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Epileptic seizures in the pediatric intensive care unit setting

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ABSTRACT – *Purpose.* The clinical features of seizures occurring in the pediatric intensive care unit (PICU) setting are not well characterized. Adult ICU studies reveal an incidence of seizures ranging from 0.8% to 3.3%, with vascular, metabolic abnormalities, and drug withdrawal being the most common etiologies. The objective of this study is to investigate the clinical characteristics of seizures in children admitted to the PICU at our institution. *Methods.* We performed a retrospective review of all patients with diagnoses of seizures or epilepsy, admitted to our PICU from 2002 to 2004. Of 6,820 admissions, 32 patients, aged one month to 19 years had seizures in the PICU. *Results.* The incidence of seizures was 0.5%. Developmental delay or mental retardation was present in 37% of patients. Seizures were generalized in 26 (81%), and focal in 6 (19%); 34% had status epilepticus. The etiology of seizures was epilepsy in 11 (34%). Seizures that do not meet the diagnosis of epilepsy were diagnosed in 21 (66%) including post-craniotomy in five (23%), febrile seizures in three (14%), encephalitis in three (14%), and hydrocephalus in three (14%). Thirty-one patients (97%) were initially treated with either lorazepam or fosphenytoin. *Conclusions.* Seizures in PICU have different clinical characteristics from those in adults. Recognizing the common seizure etiologies in PICU is likely to lead to a more prompt and effective treatment. Antiepileptic drug prophylaxis may be useful in post-craniotomy patients. A neurological consultation and EEG evaluation are of the utmost importance to help rule in or out epileptic disorders in the PICU.

Key words: epileptic seizure, intensive care unit, children, status epilepticus, PICU, post-craniotomy

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Epileptic seizures commonly occur in the adult intensive care unit (ICU) setting (Varelas and Mirski, 2001), with a reported incidence ranging from 0.8% to 3.3% (Bleck *et al.* 1993, Wijdicks and Sharbrough, 1993). Bleck *et al.* (1993) performed a two-year prospective analysis of neurological complications of adult patients in the ICU excluding those admitted to the unit with refractory status epilepticus. They found that 217 patients (12.3%) presented with neurological complications during their stay in the ICU,

and in 61 of them (28%, or 3.3% of the total number of admissions) the complication was seizures. The most frequent etiologies in the 61 patients with seizures were vascular, infectious and metabolic. Wijdicks and Sharbrough (1993) published their 10-year experience of adult patients having seizures while in the ICU. They excluded patients with a previous history of seizures and with seizures in the post-operative period or after traumatic brain injury. With these restricted criteria, the incidence of seizures in the ICU was 0.8%. The two most common causes were morphine withdrawal and hyponatremia. There are no similar studies addressing the incidence and type of seizures occurring in children while in the pediatric ICU (PICU). Moreover, the topic of seizures in the ICU has not been previously addressed properly, as highlighted by a recent publication on the subject (Varelas, 2005). The objective of this study is to identify the clinical characteristics of epileptic seizures occurring in a PICU.

Materials and methods

This study was approved by the Institutional Review Board of Drexel University College of Medicine in Philadelphia. St. Christopher's Hospital is a tertiary care pediatric facility with all pediatric specialties. A search of the medical records database was performed for discharge diagnoses with the keywords, *epilepsy*, *status epilepticus*, *infantile spasms*, *convulsions*, *fits* and *seizures not otherwise specified*. The search included records from 2002 through 2004 and was aimed at identifying patients having epileptic seizures during their stay in the PICU. Patients with seizures in the neonatal ICU were excluded. Children admitted for a change in mental status after seizures or seizures occurring only outside of the unit were excluded from this study. Those patients with non-epileptic events diagnosed by the clinical description and neurophysiologic studies during the episodes were not included. All diagnoses were reviewed to confirm that the events corresponded to epileptic seizures. Patients with a known history of seizures and epilepsy were included. The patient's epileptic diagnosis was considered the cause of the seizure if there were no other concomitant triggering factors. Conversely, if the latter were present they were identified as the cause of the seizures. A retrospective review of the records was performed. Data collected included the etiology of the seizures, associated diagnosis, antiepileptic drugs used to treat the seizures and laboratory, imaging, and EEG data. Seizures were sorted based on the classification of epileptic seizures and epilepsy from the Commission on Classification and Terminology of the ILAE, 2001 (Engel, 2001). The patients were classified as having either epilepsy or epileptic seizures that do not require a diagnosis of epilepsy (epileptic seizures-no epilepsy). The patients with epilepsy were grouped based on the same classification (Engel, 2001) as either having symptomatic, probably symptomatic or idiopathic epilepsy. Patients with epileptic seizures-no epilepsy, who did not have a history of seizures, were further divided into smaller groups according to their possible etiology. Status epilepticus was defined as seizures lasting ≥ 30 minutes or two or a series of seizures without full return to baseline lasting ≥ 30 minutes (Shinnar *et al.* 2001).
Data are presented with descriptive statistics where applicable.

