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Seizures in a Pediatric Intensive Care Unit: A Prospective Study

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ABSTRACT

Background: The aim of the research is to determine the etiology and clinical features of seizures in critically ill children admitted to a pediatric intensive care unit (PICU).

Methods: A total of 203 children were admitted from June 2013 to November 2013; 45 patients were eligible. Age ranged from 2 months to 19 years. Seizures were organized as epileptic or acute symptomatic. Pediatric risk of mortality score III, Glasgow coma scale, risk factors, coexistent diagnosis, medications administered before admission, type and duration of seizures, drugs used, requirement and duration of mechanical ventilation, length of stay and neuroimaging findings were collected as demographic data prospectively.

Results: The male–female ratio was 0.8. Mean age was 5.4. The most common causes of seizures were acute symptomatic. Most frequent coexistent diagnosis was infectious diseases, and 53.3% had recurrent seizures. Medications were administered to 51.1% of the patients before admission. Seizures were focal in 21 (46.7%), generalized in 11 (24.4%) and 13 (28.9%) had status epilepticus. Intravenous midazolam was first-line therapy in 48.9%. Acute symptomatic seizures were usually new-onset, and duration was shorter. Epileptic seizures tended to be recurrent and were likely to progress to status epilepticus. However, type of seizures did not change severity of the disease. Also, laboratory test results, medications administered before admission, requirement and duration of ventilation, mortality and length of stay were not significant between epileptic/acute symptomatic patients.

Conclusion: Seizures in critically ill children, which may evolve into status epilepticus, is an important condition that requires attention regardless of cause. Intensified educational programs for PICU physicians and international guidelines are necessary for a more efficient approach to children with seizures.

KEYWORDS: children, critically ill, mechanical ventilation, pediatric intensive care unit, seizures

INTRODUCTION

Although some of the previous adult studies reveal the incidence and etiology of epileptic disorders in intensive care units, features of seizures occurring in the pediatric intensive care unit (PICU) setting still remain inadequate [1, 2]. In recent years, seizure durations of 5–10 min have been considered sufficient for diagnosis of status epilepticus. Because all

self-limited seizures stop within 5 min, the Working Group of Status Epilepticus of the Epilepsy Foundation of America recommends that any patient with seizure duration >10 min or, in another words, any child presenting to the emergency department actively seizing should be considered to be in Status epilepticus (SE) at that point and managed accordingly for the initiation of treatment [3]. Seizures are the most common medical problem for emergency medical services transport in children, accounting for approximately 15% of all pediatric calls in the USA [4]. In addition, an improvement in seizure control and a decrease in morbidity and mortality were confirmed by early and effective treatment [5–7]. Nevertheless, there are only few studies regarding seizures in critically ill children, and they are mostly about status epilepticus [8, 9]. Another extensive study indicated that prevalence rate of febrile convulsions was found to be 3.2% [10]. We believe that recognizing the frequent seizure etiologies admitted to a PICU will guide us for a more efficient approach to critically ill patients, and more successful treatment strategies will reduce morbidity and mortality. Therefore, we aimed to investigate the etiology and clinical features of seizures in critically ill children admitted to a PICU.

