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Clinical profile and outcome of refractory convulsive status epilepticus in older children from a developing country

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ABSTRACT

Purpose: The current study evaluates the etiology, clinical course and outcome of refractory convulsive status epilepticus (CSE) in older children.
Methods: Retrospective analysis of data of 73 children with CSE, aged ≥2 and ≤12 years was performed. Odds ratios were calculated between variables for clinical course and outcome. Mortality of the group was analyzed using survival analysis.
Results: Thirty three (45.2%) children progressed to refractory status epilepticus (RSE). The most common etiology for CSE was acute symptomatic in 44 (60.3%) of which 37 had presumed CNS infections. The odds of progressing to RSE were higher in children with acute symptomatic etiology (OR 2.62; CI – 95%; 0.99–7.14; $p = 0.041$). Progression to RSE increased the chances of severe sepsis by six times (OR 6.08; CI – 95%; 1.19–31.02; $p = 0.036$) and acidosis by nearly 15 times (OR 14.77; CI – 95%; 1.19–31.02; $p = 0.020$). Overall mortality was 13.7%, higher in RSE (21.2% vs.7.5%). Amongst the 63 surviving children followed for 1 year from discharge, progression to RSE increased the odds of disability by seven times (OR 7.08; CI 29.31; $p = 0.004$).
Conclusion: Acute symptomatic etiology was the commonest cause of CSE among older children from developing country and increased the odds of progressing to RSE. RSE was significantly associated with disability at 1 year from discharge.

1. Introduction

Convulsive status epilepticus (CSE), the most common neurological emergency in childhood is associated with a substantial morbidity [1]. Data regarding precise incidence of CSE in children is obscure because it is derived from studies that either combined adult and children or included other types of status epilepticus (SE) [2]. Population based studies done in California [3] and Richmond [4] have suggested that ethnicity is an important determinant of CSE where non-white population had two–three fold increase in incidence of CSE. Amongst children, highest incidence of CSE is reported in children below 2 years of age, possibly due to high propensity for acute symptomatic causes of the immature brain [5]. Few studies on epidemiology of CSE have suggested an association between limited medical services, trauma during birth and infections with higher incidence of epilepsy in children from developing countries [6,7].

The distribution of etiology for status epilepticus is age dependent in children; febrile or acute symptomatic cause is most common in younger children below 2 years of age; whereas remote symptomatic causes predominate in children above 2 years of age [1,8]. Past history of seizures and neurological insult was more common in children with SE aged above 2 years than those below 2 years [1,8]. Mortality with CSE is higher in children below 2 years of age vastly accounted for high prevalence of acute symptomatic etiology [9]. Moreover, non-convulsive SE is also associated with increased mortality than CSE [10]. The sequel of CSE (motor deficits, behavioral problems) reported in children above 3 years of age is mere 6%; a sharp contrast to the 30% reported in children under 3 years of age [9]. However, most of this data is from developed countries and in epidemiological studies that included other types of SE also.

In more than 61% of the children, SE is terminated in 60 min after administration of first or second line anti-epileptic drugs (AEDs), in the remaining cases SE is refractory to AEDs, aptly named refractory status epilepticus (RSE) [10]. Ethnicity, seizure

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frequency, AEDs previously used, family history have previously been associated with RSE in studies done in western population that included all types of SE in children [10]. The same study has also reported significantly higher mortality in children with RSE when compared to aborted SE. Etiology of SE [11] and delay in management may influence outcome [12]. Very little is known about the outcome of children with refractory CSE in developing countries. The purpose of this study was to evaluate the etiology, clinical course and short term outcome of refractory CSE in older children.

2. Materials and methods

Retrospective analysis of data of children aged ≥2 and ≤12 years with CSE admitted between May 2011 and January 2014 at Krishna Institute of Medical Sciences and Rainbow Hospital for women and children, both tertiary care referral centers at Hyderabad in South India was performed. The study was approved after review by the Institutional Ethics Committee. Children with complex partial SE, absence SE, simple partial SE, myoclonic SE, psychogenic SE, non-convulsive SE and febrile SE were excluded for data analysis. The information about age, gender, duration of SE, associated co-morbidities, past history of epilepsy and/or SE was obtained. Etiology of SE was classified as acute symptomatic, remote symptomatic (including those with acute precipitant), those with pre-existing epilepsy and cryptogenic (cause undetermined) [13]. Acute symptomatic group included patients with central nervous system (CNS) inflammatory disease (meningitis, presumed encephalitis, tuberculosis, and neurocysticercosis), acute cerebrovascular disease (childhood stroke).

