



Nonconvulsive Status Epilepticus: Current Status and Future Perspectives

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Abstract

Introduction Nonconvulsive status epilepticus is defined as a state of impaired consciousness with subtle motor manifestations and ongoing seizure activity in the electroencephalogram (EEG) for at least 30 minutes.

Objectives and Methods This study of nonconvulsive status epilepticus and its outcomes was a retrospective analysis of the continuous bedside EEG recordings of 100 patients over 2 years (Aug 2017–July 2019) at the Neurophysiology Department in Sir Ganga Ram Hospital, New Delhi. There were two groups of patients in the study comprising of adults (72) and children (28). A comparison between the two groups was made based on the clinical presentation, etiology, EEG, MRI findings, treatment, and the consequences.

Results and Conclusions In adults, nonconvulsive status had a high mortality rate, while in children, the associated comorbidities dominated and contributed to residual neurological sequelae. Early diagnosis and treatment at any age is essential to prevent cognitive decline and psychomotor retardation. Presently, bedside and ambulatory EEG recordings are used to capture the dynamic and rhythmic features of the ictal EEG. Continuous EEG monitoring enables bedside assessment of the effectiveness of treatment.

Keywords

- ▶ nonconvulsive status
- ▶ Salzburg criteria
- ▶ antiepileptics

Introduction

Nonconvulsive status epilepticus is reported in 8 to 48% of comatose patients.^{1,2} In critically ill patients, a subtle twitch of the face or limbs, tonic eye or head deviation, mutism, or impairment of consciousness lead to a suspicion of a nonconvulsive status epilepticus^{3,4} In children, nonconvulsive status is classified according to age, the degree of cerebral maturation, and the association with encephalopathy.⁴ Minor symptoms of forgetfulness, lack of attention, excessive daytime sleepiness, hyperactivity, or gait instability should be investigated with an electroencephalogram (EEG).^{4,5} Nonconvulsive status can lead to progressive neuronal damage and psychomo-

tor retardation.^{4,5} Previously, these subtle findings were overlooked by clinicians due to ignorance. However, recent advances allow the use of bedside EEG in intensive care patients to record the dynamic and evolving patterns in the EEG.

Methods

This study was a retrospective analysis of 3,000 patients who underwent bedside EEG monitoring at Sir Ganga Ram Hospital, New Delhi, for 2 years from August 2017 to July 2019. Three thousand cases included inpatients admitted to the wards, intensive, and critical care service but not outpatients.

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Hundred patients had EEG findings characteristic of a non-convulsive status epilepticus.

Aim of the Study

Our aim was to study the electroclinical characteristics of nonconvulsive status epilepticus and its outcomes.

The inclusion criteria for the study involved patients of any age (neonates, children, or adults) with clinical features of altered sensorium, subtle seizures, or abnormal behavior. Using the Salzburg criteria,⁶ patients without pre-existing epileptic encephalopathy with EEG findings of continuous ictal discharges at >2.5 Hz/s, ictal activity with spikes at <2.5 Hz/s and improvement with benzodiazepines, and ictal rhythms of >2.5 Hz/s with focal epileptic phenomena, typical spatiotemporal evolution, and nonconvulsive status following a convulsive status were included in the study. One or more of the above-mentioned criteria with 30 minutes of ictal activity on EEG recording was sufficient for inclusion in the study.

Recording of the EEG

The bedside EEG recordings were performed for a minimum duration of 30 minutes for a maximum of 2 days. A 21-channel digital EEG recording was obtained by 10 to 20 system of placement using the bipolar montage. Filter settings were between 0.3 and 70 Hz, and paper speed was 30 mm/s. Neonatal montages were used for neonatal EEGs. All EEGs were analyzed by two certified neurophysiologists with expertise in intensive care EEG.

Classification of EEG Findings

We classified the discharges based on the Salzburg Consensus Criteria⁶: (1) patients without pre-existing epileptic encephalopathy EEG findings of continuous ictal discharges at >2.5 Hz/s, (2) ictal activity with spikes at <2.5 Hz/s and improvement with benzodiazepines, (3) ictal rhythms of >2.5 Hz/s with focal epileptic phenomena like facial twitching, gaze deviation, or nystagmus, (4) typical spatiotemporal evolution in the EEG, and (5) nonconvulsive status following a convulsive status epilepticus.

