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TREATMENT AND OUTCOME OF NON-CONVULSIVE STATUS EPILEPTICUS IN CHILDREN: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background and objective:

Incidence and prevalence of non-convulsive status epilepticus is difficult to know, especially in developing countries where access to diagnostic tools like EEG is limited. The objective of this study was to determine the treatment and outcome of non-convulsive status epilepticus in children.

Methods:

A total of 38 children were included in this prospective cross-sectional study, having EEG suggestive of non-convulsive status epilepticus. Response of the treatment given was measured by doing EEG after treatment to see resolution of non-convulsive status and improvement in clinical features too. Outcome was also assessed in terms of morbidity and mortality. The collected data were analyzed using SPSS version 20.

Results:

There were 38 patients studied who presented with NCSE. There was male predominance and most of the children presented between 2-5 years of age (n=15).These children were treated with multiple antiepileptic drugs. Majority of the patients had NCSE for more than 72 hours(n=24). There were 23 children who partially recovered from NCSE based on EEG findings while 15 got fully recovered and had less morbidity with p value of <0.000. In terms of morbidity and mortality a major chunk had no morbidity (n=16). Treatment and EEG based outcome were inversely proportional to each other. Duration of NCSE had great impact on EEG based outcome plus morbidity and mortality. The greater the duration, the more the morbidity with significant p value of < 0.0020 .

Conclusion:

Non-convulsive status epilepticus needs prompt diagnosis and treatment, as early intervention improves the prognosis in terms of morbidity and mortality.

Keywords: Non-convulsive status epilepticus, Epilepsy, Prognosis

INTRODUCTION

Status epilepticus can be defined as a condition in which a patient seizes continuously for five minutes or have frequently occurring recurrent seizures without recovery between the attacks.[1] Nonconvulsive status epilepticus (NCSE) refers to a state where a patient does not exhibit tonic clonic convulsions rather presents with subtle signs or motor movements with or without altered state of consciousness. This diagnosis is confirmed through electroencephalography (EEG), which reveals continuous electrographic seizure activity.[2]

Status epilepticus has incidence of approximately 10-20/100,000 children, with non-convulsive status epilepticus accounting for 25-50% of all the children.[3-7] Incidence and prevalence of non-convulsive status epilepticus is difficult to know, especially in developing countries where access to diagnostic tools like EEG is limited.

Common etiologies of non-convulsive status epilepticus are acute hypoxic ischemic injury, central nervous system infections, change in antiepileptic drug

regimen, refractory or inadequately treated epilepsy, cerebrovascular accidents and degenerative brain diseases. Typical clinical features of non-convulsive status epilepticus are focal seizures with impaired awareness, epigastric discomfort, hallucinations, disturbance of consciousness, abnormal eye or head movements, autonomic dysfunction and can even lead to cardiac arrest.[8,10]

Non-convulsive status epilepticus is treated initially with intravenous (IV) benzodiazepines. If seizures remain uncontrolled, IV phenytoin, valproic sodium or levetiracetam is administered. In refractory cases, third line treatment consisting of midazolam or propofol infusion is given.[11] Methylprednisolone pulses followed by oral steroid therapy are equally effective in cases of refractory status epilepticus, especially in setting of immune mediated disorders.[12]

Outcome of NCSE depends on several factors including age, gender, underlying etiology and the timing of detection and intervention. NCSE is challenging to manage, both in terms of diagnosis and treatment, posing a significant concern for neurologists, epileptologists and intensivists. Due to these complexities, research on NCSE in pediatric age group is limited. In resource constrained countries, access to diagnostic tools and treatment options is restricted and often unevenly distributed, especially in peripheral and rural areas. The primary aim of this study was to assess the outcome of NCSE across different anti-seizure medication treatment tiers. Additionally, it also aims to guide clinicians on how to opt for a structured approach in diagnosing NCSE and provide a line of direction to improve the outcome.

METHODS

This prospective cross-sectional study was conducted in the High Dependency Unit of Department of Pediatric Neurology, University of Child Health Sciences and The Children's Hospital, Lahore, over a period of six months from September 2020 to February 2021 after ethical approval. Based on the reported incidence of status epilepticus at 10 per 100,000 children, with NCSE accounting for 25% of cases, the sample size was calculated to be 38 patients, with confidence interval of 95% and margin of error of 5%.[3] The patients were selected by non-probability, consecutive sampling. The study included all patients from one month to 18 years of age, of either gender, having EEG-confirmed NCSE, with and without coma. Patients with EEG not suggestive of NCSE or convulsive status epilepticus were excluded from the study.