2.1. Definitions

Status Epilepticus was defined as seizures lasting for more than 5 min or recurrent epileptic activity over a period of more than 5 min without regain of pre-existing level of consciousness [14]. Refractory SE (RSE) was defined as SE resistant to one first line, and one second line AED, requiring general anesthesia (GA) [15]. If SE recurred days after withdrawal of anesthetic drugs and warranted re-administration of similar drugs, the length of hospital stay included the seizure free days too. The RSE group included children who progressed to RSE after admission to the study centers as well as those who progressed to RSE at presentation. Presumed encephalitis was defined as encephalopathy (depressed or altered level of consciousness) lasting >24 h with fever, and seizures along with one or more than one of the following symptoms: focal neurological deficits, cerebrospinal fluid (CSF) mononuclear pleocytosis, electroencephalogram (EEG) or neuroimaging findings consistent with encephalitis, after excluding systemic infective causes [16] and metabolic etiologies.

2.2. Investigations

All children underwent baseline imaging with MRI brain; CSF analysis was done in 58 children. Continuous EEG (cEEG) monitoring was performed in 48 children (including those who progressed to RSE) while short EEG or intermittent EEG recording was performed in the rest of the children. Cerebrospinal fluid for anti N-methyl-D-aspartate receptor (NMDAR) antibodies, antibodies against voltage-gated potassium channels (VGKC), and antiglutamic acid decarboxylase (GAD) antibodies were done in nine children with RSE.

2.3. Treatment

All the children were treated according to established guidelines [17]. The initial treatment included benzodiazepines (lorazepam or midazolam) followed by intravenous AEDs (phenytion, phenobarbitone, sodium valproate or levetiracetam alone or in combination). The first line AED administered was lorazepam (0.1 mg/kg body weight) in 32 children while the rest were administered midazolam (0.2 mg/kg body weight). Sixty nine children were given phenytoin (20 mg/kg body weight) and four children received phenobarbitone (20 mg/kg body weight) as second line AED. Third line AED was Levetiracetam (30 mg/kg body weight) in 17, and sodium valproate (40 mg/kg) in 13 children. Phenobarbitone and Lacosamide (8 mg/kg body weight) were given in nine and four children respectively as the fourth line AED. Six children received oral Topiramate (10 mg/kg body weight) as loading dose followed by maintenance oral topiramate. We limited the use of phenobarbitone and avoided use of frequent doses of benzodiazepines to avoid respiratory depression and subsequent need for ventilatotory care. For intravenous anesthesia thiopental (2 mg/kg body weight as bolus followed by infusion of 1–5 mg/kg/h) and/or midazolam (0.2 mg/kg as bolus followed by continuous infusion of 0.1–2.0 mg/kg/h) infusion was used. Six children received ketamine (bolus 0.5 mg/kg, 0.4–3 mg/kg/h) with midazolam infusion. Intravenous methyl prednisolone was administered in children who failed to respond to standard AEDs and was of presumed inflammatory/autoimmune etiology. This was tried by day 3–5 of admission in 21 children with RSE and three with CSE. Eight children with RSE received IVIG while five children were given Ketogenic diet. IVIG was administered when there was no evidence of encephalitis on neuroimaging, and seizures were refractory. Whereas, ketogenic diet was tried in children with generalized seizures refractory to more than three AEDs. Ketosis was achieved within 1 week. Appropriate management of the underlying medical/neurological condition was done.

2.4. Complications and outcome

Severe sepsis, acute kidney injury and acute hepatic failure were defined according to established guidelines [18]. The immediate outcome in hospital was classified as death or discharge from the hospital. The outcome at 12 months was graded according to the Glasgow outcome scale (GOS) [19] that grades patients' functional status into the following five categories: 1 – death, 2 – persistent vegetative state, 3 – severe disability, 4 – moderate disability and 5 – low disability. Among the remote symptomatic etiology group, three children with findings of gliosis on imaging had premorbid neurological deficit at presentation, however all three children were independent for their age.

2.5. Statistical analysis

After testing for the normal distribution of the data, the study population was divided into groups based on progression of SE and outcome. Differences between the groups for continuous variables were analyzed using independent student *t*-test, accounting for variance amongst group using Levene's test for equality of variance. Categorical variables were analyzed using chi-square test. A $p \leq 0.05$ was considered significant. Association between variables for progression to RSE and outcome was done using odds ratio. Mortality of the group was analyzed using survival analysis to evaluate median survival time; whereas life tables were utilized to analyze chronological order of deaths at intervals of every 3 days. Statistical Package for Social Sciences (SPSS, ver. 17.0, IBM computers, New York, USA) was used for all statistical analysis.

3. Results

Among a total of 323 patients with CSE admitted at both the centers during the study period 79 were children aged ≥2 and ≤12