Statistics

Descriptive summaries were reported as percentages for categorical variables and mean \pm standard deviation for numerical variables. Statistical analysis was done by descriptive statistics using the chi-square test, and software used in the analysis was SPSS 22.0 version and GraphPad Prism 6.0 version, and $p < 0.05$ was considered as the level of significance.

Results

Hundred patients were included in this retrospective study (28% children and 72% adults; 44% females and 58% males). The presenting complaints of adult patients and children were summarized as coma, confusion, behavioral changes, psychiatric symptoms, psychomotor regression, and myoclonus (**►Fig. 1A, B**). The underlying diseases contributing to nonconvulsive status in adults and children were hypoxic and septic encephalopathy, viral and autoimmune encephalitis, absence status, and epileptic encephalopathies (**►Fig. 2A, B**). The findings on continuous EEG monitoring are given in **►Fig. 3A, B**. The MRI features of the study group are represented in **►Fig. 4A, B**. Post-cardiac arrest hypoxic brain damage, encephalitis, brain tumors, strokes, and head injury were important causes in adults, while children had a different spectrum comprising of viral encephalitis, hypoxic-ischemic encephalopathy, polymicrogyria, lissencephaly, and tuberous sclerosis. The outcomes of the two groups with the mortality rates are represented as follows (**►Fig. 5**). About 61.1% adults recovered, 25% had residual sequelae and 13.9% died. About 42.9% children recovered and 57.1% children had residual sequelae. The treatment measures are given in **►Table 1**. Eighty percent of patients received IV midazolam, IV phenytoin was administered to 60% patients, and others received IV valproate (38%), levetiracetam (22%), lacosamide (8%). Forty percent patients were on ventilator support, and 22% received anesthetic medication. Patients were followed-up for 6 months after non-convulsive status.

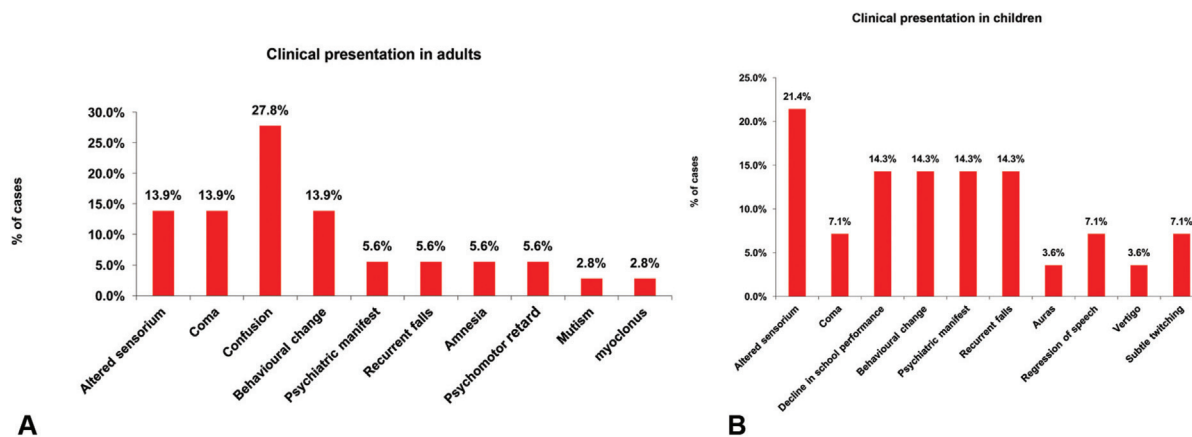


Fig. 1 (A) Presenting complaints in adults. (B) Presenting complaints in children.

