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The etiology and prognosis of super-refractory convulsive status epilepticus in children

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ABSTRACT

Background: Both refractory convulsive status epilepticus (SE) and super-refractory SE are medical emergencies. However, there are limited data on super-refractory SE in children. Thus, this study focuses on characterizing the demographics, outcomes, and prognostic factors for super-refractory SE in children.
Methods: This study was a retrospective analysis of super-refractory SE treated in a tertiary referral center in Taiwan. The functional outcome was evaluated by modified Rankin scale (mRS). Significant functional decline was defined as an mRS difference (before hospital admission and at discharge) of more than 2. The variates and the follow-up mRS values were then analyzed statistically.
Results: We enrolled 134 patients with 191 episodes of convulsive SE and identified 30 patients with 38 episodes of convulsive super-refractory SE. The incidence of convulsive super-refractory SE in the group with SE was 19.9%, and the age ranged from 2.5 months to 17 years. In-hospital mortality was 13.3%, which was much lower than that of adult cohorts. Newly acquired epilepsy and cognitive deficit occurred in 100% and 88.5%, respectively. Newly acquired epilepsy, as a sequel of super-refractory SE, was observed in all 18 patients (100%) who survived and had no history of epilepsy. Significant functional decline (mRS difference of more than 2) at discharge occurred in 76.7%. Poor functional outcome was associated with acute symptomatic etiology ($P < 0.001$) and the number of anesthetic agents ($P = 0.002$). The functional outcome improved after 1 year of follow-up in our population.
Conclusions: Super-refractory SE is associated with significant morbidity and mortality in children. However, the in-hospital mortality rate is much lower compared with adults. The functional outcome in children is associated with acute symptomatic etiology and the number of anesthetic agents and may improve after long-term follow-up.

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1. Introduction

Convulsive status epilepticus (SE) is the most common pediatric neurological emergency that needs prompt treatment [1,2]. Even with advances in medical treatment, refractory SE is associated with significant morbidity and mortality. Variable definitions for refractory SE exist [3–5]. It is defined as seizures that do not respond to 2 or 3 different antiepileptic medications at acceptable doses [6,7]. Alternately, it is also defined as the duration of seizure activity that lasts for 1 or 2 h [6]. At this stage, treatment varies according to the type of SE (i.e., convulsive versus nonconvulsive) and the comorbidities of the individual patient [7]. In contrast, super-refractory SE is a new subdefinition that first appeared in 2011 in the summary of the Third London–Innsbruck Colloquium on SE [8]. The term refers to SE that continues or recurs 24 h or longer after the onset of anesthetic therapy, including those recurring on reduction or withdrawal of anesthesia [3,9–11].

In previous studies in adults, it was found that approximately 10–15% of those presenting to the hospital with SE developed super-refractory SE [9,10,12]. The mortality rate of refractory SE ranged from 20% to almost 50% [4,5,13,14]. In a recent analysis that focused on super-refractory SE, it was found that the mortality rates in adults were as high as 30–50% [10]. Also, patients with refractory SE had a longer hospital stay [5,14,15], lower return to baseline, and a significant functional decline [3,5,14,16]. Other associated neurological sequelae, including secondary epilepsy [1,4,15,17,18], cognitive deficit, and behavioral problems, were also very common [1]. The reported mortality rate in

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children due to SE is approximately 1–5% [1,19–23]. However, the mortality rate and neurological sequelae in children with super-refractory SE remain unclear [21,22,24,25].

Previous studies have reported risk factors for poor outcome in adults with SE. These include an older age (≧65 years old) [3,26,27], etiology of SE [26,28], coma or stupor at presentation [7,21,26], increased duration of SE [15], and a new-onset seizure [7,29]. Other risk factors include in-hospital complications such as arrhythmia requiring intervention, pneumonia, prolonged mechanical ventilation [27], and prolonged hospital stay [3,15]. However, the effect of duration of SE on the prognosis remains controversial. According to recent reports, the prognostic effect of the duration of SE only counts in the early stage of SE and may lose significance after 10 h of onset [21,30,31]. Although several studies have been conducted for refractory SE in adults, the risk factors for poor outcome in children with super-refractory SE are poorly studied [1,21,32,33]. In the present study, we investigated and analyzed the outcomes and prognostic factors for super-refractory SE in children with the aim of having better clarity about the risk factors for poor outcome in children with convulsive super-refractory SE.

2. Materials and methods

2.1. Study design

The study was a retrospective analysis of children treated for convulsive super-refractory SE at National Taiwan University Hospital, Taiwan between April 2001 and June 2013.

2.2. Ethical approval

The study was approved by the Institutional Review Board of National Taiwan University Hospital.