Results

There were a total of 6,820 admissions to the PICU during the period of the study. Eighty-three patients were detected by the database with one of the keywords. Fifty-one patients were excluded because seizures occurred only outside of the PICU or had non-epileptic events. The remaining 32 children (23 males, nine females) were included in the study *(Tables 1 and 2)*.
The overall incidence of seizures in our PICU was 0.5%. The patients' ages ranged between one month and 19 years (mean 6.4 years, SD 6). Thirty-seven percent of them had some degree of developmental delay or mental retardation. Eighty-one percent of the patients had generalized tonic-clonic (GTC) seizures, and 19% focal seizures. In two of the patients with focal seizures (Patients #16 and 19), seizures were not initially suspected, but were later confirmed after neurological consultation along with EEGs identifying electrographic seizure activity. The median duration of stay in the PICU for all patients was 4.5 days (range 1 to 240 days). One patient had a prolonged stay of 8 months. Two patients died due to complications of infection, with multi-organ failure (Patients #11 and 24). The other 30 patients were transferred out of the PICU to home or to the hospital floor in a baseline neurological condition.
The etiology of seizures was classified as epileptic seizures-no epilepsy in 21 children (66%), and as epilepsy in the remaining 11 (34%) children *(Table 1)*. The most common associated diagnoses in the first group were postoperative craniotomy in five (24%), encephalitis in three (14%), hydrocephalus in three (14%), and febrile seizures in three (14%). Other diagnoses are shown in *Table 1*.

Of the five patients with *seizures in the postoperative period*, four had scheduled cranial surgery and in one it was an emergency (Patient #5). Seizures occurred within a few hours of surgery in two patients, within 48 hours in two other patients and on the 4th day after surgery in one patient. Only patient #5 received prophylactic antiepileptic medication with phenytoin before the surgery, but the blood level was low at the time of the seizure (phenytoin: 0.9 mg/L). One patient (Patient #3) had to be intubated for

less than 24 hours due to respiratory depression related to the treatment of seizures (lorazepam). Other complications presented during the stay in the unit not necessarily related to the seizures included aspiration pneumonia, hematemesis, disseminated intravascular coagulation and rabdomyolysis.

Of the three patients with hydrocephalus, two had seizures in the setting of acute onset ventricular enlargement, and one due to shunt malfunction. Patients with encephalitis presented to the hospital with change in mental status and fever. Two patients had additional seizures in the field before presenting to the PICU (Patients #9 and 11). Three patients had a known history of febrile seizures and all of them had either a viral or bacterial respiratory infection. Of the patients with meningitis, one presented with change in mental status (Patient #15) and one with fever and rash (Patient #16). Of the two patients with brain tumors, one was admitted to the unit due to severe headache (Patient #17) and the other one due to increased right hemiparesis (Patient #18).

Of the 11 children in the *epilepsy subgroup*, seven patients (64%) had generalized or partial symptomatic epilepsy, two (18%) probably symptomatic and two (18%) idiopathic epilepsy. Seven children in the epilepsy group (Patients # 22, 23, 26, 27, 30, 31 and 32) had seizures during their PICU stay, due to their underlying epilepsy. In four patients (Patients #24, 25, 28 and 29), seizures were facilitated by an intercurrent pneumonia. One patient (#31) had refractory juvenile myoclonic epilepsy and was admitted due to a cluster of GTC seizures.