Data was collected after taking written informed consent from parents and guardians of children. Their demographic details were collected on a pre-designed proforma. Comprehensive history was taken with detailed clinical neurological examination for etiological purpose, followed by review of antiepileptic drugs and other regimens given to control the NCSE. EEG was considered the gold standard for diagnosis and EEG tracings were reviewed by pediatric neurologist according to the criteria of non-convulsive status epilepticus including frequency, distribution, type of epileptiform discharges and focus of onset. Response of the treatment given was measured by doing EEG after treatment to see resolution of NCSE and improvement in clinical features too. Outcome was also accessed in terms of morbidity and mortality.

Lumbar puncture and neuroimaging were also done where ever applicable for identification of underlying etiology, as they play a crucial role in determining patient's outcome. Additional investigations, such as fundoscopy, complete blood count (CBC), C-reactive protein (CRP), electrocardiography (ECG), echocardiography, antinuclear antibodies (ANA), complement levels C3 and C4, and other relevant tests, were performed based on suspected etiologies.
The collected data were analyzed using SPSS version 20. Quantitative variables, such as age, were presented as mean and standard deviation, while qualitative variables, such as gender, were expressed as frequencies and percentages. A p-value of <0.05 was considered statistically significant in determining associations between EEG based outcome and etiology, duration of seizure, mortality and morbidity.

RESULTS

There were 38 patients with NCSE and male to female ratio turned out to be 2:1. Most of the children presented between 2-5 years of age (n=15). These children were treated with multiple antiepileptic drugs including midazolam and phenytoin for acute management followed by valproate sodium, levetiracetam, lacosamide, carbamazepine, topiramate, lamotrigine and vigabatrin in maintenance therapy in descending order. Out of 38 children, 11 responded to two drugs, 10 to three drugs, eight to four drugs, and nine required more than four drugs to achieve a response.

Following treatment, EEG normalized in nine children while six displayed focal Non - convulsive status epilepticus. Despite treatment, three patients showed a persistent pattern of generalized NCSE. In three patients EEG pattern was of generalized non-convulsive status epilepticus despite the treatment given to them.

Among patients with NCSE lasting more than twenty-four hours, six (75%) fully recovered and two (25%) partially recovered. In those with NCSE duration exceeding 48 hours, the rate of full recovery dropped to 50 percent (three out of six), with the remaining three patients showing only partial recovery. Notably, in the group with NCSE extending beyond 72, only six (25%) achieved full recovery, whereas a significant majority of 18 patients (75%) experienced only partial recovery. Increasing duration of NCSE was therefore significantly associated with worse outcomes ($p<0.002$).

The main etiology in non-convulsive status epilepticus was found to be epilepsy which was about 63.2 %(n=24). Second most common cause was due to CNS infections in 18.4 % (n=7) children. Degenerative brain diseases causing non convulsive status epilepticus was in 13.2 % (n=5) children. While 2.6 % (n=1 for each) children were having non convulsive status epilepticus due to epileptic encephalopathy and post asphyxia brain damage respectively.

Outcome of NCSE was divided into two categories: EEG based outcome and mortality & morbidity. Based on EEG findings, 23 (60.5%) showed 50% reduction in epileptiform activity, while 15 (39.5%) had 100% reduction in epileptiform discharges, with minimal morbidity ($p= <0.000$). In addition to this, when the duration of NCSE was > 72 hours, EEG based outcome became poor with p value of < 0.037.

Regarding morbidity and mortality, the majority of patients 16 (42%) had no morbidity, while 21(55%) had some morbidity. Among patients with NCSE lasting more than 24 hours, seven had no morbidity, while one exhibited behavioural issues. No cases of hemiparesis, seizures, or mortality were recorded in this group. In the group with NCSE exceeding 48 hours, five patients had no morbidity, while one developed seizures. Notably, in the group with NCSE lasting more than seventy-two hours, morbidity was significantly higher: 12 patients had seizures, five had behavioural issues, two developed hemiparesis, and one patient succumbed to the illness. Only four patients in this group had no morbidity. Overall, among 38 patients, 16 had no morbidity, while the remaining exhibited various complications.