METHODS

Two hundred three children were admitted as a total to our unit consecutively from June 2013 to November 2013. Forty-five patients who had clinical seizures were observed by the PICU physician, and they were included into the study after approval from the Local Ethics Committee. Informed consent was obtained from the parents/caregivers of the patients. The PICU is a 14-beded, tertiary referral center with all pediatric specialties, in which nearly 500 patients are followed-up in a year. The seizures occurring only outside of the unit—those presenting to the Emergency department (ED) with seizure and then had no repeated seizure after PICU admission—($n = 2$) and patients with duration of internalization in the PICU <48 h ($n = 2$) were excluded from the study. Their ages ranged from 2 months to 19 years. The pediatric risk of mortality score (PRISM) III and Glasgow coma scale (GCS) were used for the estimation of the severity of disease [11, 12]. Distribution of seizures was organized as epileptic (including patients with a known history of seizures and epilepsy or proved to be epileptic) or acute symptomatic [seizures that do not meet the diagnosis of epilepsy, such as febrile seizures, intracranial infections (meningitis, encephalitis or ventriculoperitoneal shunt infection), hypoxic ischemic encephalopathy, cranial tumors/cranial involvement of leukemia, metabolic disorders, afebrile first seizure/electroencephalogram (EEG) normal and others (congenital CMV infection, sinus vein thrombosis and drowning)]. Status epilepticus was defined as seizures lasting >30 min. Besides seizures, patients were classified according to the coexistent diagnosis at admission to the PICU. Demographic data such as age; gender; PRISM III; GCS; risk factors like prematurity, history of perinatal asphixia and admission to neonatal intensive care unit, primary illness, developmental delay and mental retardation; any medications administered before being admitted to the PICU prehospital or in emergency room; type and duration of seizures; drugs used; duration of controlling seizures; requirement of mechanical ventilation; duration of mechanical ventilation; and length of stay in the PICU were collected and documented prospectively for statistical evaluation. All patients included in the study were subjected to history taking, physical examination and routine laboratory investigations, such as complete blood count, biochemical tests and blood gases analysis. Results were determined as low, normal and high according to ages in the reference lists [13].

According to our hospital's protocol, in seizures lasting for 5 min, an intravenous bolus dose of 0.1–0.2 mg/kg midazolam (maximum 5 mg) was initiated and repeated if necessary. If seizure control was not achieved despite three doses of midazolam, the loading of 20 mg/kg phenytoin was initiated. In patients resistant to phenytoin loading, an additional 10 mg/kg phenytoin was loaded 10 min after the initial phenytoin loading, followed by a second 5 mg/kg phenytoin loading. Valproic acid loading (30 mg/kg) was initiated intravenously instead of a second phenytoin loading if the patient was receiving valproic acid previously. An intravenous infusion of midazolam was initiated at a dose of 0.1 mg/kg/h and increased by 0.1 mg/kg/h every 5 min until seizure control was achieved in the case of patients unresponsive to these

drugs. The maximum dose of midazolam included 1 mg/kg/h. After a seizure-free period of 24 h, the infusion of midazolam was decreased to 0.05–0.1 mg/kg/h and discontinued. Patients unresponsive to the maximum dose of midazolam infusion were initiated on an initial loading dose of 10 mg/kg intravenous thiopental, followed by a continuous intravenous infusion of 3–5 mg/kg/h.

Table 1. Demographic characteristics of the patients

Variables	$n = 45$
Age (years)	
Mean ± SD (median)	5.4 ± 5.6 (2.5)
Gender	
Male, *n* (%)	20 (44.4)
Female, *n* (%)	25 (55.6)
PRISM III	
Mean ± SD (median)	14.2 ± 9.1(13)
GCS	
Mean ± SD (median)	8.6 ± 3.2 (9)
Prematurity, *n* (%)	9 (20)
Perinatal asphixia, *n* (%)	10 (22.2)
Admission to neonatal intensive care unit, *n* (%)	11 (24.4)
Developmental delay, *n* (%)	19 (42.2)
Mental retardation, *n* (%)	20 (44.4)
Mechanical ventilation, *n* (%)	35 (77.8)
Duration of mechanical ventilation (days)	
Mean ± SD (median)	16.7 ± 19.1 (9)
Length of stay in PICU (days)	
Mean ± SD (median)	18.7 ± 18.4 (12)

As a result of the consultations that were made by the attending PICU physician with the pediatric neurology, metabolism and infection specialists, lumbar puncture, metabolic screening, EEG evaluation and cranial neuroimaging methods [cranial computer tomography (CT), magnetic resonance imaging (MRI) and diffusion MRI] were performed.

Statistical analysis

Descriptive statistics were summarized as counts and percentages for categorical variables and as medians, minimums and maximums for continuous variables. None of the variables were normally distributed; therefore, the data were analyzed by using Mann–Whitney U-test to compare continuous variables. All the data were analyzed using statistical software SPSS (Statistical Package For Social Sciences) for Windows 20 (SPSS Inc, Chicago, IL). A level of $p < 0.05$ was considered statistically significant.