2.3. Patients and setting

Inclusion criteria were the following: (1) patients aged between 2 months and 18 years; (2) super-refractory SE, defined as SE that continued for 24 h or longer after the onset of anesthesia, including those that recurred on reduction or withdrawal of anesthesia; and (3) a convulsive seizure pattern. The treatment protocol was standardized for patients with refractory SE in the institute. In addition to intravenous antiepileptic drugs such as phenytoin or phenobarbital, the first-line anesthetic agent midazolam was used for persistent seizures. Propofol or thiopental was administered if midazolam was ineffective at adequate dose, and ketamine was added in those patients with persistent convulsive seizures or side effects of previous anesthetic agents. Clinical convulsive seizure episodes were monitored. Serial electroencephalogram (EEG) monitoring was applied following the 10–20 international system of electrode placement. The EEG readers included the fellows and pediatric neurologists of the Department of Pediatric Neurology. The EEG recordings during one admission were with the same readers. We routinely read the EEG recordings every day. The neurologist who was in charge of the patient would check the EEG patterns whenever there were suspicious clinical or electrographic seizures. In addition, during critical stages, for example, when titrating or tapering medications, the neurologists often read the EEG much frequently to ensure that the patient's status was stable. The treatment goal was to stop clinical seizures. When EEG showed burst-suppression patterns, and there were persistent clinical seizures, another anesthetic agent would be given. The anesthetic medications would be tapered gradually after seizures were brought under control for 24 h. The patients were classified into 3 groups based on the etiology of SE: acute symptomatic, remote symptomatic, and acute-on-remote symptomatic. Acute symptomatic etiology was defined as super-refractory SE in a previously neurologically normal child, with an identified acute neurological insult, including central nervous system (CNS) infection, head injury, and hypoxia. Remote symptomatic etiology was defined as super-refractory SE in the absence of an identified acute insult but with a history of a preexisting CNS abnormality of more than 1 week previously. Acute-on-remote symptomatic etiology was defined as super-refractory SE occurring within a week of an acute neurological insult or febrile illness; it also included SE that was not of CNS origin and occurring in a child with a history of previous neurological abnormality, including epilepsy and cerebral palsy.

Scores on the modified Rankin scale (mRS) were determined on admission, discharge, and postdischarge for 1 year. Scores on the mRS run from 0 to 6, with the following definitions: no symptoms (score 0), no significant disability and could achieve the milestones of development despite some symptoms (score 1), slight disability—need no assistance for the functions based on patients' age and could achieve the gross motor milestones (score 2), moderate disability—requires some help but could still achieve the gross motor milestones (score 3), moderately severe disability—always need assistance and could not achieve the gross motor milestones (score 4), severe disability including being bedridden (score 5), and dead (score 6). Significant functional decline was defined as the mRS difference (before hospital admission and at discharge) of more than 2, which meant the patients needed help to fulfill daily functions. Cognitive decline (e.g., memory loss), psychosis, behavioral problems, and in-hospital systemic complications were also analyzed. Cognitive function was evaluated by child neurologists before discharge by neurological assessment.

2.4. Statistical analysis

Clinical data were obtained on admission and during hospital stay. The mean values of the age, duration of anesthesia, and length of hospital stay between mRS difference <3 and ≧3 groups were analyzed via Wilcoxon rank-sum test. Then, the individual values on age, duration of anesthesia, and length of hospital stay were further classified into different subgroups. Thus, the values would become categorical variables. The association between each variable (including age, gender, etiology, duration of anesthesia, the number of anesthetic agents and complications, and length of hospital stay) and poor functional outcome (defined as mRS difference >2) was analyzed using Fisher's exact test followed by a univariate logistic regression. The statistically significant variables were then further analyzed through multivariate logistic regression. For analyzing follow-up data for mRS, we used a signed-rank test. $P < 0.05$ was considered as statistically significant.

3. Results

Overall, 134 patients with 191 episodes of convulsive SE were identified, and 30 patients with 38 episodes of convulsive super-refractory SE were reviewed for analysis (Table 1). The incidence of convulsive super-refractory SE in the group with SE was 19.9%. The age ranged from 2.5 months to 17 years.

The premorbid (before the first super-refractory episode) mRS values were the following: 0 in 20 patients (66.7%), 1 in 1 patient (3.3%), 3 in 2 patients (6.7%), 4 in 2 patients (6.7%), and 5 in 5 patients (16.7%) (Table 4). Of these children, 20 (66.7%) belonged to the acute symptomatic group, 3 (10%) belonged to the remote symptomatic group, and 7 (23.3%) belonged to the acute-on-remote symptomatic group. The mRS differences measured at premorbid condition and at discharge in the acute symptomatic group were as follows: 6 in 3 patients (15%), 5 in 2 patients (10%), 4 in 8 patients (40%), 3 in 5 patients (25%), and 2 in 2 patients (10%) (Table 4). A total of 18 (90%) out of 20 patients had a significant functional decline (mRS difference of more than 2). All patients with head trauma had a poor outcome (mRS = 4). Three patients with encephalitis died because of complications. A higher incidence of functional decline was identified in this group compared with the nonacute symptomatic group ($P < 0.001$).

The underlying neurological diseases for the remote symptomatic group (n = 3) and acute-on-remote symptomatic group (n = 7) are

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