There was a total of 10 children *less than one year of age* in our group (Patients #1, 2, 3, 6, 7, 9, 12, 15, 16, and 22). All but one (Patient #22) belonged to the epileptic seizures - no epilepsy group. There were three patients with seizures following craniotomy, two with hydrocephalus, three with infection (meningitis or encephalitis), one with febrile seizures and one with Ohtahara syndrome.

Patients were treated with antiepileptic medications for any single seizure lasting more than five minutes or for a cluster of two or more seizures. First line seizure treatment was lorazepam in 18 (56%) patients, fosphenytoin in 13 (41%) and phenobarbital in one (Patient #29) (3%), a six-year-old with probably symptomatic epilepsy who had been on this medication. Sixteen patients (50%) required a second dose of the first antiepileptic drug or another anticonvulsant to stop the seizures. Five patients (16%) required a third antiepileptic drug.

Eleven patients (34%) had status epilepticus while in the PICU. These were evenly distributed between the epileptic seizures-no epilepsy and the epilepsy groups. Two patients who had a prior history of seizures received rectal diazepam before admission. One patient had refractory status epilepticus (Patient #24) and died from complications of multi-organ failure.

Electroencephalograms (EEGs) were performed in 30 patients in the form of routine studies, continuous bedside monitoring without video, or video EEG monitoring. The usefullness of the EEGs was very high, with abnormal results in 29/31 patients (94%). Sixteen (52%) had diffuse background slowing with or without additional features. Electrographic seizures were captured in six patients (19%), and bilateral independent periodic lateralized epileptiform discharges (De la Paz and Brenner, 1981; Brenner, 2005) hemihypsarrhythmia (Kramer *et al.* 1997) and burst suppression (Ohtahara and Yamatogi, 2003) were found in one patient each. Six patients (19%) had epileptic interictal activity in the form of generalized, focal or multifocal epileptiform activity. Six patients had more than one finding on their EEGs. One patient with a seizure in the postoperative period of craniotomy did not have an EEG performed. EEGs were helpful in all 29 patients with abnormal results, supporting the diagnosis of epileptic seizures by either the presence of ictal recording, interictal epileptiform discharges, post-ictal slowing or a combination of these features.

Neuroimaging studies were performed in all of them*(Table 2)*. Nineteen patients a head CT, eight patients a brain MRI and five patients both. Anatomical imaging abnormalities were found in 24 patients (75%). Four had developmental anomalies, all of whom fell in the symptomatic epilepsy group (Patients # 22, 23, 26 and 27). The developmental anomalies included partial agenesis of the corpus callosum, microdysgenesis, agyria/pachygyria complex and Chiari II malformation. Five patients had imaging suggestive of a previous injury (Patients # 19, 20, 24, 25, 28). Two patients (Patients #17 and 18) had astrocytic brain tumors. Two children had bacterial meningitis; neuroimaging was normal in one, the other showed bilateral subdural effusions. Three neuroimaging studies showed hydrocephalus, and five demonstrated postoperative changes (Patients #1-5), one with residual hemorrhage and one with residual empyema.

The CSF reports and cultures from six patients with CNS infections are shown in *table 2*. One patient in the postoperative period of craniotomy had a subdural empyema. The CSF biochemical values and cytology were grossly abnormal and the microbial culture was positive. The three patients with encephalitis showed mild pleocytosis, between 11 to 26 cells/mm^3, and one had a significant increase in protein. Despite extensive microbiological studies in all three patients, a definitive diagnosis could only be established in one of them. Patient #10 had Epstein Barr virus encephalitis with positive CSF titers. Two patients had bacterial meningitis, one due to group B streptococcus and the other one due to meningococcus.

Table 1. Clinical characteristics of 32 children with seizures while in the PICU.