RESULTS

Forty-five children were eligible for the 6 month study period. The male–female ratio was 0.8. Demographic characteristics of the patients are listed in Table 1. Mean age was 5.4 ± 5.6 (median = 2.5) years. The most common causes of seizures in our PICU setting were acute symptomatic in 24 (53.3%) and epileptic in 21 (46.7%) patients. Most frequent coexistent diagnosis at admission was infectious diseases in 17 (37.8%) patients, followed by pulmonary diseases in 3 (6.7%), syndromes in 3 (6.7%) and postoperative care (not craniotomy) in 3 (6.7%); (Table 2). It was the first (new-onset) seizure in 21 (46.7%) patients, whereas 24 (53.3%) patients had recurrent seizures (prior history of epilepsy).

Table 2. Coexistent diagnosis at admission, n (%)

Infectious diseases	17 (37.8)	Pneumonia: 14 (28.9), sepsis: 4 (8.9)
Pulmonary diseases	3 (6.7)	Bronchopulmonary dysplasia, pneumothorax, chronic lung disease
Syndromes	3 (6.7)	Waardenburg, Crisponi, Mowat Wilson
Postoperative care	3 (6.7)	Idiopathic hypertrophic subaortic stenosis, scoliosis, inguinal hernia
Endocrinologic disorders	2 (4.4)	Hypothyroidism, diabetes insipidus
Cardiologic diseases	2 (4.4)	Congenital heart diseases
Gastroenterologic diseases	2 (4.4)	Gastrointestinal bleeding
Others	10 (17.6)	Acute renal failure, SCID, aplastic anemia, poisoning

Medications were administered to 23 (51.1%) patients prehospital or in emergency room before getting admitted to the PICU. Seizures were focal in 21 (46.7%) patients, generalized in 11 (24.4%) and 13 (28.9%) had status epilepticus. Duration of the seizures was <30 min in 32 (71.1%) patients.

Intravenous midazolam was administered to 22 (48.9%) patients in first-line therapy. Eighteen (40%) patients required a second anticonvulsant to stop the seizures, whereas eight (17.8%) patients required a third antiepileptic drug; eight (17.8%) of them required a midazolam infusion and one (2.2%) patient required a sodium thiopental infusion. A complication presented related to the seizures was respiratory depression. Two patients had to be intubated for <24 h related to the treatment of seizures in the emergency room with rectal diazepam and intravenous midazolam.

In our study, five (11.1%) patients had hyponatremia, two (4.4%) had hypoglycemia, three (6.7%) had hypokalemia, four (8.9%) had hypophosphatemia and seven (15.6%) had hypocalcemia. Laboratory test results are summarized in Table 3. Eighteen (40%) patients were indicated lumbar puncture, and despite extensive microbiological studies in all patients, biochemical values and cytology of cerebrospinal fluid were nonspecific for a definitive diagnosis, and culture was positive in only one patient who had purulent meningitis by *Haemophilus influenzae*. Metabolic screening was indicated in 19 (42.2%) patients, and 4 (8.9%) of them were diagnosed with a metabolic disease (propionic acidemia, Tay–Sachs disease, cytochrome c oxidase enzyme deficiency and maple syrup urine disease).

Table 3. Laboratory test results of patients with seizures

Laboratory test	LOW	NORMAL	HIGH
White blood cell count, *n* (%)	5 (11.1)	25 (55.6)	15 (33.3)
Hemoglobin, *n* (%)	25 (55.6)	20 (44.4)	Ø
AST, ALT, *n* (%)	Ø	35 (77.8)	10 (22.2)
BUN, creatinine, *n* (%)	Ø	42 (93.3)	3 (6.7)
Glucose, *n* (%)	2 (4.4)	28 (62.2)	15 (33.3)
Sodium, *n* (%)	5 (11.1)	38 (84.4)	2 (4.4)
Potassium, *n* (%)	3 (6.7)	39 (86.7)	3 (6.7)
Phosphate, *n* (%)	4 (8.9)	33 (73.3)	8 (17.8)
Calcium, *n* (%)	7 (15.6)	38 (84.4)	Ø