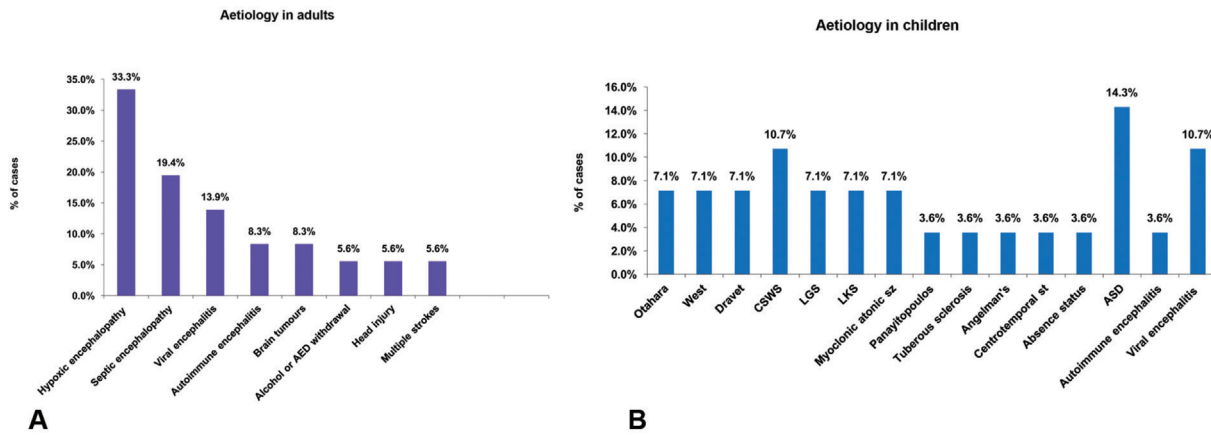


Fig. 2 (A) Underlying etiological causes of nonconvulsive status in adults. (B) Underlying etiological causes of nonconvulsive status in children.

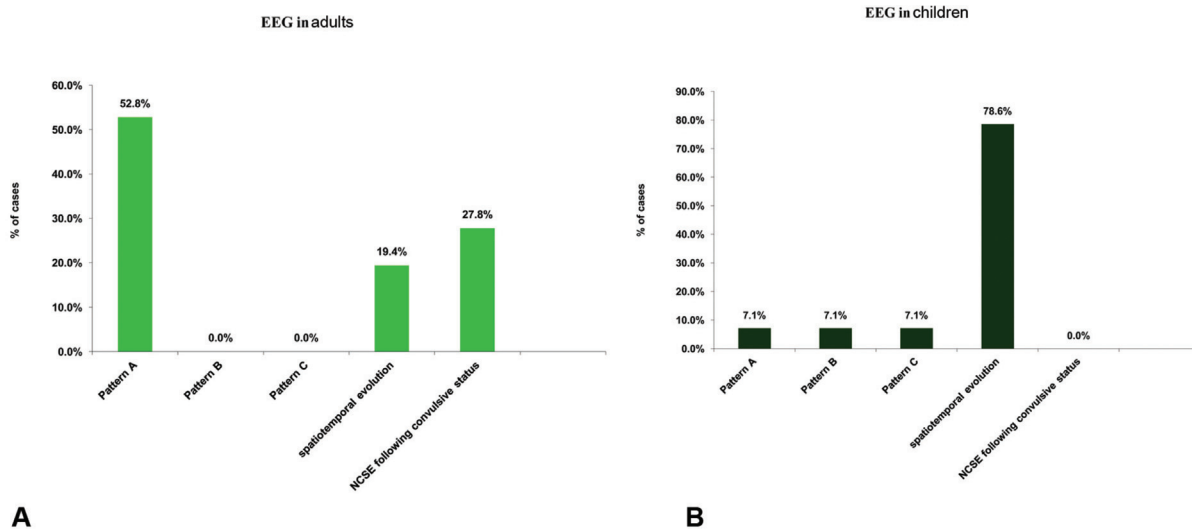


Fig. 3 (A) Electroencephalographic findings on continuous EEG monitoring in adults. Pattern A: continuous ictal discharges >2.5 Hz, Pattern B: continuous ictal discharges <2.5 Hz and clinical improvement with benzodiazepines, Pattern C: ictal rhythms of <2.5 Hz with a focal epileptic phenomenon. Spatiotemporal evolution. Nonconvulsive status following convulsive status. (B) Findings on continuous EEG monitoring in children. Pattern A: continuous ictal discharges >2.5 Hz, Pattern B: continuous ictal discharges <2.5 Hz and clinical improvement with benzodiazepines, Pattern C: ictal rhythms of <2.5 Hz with a focal epileptic phenomenon, Spatiotemporal evolution. Nonconvulsive status following convulsive status.