#	Age	Sex	Final etiology	Main diagnosis	Other diagnoses	SE	DD
1	4m	M	**Epileptic seizures that do not require a diagnosis of epilepsy**	POP Craniotomy	Sagittal Synostosis, prematurity	N	N
2	4m	M		POP Craniotomy	Congenital interhemispheric cyst	N	Y
3	8m	M		POP Craniotomy	Choroid plexus papilloma	N	N
4	3y	F		POP Craniotomy	Third ventricle tumor, subdural hygroma	N	N
5	6y	M		POP Craniotomy	Subdural empyema	N	N
6	1m	M		Hydrocephalus	Prematurity, anemia	N	N
7	6m	M		Hydrocephalus	Congenital interhemispheric cysts, subdural hygroma	N	Y
8	11y	F		Hydrocephalus	H/o craniopharyngioma, panhypopituitarism	Y	N
9	1y	M		Encephalitis	Viral encephalitis	N	N
10	6y	M		Encephalitis	EBV encephalitis	Y	N
11†	14y	M		Encephalitis	Rhabdomyolysis, sepsis, hypercalcemia, MOF	N	N
12	10m	M		Febrile seizures	Pneumonia	N	Y
13	15m	F		Febrile seizures	URI	Y	N
14	6y	M		Febrile seizures	URI	Y	N
15	1m	F		Meningitis	Group B Strep Meningitis, subdural effusion	N	N
16	8m	M		Meningitis	Neisseria Meningitis	N	N
17	14y	F		Glioblastoma Multiforme	NF type I, chemotherapy	N	N
18	16y	F		Astrocytoma G II		N	N
19	2.5y	M		HIE		N	Y
20	15y	M		Encephalomalacia	Otitis media, history of subdural empyema	Y	N
21	18y	M		Benzodiazepine withdrawal	Intentional overdose	Y	N
22	1m	M	**Epilepsy**	Symptomatic	Ohtahara Syndrome	Y	Y
23	20m	M		Symptomatic	Brain dysgenesis	Y	Y
24†	2yr	M		Symptomatic	Pneumonia, liver failure, metabolic disorder, MOF	Y	Y
25	4.5y	F		Symptomatic	Pneumonia, liver failure	N	Y
26	9y	M		Symptomatic	Congenital CMV	Y	Y
27	19y	M		Symptomatic	POP renal transplant, myelomeningocele, hydrocephalus	N	Y
28	13m	M		Symptomatic	Pneumonia	N	Y
29	6y	M		Probably symptomatic	Hematemesis, pneumonia	Y	Y
30	11y	F		Probably symptomatic		N	N
31	16y	F		Idiopathic	Juvenile myoclonic epilepsy	N	N
32	16y	M		Idiopathic	Intentional AED overdose	N	N

Note: m = months, y = years, M = male, F = female, POP = postoperative, HIE = hypoxic ischemic encephalopathy, H/o = history of, URI = upper respiratory infection, SE = status epilepticus, DD = presence of either developmental delay or mental retardation, †= died, NF = neurofibromatosis, EBV = Epstein Barr virus, CMV = cytomegalovirus, AED = antiepileptic drug, MOF = multiorgan failure.

Table 2. Laboratory and imaging information on 32 patients with seizures in the PICU.