EEGs were performed in 29 patients; 9 (20%) had normal findings, whereas 8 (17.8%) had diffuse background slowing. Electrographic seizures were captured in eight (17.8%) patients with focal epileptiform discharges and four (8.9%) patients with generalized epileptiform discharges. Anatomical, developmental and other neuroimaging abnormalities were as follows (including more than one finding in most patients): 20 patients were indicated cranial CT of whom 11 (55%) had pathological imaging findings—3 had hydrocephalus, 3 had brain edema, 2 had sinus vein thrombosis, 2 had cerebral atrophy and 1 had venous malformation, hypodense area in the medulla oblongata and mastoiditis one after the other. Cranial MRI was performed in 23 patients of whom 18 (78.2%) had pathological findings:5 had cerebral atrophy, 3 had partial agenesis and 2 had total agenesis of the corpus callosum, 2 had hydrocephalus, 2 had mega cisterna manga, 2 had retardation of myelinization and 1 had brain edema, sinus vein thrombosis, pachygyria, agyria, subacute hematoma, pnemosinus dilatans, subdural effusion, cephalohematoma, porencephaly, hyperintense gliomatous lesion in the pons, periventricular leukomalacia, venous angioma and acute disseminated encephalomyelitis. Cranial diffusion MRI was indicated in 11 patients of whom 6 (54.5%) had pathological diffusion restriction.

The study demonstrated that acute symptomatic seizures were usually new-onset (75%), and duration of seizures was shorter (<30 min), whereas epileptic seizures tended to be recurrent (85.7%) and may progress to status epilepticus ($p < 0.05$). However, type of seizures did not change PRISM and GCS and therefore severity of the disease. Also, laboratory test results, medications administered prehospital or in the emergency room before getting admitted to the PICU, requirement of mechanical ventilation, duration of ventilation, mortality and length of stay in the PICU were not statistically significant between epileptic and acute symptomatic seizure patients ($p > 0.05$).

DISCUSSION

In this study, we aimed to determine the clinical features of seizures occurring in the PICU. To our

knowledge, this is the second study that evaluates the etiology and characteristics of seizures in a PICU. The most common causes of seizures in our PICU setting were acute symptomatic seizures, which contrasts with the findings of Valencia *et al.*, where symptomatic epilepsy and seizures after postoperative craniotomy were the most common underlying etiologies [9]. This might be because of the cross-sectional nature of the study, and incidentally, we had no postcraniotomy patients during the duration of the study. Nevertheless, in one study, the most common etiology of seizures was infection (meningitis and encephalitis), just like ours, and seizures occurred at a rate of 15%, with a significant mortality of 8% [14]. Although some sources reported that seizures occurred after administration of imipenem-like antibiotics in children [15, 16], none of our patients had seizures because of antibiotic toxicity [9].

It was the first (new-onset) seizure in 21 (46.7%) patients, whereas 24 (53.3%) patients had prior history of epilepsy. Consistent with the literature, we observed that epileptic seizures tended to be recurrent and may progress to status epilepticus [8, 17].

Rectal diazepam and nasal or buccal midazolam have been recommended by various centers as antiepileptic drug alternatives outside the hospital and in the emergency room [4, 5, 17, 18]. Before being admitted to the PICU, 51.1% of our patients had medication, five (11.1%) had rectal diazepam, one (2.2%) had intravenous diazepam and 16 (35.6%) had intravenous midazolam. Some authors stated that rectal diazepam reduced the incidence of SE and refractory status epilepticus in patients [6, 19]. Pellock and colleagues reported the exposure to 2 million doses of rectal diazepam, and found nine patients with respiratory depression in children [20]. The complication presented before admission to the PICU related to the seizures was respiratory depression, similar to the literature [21]. Fortunately, two patients survived but had to be intubated for less than <24 h related to the treatment of seizures with rectal diazepam and intravenous midazolam. Some authors pointed that low rate of prehospital treatment results with high mortality rate [22], while others state that children who received more than two doses of benzodiazepines were at high risk of requiring assisted ventilation and intensive care. Therefore prehospital administration of benzodiazepines and seizure duration must be taken into consideration when approaching a child with seizure, especially if status epilepticus was present [21].