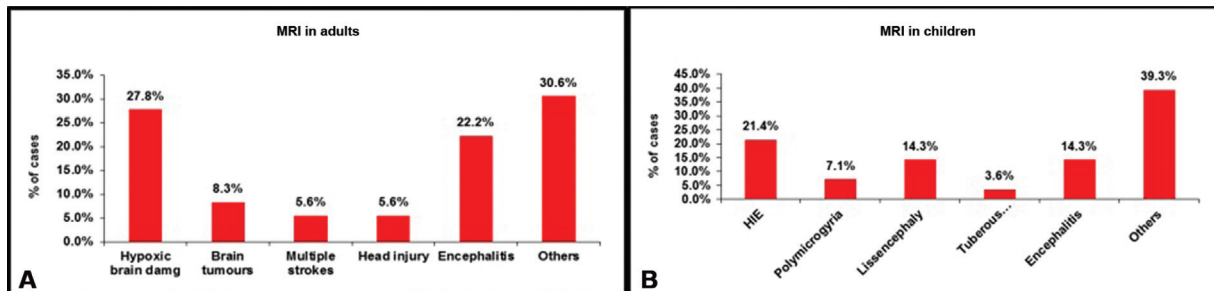


Fig. 4 (A) MRI findings in adults. (B) MRI finding in children.

Discussion

Nonconvulsive status epilepticus has been described and studied since the 1950s.¹⁻³ Nonconvulsive status epilepticus accounted for 37% of cases of altered sensorium and 8% cases

of coma in the intensive care unit.^{3,4} An alteration of behavior, automatisms, blinking, hallucinations, or a prolonged encephalopathy in the intensive care unit should prompt investigations.^{3,4} In recent years, this clinical spectrum has been expanded to include persistent laughing, catatonia,

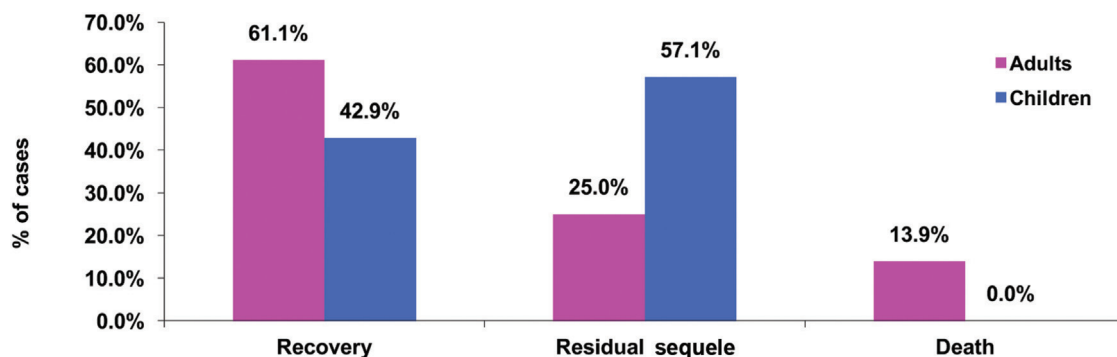


Fig. 5 Outcomes of the study groups with the mortality rate in numbers.

Table 1 Treatment measures employed in the patients

Treatment	%
IV Benzodiazepines	80
IV Phenytoin	60
IV Valproate	38
IV Levetiracetam	22
IV Lacosamide	08
Anesthetic medication	22
Ventilatory support	40

psychosis, visual hallucinations, autonomic dysfunction, prolonged apnoea, cardiac arrest, and sudden unexplained death in epilepsy.⁴⁻⁶ Currently, nonconvulsive status is defined as a state of prolonged unconsciousness or altered sensorium with behavioral, vegetative, or subjective symptoms like auras without major convulsive movements lasting for >5 minutes associated with continuous epileptiform activity in the EEG.⁴⁻⁶ Epileptic encephalopathies like Lennox-Gastaut, Landau-Kleffner, and electrical status in slow-wave sleep have altered neuronal networks which lead to a nonconvulsive status.⁴⁻⁸ In these children, nonconvulsive status manifests either as an absence status or a complex partial status epilepticus.⁴⁻⁸ Nonconvulsive status, thus, is an epileptic cerebral response dependent on the stage of neuronal maturation, the presence or absence of encephalopathy, and the type of epilepsy syndrome.⁹ During an ongoing nonconvulsive episode, there is increased cerebral blood flow, raised intracranial tension, increased cerebral oxygen demand, and excitotoxic neuronal damage.^{9,10}