#	Electrophysiology	Imaging	CSF results and cultures
1	DBS	CT: Sagittal synostosis	
2	Right sided delta	CT: Postoperative changes	
3	Normal	CT: Status post removal of choroid plexus papilloma, with residual hemorrhage.	
4	Not done	CT: Postoperative changes	
5	DBS	CT: Post operative changes, small residual frontal parafalcine empyema	P: 127, G: 16, WBC: 2115, Empyema Culture + for Staph coagulase - and Strep milleri
6	Normal	CT: Hydrocephalus	
7	Right breech rhythm	CT: Hydrocephalus and subdural hygromas	
8	DBS and right posterior quadrant focal slowing	CT, MRI: Hydrocephalus	
9	BIPLEDS	CT: Hypodense basal ganglia, cerebral edema	P: 194, G: 45, WBC: 11, Viral studies, PCR herpes and enterovirus all negative
10	DBS	CT: Right Parietal cystic lesion	P: 35, G: 78, WBC: 16, EBV VCA IgG and IgM +: >1:10
11	Multifocal SW and several generalized EEG seizures	MRI: Extensive white matter changes	P: 34, G: 86, WBC: 26. HSV, entero PCR, cultures and other viral studies were negative
12	DBS	CT: Normal	
13	Diffuse beta activity	CT: Normal	
14	DBS	CT: Normal	
15	DBS	CT, MRI: bilateral subdural effusions with areas of enhancement	P: 25, G: 48, WBC: 26, Cultures + for Group B strep
16	Frequent independent bilateral EEG seizures	CT, MRI: Normal	P: 68, G: 34, WBC: 85, Latex + for Neisseria meningitides
17	DBS	CT, MRI: Right Hemispheric mass	
18	DBS	CT: Left hypodensity	
19	Multiple independent EEG seizures	MRI: Polycystic encephalomalacia	
20	3 EEG seizures from R frontal area	CT: Right Frontal encephalomalacia	
21	DBS	CT: Normal	
22	Burst suppression	MRI: Partial agenesis of the CC	
23	Hemihypsarrhythmia	MRI: Microdysgenesis	
24	Multiple independent EEG seizures	MRI: PVL	
25	DBS and L posterior quadrant sharp waves	CT: Old ischemic injury	
26	DBS and frequent slow SW	MRI: Agyria, pachygyria complex	
27	Frontal lobe seizures	CT, MRI: Chiari II, shunt placement	
28	DBS	MRI: PVL, cortical and cerebellar atrophy	
29	DBS and multifocal spikes	MRI: Normal	
30	DBS	CT: Normal	
31	Generalized SW	CT: Normal	
32	DBS	CT: Normal	

Note: DBS: diffuse background slowing, BIPLEDS: bilateral periodic lateralized epileptiform discharges, SW = spike and wave, CC = corpus callosum, P = protein, G = glucose, PVL = periventricular leukomalacia, EBV = Epstein Barr virus.

Discussion

To our knowledge, this is the first study that evaluates the etiology and characteristics of seizures encountered in a pediatric intensive care unit.

The incidence of seizures in the PICU at our institution was 0.5%, a figure lower than the reported incidence of 0.8%-3.3% in adult ICUs (Bleck *et al.* 1993, Wijdicks and Sharbrough, 1993). The most common causes of seizures in our pediatric PICU setting were symptomatic epilepsy and seizures after postoperative craniotomy. This contrasts with the findings in adult ICUs, where drug withdrawal, vascular, infectious and metabolic (*i.e.* hyponatremia) are the most common underlying etiologies (Bleck *et al.* 1993, Wijdicks and Sharbrough, 1993). In a previous study of children presenting to the emergency room with unprovoked seizures, we found that hyponatremia is seldom the cause of seizures unless suggested by the history (Valencia *et al.* 2003). Furthermore, in our group of 32 children who had extensive chemistry screening including electrolytes, no recognizable metabolic abnormalities were deemed to be responsible for the development of seizures. Other investigators have reported the presence of seizures after administration of imipenem-like antibiotics in children (Karadeniz *et al.* 2000), with a greater risk in children less than seven months of age (Schuman and Varelas, 2005). Despite its use in the ICU setting, none of our patients had seizures due to antibiotic toxicity. One of the patients included in this series had seizures related to withdrawal of benzodiazepines. We did not come across seizures due to narcotic withdrawal (Varelas and Mirski, 2001), although narcotic compounds are used in children for sedation purposes in the ICU; no cases of chronic usage were present in our study.