Regarding factors affecting the EEG based outcome, we studied gender, presenting symptom and etiology. Among children who fully recovered from NCSE, 11 (29%) were males and four (10.5%) were females. In contrast, partial recovery was observed in 15 males (39.5%) and eight females (21%). The highest rate of full recovery was seen in children presenting with an overlap of symptomatology in 10 (26%), followed by those with abnormal behavior in two (5%), complex febrile seizure, altered sensorium and staring gaze with one (2.6%) in each.

The relationship between the number of antiepileptic drugs (AEDs) used and morbidity or mortality was assessed. Among patients treated with two AEDs, one developed hemiparesis, four had seizures, two experienced behavioural issues, and four had no morbidity. There were no deaths in this group. In the three AED group, none developed hemiparesis or behavioural issues, two had seizures, and eight had no morbidity. In the four AED group, one patient developed hemiparesis, two had seizures, two had behavioural issues, one patient died, and two had no morbidity. In the group receiving more than four AEDs, five patients developed seizures, two had behavioural issues, and two had no morbidity. No hemiparesis or mortality occurred in this group. Overall, out of 38 patients, two developed hemiparesis, 13 experienced seizures, six had behavioural issues, one died, and 16 had no morbidity.

The association between EEG-based outcomes and the number of AEDs administered were compared. In the two AED group, three patients fully recovered while eight showed partial recovery. In the three AED group, six patients fully recovered and four had partial recovery. The four AED group had three full recoveries and five partial recoveries. In the group treated with more than four AEDs, three patients fully recovered while six showed only partial recovery. In total, out of 38 patients, 15 fully recovered and 23 had partial recovery.

DISCUSSION

NCSE remains a challenging neurological emergency in pediatric populations. Its diagnosis and management are complex, as it is not only difficult to predict but also challenging to hit at right time to detect and treat

promptly. If left untreated for more than 24 hours, the outcomes can be devastating.[1,11]

Both convulsive and non-convulsive status epilepticus have the potential to cause irreversible neurological injury, which underscores the necessity of early intervention for both conditions. The electroencephalogram (EEG) plays a crucial role in diagnosing NCSE, providing essential confirmation for its detection and guiding treatment decisions.[12,14]

Our findings demonstrated a male predominance, with the most vulnerable age group being 2-5 years, which differs from the findings of Brophy GM et al who reported a slightly different age distribution.[1]

A majority of children responded well to treatment with two AEDs, although some patients exhibited resistance, necessitating the escalation of therapy to more than four drugs. Galimi et al. similarly observed the need for therapy escalation due to partial response to initial AED treatment.[2,11] Benzodiazepines remain the first line anti seizure medication. Phenytoin, Levetiracetam, sodium valproate and lacosamide could be considered as the first choice, second-line ASM in the management of both convulsive and non convulsive status epilepticus.[15-19]

Regarding EEG findings, our study identified a substantial number of patients with EEG-confirmed NCSE. out of these 7 exhibited focal NCSE and 31 demonstrated generalized NCSE.Most patients in our study had NCSE lasting longer than 72 hours. The prognosis and outcome were better for patients whose NCSE lasted less than 24 hours, with fewer sequelae observed.

Etiological factors were also significant in determining outcomes. Patients with a known history of epilepsy showed partial improvement (n=15), while those with acute or acquired central nervous system (CNS) infections exhibited a favorable response (n=5). However, children with congenital brain malformations, degenerative brain diseases, and ischemic brain injuries had poor prognoses, a pattern that has been consistently observed in the literature.[1,14,20]

Additionally, NCSE can lead to multisystem organ failure, making early recognition and treatment even more critical. Despite progress in the management of NCSE in children, further advancements are needed to optimize treatment outcomes. The key to successful management remains a rapid, multidisciplinary approach for timely recognition and intervention.[1,21]

CONCLUSION

The treatment of NCSE and its prognosis are closely intertwined, with better outcomes associated with fewer AEDs and less drug resistance. Children who require fewer medications tend to have a better prognosis with fewer long-term sequelae compared to those with multidrug-resistant NCSE. Early identification, thorough investigation, prompt treatment, and vigilant monitoring are crucial for reducing morbidity and mortality in children with NCSE.

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Authors' contribution:
Shaila Ali: concept and design. data collection, manuscript writing and manuscript review
Natasha Ghani: Data analysis and interpretation, manuscript writing
Tipu Sultan: concept and design, manuscript review

All the authors have approved the final version to be published, and agree to be accountable for all aspects of the work.

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