overlooked, especially in NICU patients. Therefore, for patients with coma in the ICU, it is necessary to be alert to the possibility of nonconvulsive SE.

Because NCSE presents no obvious seizures in the clinic, EEG abnormalities are the most important signs of NCSE. The EEG findings associated with NCSE can indicate various forms of persistent episodes, such as typical or atypical spikes and/or spike slow-wave complexes; sharp waves and/or sharps-low-wave complexes; multiple spikes and/or multiple spine slow-wave complexes; or mixed rhythm, evolved rhythmic theta or delta waves. After AED treatment, EEG and clinical symptoms are relieved, which contribute to diagnose NCSE (Leitinger *et al.* 2016). In our study, continuous EEG recordings of all patients (n=20) showed epileptic activity; 15 patients (75%) had bilateral, and 5 patients (25%) had lateralized epileptiform discharges. 10 patients (50%) had continuous generalized spikes or spikes slow-wave complexes or sharp waves or sharp slow-wave complexes. 9 patients (45%) had generalized rhythmic delta or theta activity; 1 of them (5%) had bilateral frequency asymmetry, and 1 of them (5%) showed a drop-in EEG voltage. It was usually difficult to interpret the EEG patterns mentioned above. An improvement in the EEG changes and clinical features with intravenous AEDs supported for the diagnosis of NCSE, but it was not necessary for the diagnosis NCSE when patients had no response to AEDs.

NCSE may be a clinical manifestation after the onset of generalized tonic-clonic seizures (GTCSs), but it may also be a clinical manifestation before seizure. After excluding organic lesions and metabolic encephalopathy, the use of AEDs under EEG monitoring can help control seizures and protect the brain. EEG improvements can also be used to assess the condition before the administration of AEDs. Although some studies have described a positive association between a delay in initial treatment in NCSE patients and a poor prognosis (Sagduyu *et al.* 1998),to our knowledge, the existing literature has not documented the long-term effects of active treatment in these patients.

In our study, we were unable to determine the total duration of NCSE in patients because their onset was unknown, so we could not correlate the total duration of NCSE and the initiation of medication with outcomes. Although our study had a small sample size and retrospective design, our research showed that EEG monitoring in NICU patients with altered consciousness was essential for identifying NCSE, thereby improving the prognosis of NCSE and the therapeutic effects of AEDs. Due to our limited medical conditions, this monitoring has not been carried out for the time being. In the future, we will improve the EEG monitoring equipment to improve the level of diagnosis and research, and we need more detailed prospective research to establish appropriate diagnostic criteria and new treatment strategies. Despite these limitations, our study data indicated that the underlying etiology is an important determinant of outcome, and that cautious monitoring is essential for identifying and preventing complications. NCSE is an epileptic syndrome that is difficult to treat. To determine the natural onset history of NCSE, establish appropriate diagnostic criteria and develop new treatment strategies for NCSE, well-designed prospective studies are needed.

Ethics approval and consent to participate

Informed consent form was obtained from each study participant, and the study was approved by the Research Ethics Committee of the First Affiliated Hospital of Army Medical University, ((B) 202261).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed in the study are not publicly available due potential identifiability but are available from the corresponding author on reasonable request are available from the corresponding author on reasonable request.

Competing interests

The authors declare tat they have no competing interests.

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Authors' contributions

Yuanyuan Huang: study design, statistical analysis, drafting of manuscript, and manuscript revision. Dezhi Yuan: statistical analysis, and significant review of the manuscript. Xianhua Hou: study design and manuscript revision. Li Gui: study design, interpretation of study findings, and significant review of the manuscript. All authors reviewed the manuscript for intellectual content, approved the final version, and agreed to be accountable for the work.

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