According to our results, 13 patients had status epilepticus during their stay in the PICU, 10 in epileptic group and 3 in acute symptomatic seizures group. In a study conducted on 98 children with SE admitted to the PICU, the incidence of SE was 4%, where they emphasized the need for PICU admission and early treatment to decrease morbidity and mortality [5].

Intravenous midazolam was administered to 48.9% of the patients in first-line therapy consistent with the literature [8, 23]. Forty per cent of the patients required a second anticonvulsant, while 17.8% patients required a third antiepileptic drug and 17.8% required midazolam infusion. Various rates of seizure control with midazolam infusion ranging from 75 to 95% were reported previously [24, 25]. Only one patient required a sodium thiopental infusion. In one study, infusion of thiopental was initiated in 9% patients in whom seizure control could not be achieved, despite the maximum dose 0.6 mg/kg/h of midazolam [8]. The reason for this may be the augmentation schedule of midazolam up to 1 mg/kg/h in our unit. In another study, authors confirmed that midazolam can control refractory status epilepticus without significant morbidity, even though increasing the administration of midazolam at 24 μg/kg/min aggressively [26].

In our study, five (11.1%) patients had hyponatremia, two (4.4%) had hypoglycemia, three (6.7%) had hypokalemia, four (8.9%) had hypophosphatemia and seven (15.6%) had hypocalcemia. This condition may not be associated directly with the development of seizures, but our opinion is that these are worth mentioning because they might precipitate seizures, and in these patients, administration of supportive treatment was required. In a previous study of children presenting to the emergency room with unprovoked seizures, the authors stated that hyponatremia was a rare cause of seizures unless suggested by the history [27]. In a study conducted in a PICU, none of the children had recognizable metabolic abnormalities attributed to be responsible for

the development of seizures [9], and in another study, no significant electrolyte imbalance was observed in patients with gastroenteritis experiencing febrile convulsion [28]. Also the prevalence of hypophosphatemia in critically ill patients is significant, particularly in those undergoing treatment of diabetic ketoacidosis. Although mild hypophosphatemia is self-limited, severe phosphate reduction might be associated with seizures in a child with diabetic ketoacidosis [29, 30]. In a study, the rate of hypophosphatemia was 61% during the first 10 days of PICU stay related with malnutrition [31].

EEGs were performed in 29 patients, 9 (20%) had normal findings, whereas 8 (17.8%) had diffuse background slowing. Electrographic seizures were captured in eight (17.8%) patients with focal epileptiform discharges and four (8.9%) patients with generalized epileptiform discharges. Valencia and colleagues stated that EEGs were helpful in the great majority of their patients for supporting the diagnosis of epileptic seizures [9]. In a study, EEG evaluation for patients in the PICU and neurologic consultation were of the highest importance to help ruling out epileptic disorders in emergency situations [32].

The authors are aware of the limitations related to its single-centered design and the scarcity/restrictions of available opportunities in a developing country environment. We planned to include not only the fate/outcomes of our patients but also the degree of affection and morbidity rates, wishing to address the neurologic fate in detail. Also, the exact timing of EEG might be one of our limitations. We plan to restudy these aspects with large patient groups for longer durations with further statistical analysis.

In our study, 20 patients were indicated cranial CT resulting with anatomical, developmental and other neuroimaging abnormalities. Eleven (55%) patients revealed pathological imaging findings. Cranial MRI was performed in 23 patients of whom 78.2% had pathological findings. In a recent study, regarding the role of head CT in the evaluation of children admitted to the PICU with new-onset seizure, head CT findings were frequently abnormal and changed acute management. Children admitted to the PICU with first/multiple seizures and aged <2 years were recommended to have immediate CT or MRI scanning [33].

CONCLUSION

Seizures in critically ill children, which may evolve into status epilepticus, is a serious concern for PICU clinicians. We found that the type of seizures did not change severity of the disease. In addition, laboratory test results, medications administered before admitted to PICU, requirement of mechanical ventilation, duration of ventilation, mortality and length of stay in PICU was not significant between epileptic and acute symptomatic seizures. Based on our results, we must foresee that seizing is an important condition that requires attention regardless of cause. Intensified educational programs for PICU physicians and international guidelines are necessary for a more efficient approach to critically ill children with seizures.

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