Nonconvulsive Status Epilepticus in Adults

Nonconvulsive status epilepticus was recognized in 72% adult patients (►Fig. 1A). The clinical manifestations were altered sensorium, coma, behavioral changes, psychiatric manifestations, recurrent falls, psychomotor retardation, and myoclonic jerks (►Fig. 1A).⁹⁻¹² Recently, aphasia, amnesia, and mutism have been included as symptoms of nonconvulsive status in critically ill patients (►Fig. 1A). Common

precipitants include metabolic and electrolyte imbalance with hypoglycemia, hyperglycemia, hypercalcemia, hypocalcemia, hyponatremia, and hypomagnesemia.⁹⁻¹² Central nervous system or systemic infections, immune deficiency states related to human immunodeficiency virus, and cerebral toxoplasmosis trigger abnormal electrical phenomena.⁹⁻¹¹ Medications like carbamazepine, ceftazidime, ifosfamide, and antipsychotics cause an altered mental status.⁹⁻¹¹ An abrupt withdrawal of benzodiazepines, psychotropics, and anticonvulsants trigger a nonconvulsive status.^{10,11} Nonconvulsive status can follow changes in anti-epileptic medication, drug interaction, or alcohol withdrawal.⁹⁻¹¹ Paraneoplastic syndromes lead to refractory nonconvulsive status epilepticus with an increase in neuronal excitability and changes in neuronal permeability.¹²

Nonconvulsive Status in the Intensive Care Unit

There were cases of hypoxic encephalopathy, septic encephalopathy, and viral and autoimmune encephalitis from the intensive care unit (►Fig. 2A). Critical care patients presented in an epileptic twilight state with fluctuating levels of consciousness and automatisms.¹³ Electrographic status following cardiorespiratory arrest has high mortality leading to death in unsuspected cases.¹³ Induced hypothermia with rewarming from hypothermic states is complicated by epileptiform discharges in 33% cases.^{14,15} Continuous nonconvulsive ictal activity is associated with lethal complications like cerebral edema, midline shifts, and vascular compromise.¹⁵ Comorbidities like meningitis, systemic infections, head injuries, spontaneous intracerebral hemorrhages, pneumonia, electrolyte disturbances, and hormonal changes promote epileptogenesis.^{14,15} DeLorenzo et al detected a nonconvulsive status following a generalized status epilepticus in 14%, while we have reported a nonconvulsive status following a convulsive status in 27.8% patients in the intensive care unit (►Fig. 3A).

Nonconvulsive Status Epilepticus in Children

Nonconvulsive status in children is an epileptic response to the stage of development and maturation of the brain.¹⁶ Enduring epileptic syndromes can have an increased

incidence of a nonconvulsive status.¹⁶ In a series by Stores et al nonconvulsive status was reported in 50 children, wherein three children presented with typical childhood absence epilepsy, 18 had Lennox Gastaut syndrome, and 13 cases had myoclonic atonic epilepsy.¹⁶ In our series of 28 children, absence status was recorded in two, children epileptic syndromes in syndromes in 16 cases, myoclonic atonic epilepsy in two children, and autism spectrum disorders in four children (→ Fig. 2B). Children can have subtle presentations with declining school performance, forgetfulness, sleepiness, vacant stares, recurrent falls, and nocturnal enuresis.^{16,17} Clinically, children manifest with an absence status or complex partial nonconvulsive status.^{16,17} A simple counting test can be done at the bedside to detect the absence status.¹⁷ Childhood epileptic syndromes present in young children with the regression of previously achieved milestones and psychomotor retardation.¹⁸ In the Landau-Kleffner syndrome, undetected epileptic seizures worsen language skills and impair social interaction, while treatment with antiepileptics improves social communication.¹⁹ Autism spectrum disorders are characterized by the impairment of social communication and a restricted repertoire of interests.^{18,19} Convulsive or nonconvulsive episodes occur in 25% of autism spectrum disorders with abnormalities in genomic copy variation or single-gene mutations.¹⁹

Nonconvulsive Status Epilepticus in Adolescents

Nonconvulsive status can be a sequelae to head injuries caused by road traffic accidents manifesting with concussion, contusions, intracerebral bleeds, or subarachnoid hemorrhages.²⁰ In cases of cerebral trauma, abnormal neural metabolites like lactate, pyruvate, and neurofilament light chains accumulate with unfavorable neurological outcomes.²⁰ In adolescents, infections like bacterial meningitis, tuberculous meningitis, Lyme disease, leptospiral meningitis, viral encephalitis, and autoimmune encephalitis lead to drug-refractory epilepsy with a nonconvulsive status.²⁰ In autoimmune encephalitis, autoantibodies targeting cell surface antigens like N-methyl-D-aspartate receptor and intra-cellular synaptic proteins like GAD 65 manifest as convulsive or nonconvulsive status epilepticus.²¹ In our series of 100 patients, viral encephalitis contributed to 10 cases, autoimmune encephalitis six cases, and head injury four cases (→ Fig. 2A, B).

Nonconvulsive Status in the Elderly

Nonconvulsive status is often missed in the elderly who are on multiple medications for chronic illnesses.²² Nonconvulsive status can present with recurrent falls, confusion, automatisms, or decreased consciousness.²² Bottaro et al detected 19 cases of nonconvulsive status in the elderly aged over 75 years, while we detected 10 cases of NCSE in elderly patients who had brain tumors, strokes, and encephalitis.²² Ongoing seizure activity with secondary neuronal injury, cerebral hypoxia, and neuronal death contributed to high mortality.^{22,23} Early diagnosis and immediate treatment could prevent progressive memory impairment.²³ Nonconvulsive status caused memory impairment and altered sensorium in the elderly.^{22,23} Withdrawal of benzodiazepines,

cerebrovascular accidents, head injury, Alzheimer's disease, and systemic infections contributed to a nonconvulsive status.^{22,23} Head injuries in the elderly lead to increased metabolic demands in an already compromised brain.²³ Shneker and Fountain detected an 18% mortality rate in elderly patients with a nonconvulsive status, while we had 13.9% deaths of which 12% were in the elderly.²³ Young et al attributed the high mortality to a prolonged duration of the illness and a delay in the diagnosis of nonconvulsive status.²³

Diagnosis and Treatment of Nonconvulsive Status

Continuous EEG monitoring in the intensive care unit has revolutionized critically ill patient care.^{24,25} In most patients, the response to intravenous benzodiazepines and other antiepileptics is dramatic in the absence of enduring epilepsy syndromes.^{24,25} A high index of suspicion and prompt bedside EEG recording in patients with decreased responsiveness help in the recognition of this potentially treatable condition.²⁵ In the setting of hypoxia and sepsis, the clinical picture is obscured by coexisting ailments and age-related co-morbidities.²⁵ In such a situation, one's clinical judgment and immediate treatment measures prevent ongoing neuronal injury and irreparable brain damage.^{24,25}

Conclusion

In conclusion, nonconvulsive status is a medical emergency that needs to be detected at the bedside by EEG. Once diagnosed, treatment should be prompt with intravenous benzodiazepines and antiepileptics to halt neuronal injury and prevent cognitive impairment. In our series of 100 patients, the response to benzodiazepines and other antiepileptics was dramatic. If undiagnosed, nonconvulsive seizures progressed to a refractory status epilepticus with irreparable brain damage. In this retrospective study of 100 patients, 13.9% adult patients succumbed and 86.1% survived (→ Fig. 5). Our case series on nonconvulsive status is unique as it spans all ages and highlights the multifarious presentations to clinicians. We have included patients from all specialties under the umbrella of nonconvulsive status. Besides, this study is comprehensive as it showcases the magnitude of the problem and includes intensive care patients who have received multiple treatment modalities including induced hypothermia and rewarming.

Note

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Conflict of Interest

None declared.

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