The risk of seizures is increased in the postoperative period (Manaka *et al.* 2003). Early postoperative seizures are accompanied by cerebral hypoxia and acidosis, making evaluation of the state of consciousness in relation to cerebral edema difficult (Lee *et al.* 1989). In a series of 23 patients with seizures following craniotomy (Kvam *et al.* 1983), inadequate anticonvulsant prophylaxis was the most common cause. Only one of our patients received prophylaxis with phenytoin in the post-operative period, although the blood level was low at the time of the seizure. The other four patients did not receive anticonvulsant prophylaxis. Prophylactic antiepileptic treatment decreases the incidence of early, postoperative seizures (Manaka *et al.* 2003). It has also been recommended in the parietal lobe region, with extension to the cortex, and with concurrent meningitis or if surgical treatment is indicated (Ziai, 2005). Postoperative seizures occurred within four days of surgery in all five patients. Seizures in the postoperative period may be associated with significant morbidity as one of our patients had to be intubated to protect the airway. Although the authors did not to elucidate the incidence of seizures in the postoperative period, a careful review on this topic is warranted in the pediatric population to determine the need for EEG evaluation, anticonvulsant prophylaxis and/or neurological consultation.

López Pisón *et al.* (2000) described the relative frequency of neurological diagnoses as a reason for admission of children to a PICU. Fifteen percent of their cases were due to seizures and they reported a significant mortality of 8%. The most common etiology of seizures was infection (meningitis and encephalitis). Although this study looked at the indications for admission to the PICU, they did not investigate the cause of seizures while in the unit. The divergence of our results may rest with the fact that we excluded patients who had seizures diagnosed outside the PICU.

The epidemiology of status epilepticus (SE) in a hospital setting has been investigated in children. Lacroix *et al.* (1994) published their 10-year experience of pediatric SE admitted to the PICU defined as seizures lasting more than 30 minutes or repetitive tonic-clonic seizures with no recovery of consciousness. Epilepsy was the most common cause of SE in their series of 147 children. Gulati *et al.* (2005) studied the incidence of SE in a group of 451 children with neurological emergencies during a seven-year period. SE was present in 30 children (6.7%), 14 of whom had a history of epilepsy, and 12 had acute symptomatic SE, most frequently due to septic shock in two, chronic renal failure in two, and aspiration pneumonia in two. Nine children (30%) died due to SE. Chin *et al.* (2004) retrospectively studied a group of 98 children with SE admitted to the PICU in the United Kingdom. The incidence of SE was 4%. Out of 24 children with an acute symptomatic etiology, 18 had CNS infections. They emphasized the need for PICU admission and early treatment to decrease morbidity and mortality. Similarly, Kwong *et al.* (2004) reported their findings in 25 children with SE admitted to a PICU. Acute symptomatic causes were more frequent in children less than three years old, and remote symptomatic causes were more frequent in those older than four years. Eleven patients had a history of seizures. All patients with major neurological sequelae belonged to the acute or remote symptomatic groups. Children with idiopathic or febrile SE had a favorable outcome.

In another study, Sahin *et al.* (2001) looked at a group of 22 children with refractory SE in the PICU. The morbidity and mortality was higher in patients with more prolonged status (longer than eight days), acute symptomatic etiology, progressive encephalopathy, and age younger than three years.

In our series, 11 patients had SE during their stay in the PICU and were about equally distributed between the epilepsy and epileptic seizures-no epilepsy groups. Two of them had received rectal diazepam before admission to the hospital. The introduction of rectal diazepam gel in recent years (Cloyd *et al.* 1998, Dreifuss *et al.* 1998) has

probably decreased the incidence of SE in patients with known seizure disorders (O'Dell *et al.* 2005). Pellock and Shinnar, (2005) recently reviewed the exposure to two million doses of rectal diazepam, and found nine patients with respiratory depression and three deaths in children, probably not related to the use of rectal diazepam. The number of patients with respiratory depression may be higher when two or more doses of benzodiazepines are given to a patient (Chin *et al.* 2004).

Conclusion

We present the data of a group of 32 patients who had seizures during their admission to the PICU at our institution. This study emphasizes awareness of the complication of seizures in the PICU. Seizures in the PICU can be a serious problem, as a percentage of them may evolve into status epilepticus. This study also underscores the need for thorough, postoperative clinical, and maybe EEG, monitoring in children who have undergone craniotomy. Prophylactic, antiepileptic treatment before and during the first five days after craniotomy may be advisable in pediatric patients. Although early prophylaxis has not been found to decrease the incidence of epilepsy, it may help to abate seizure-related complications incurred during the early postoperative period. In our experience, EEGs were helpful in the great majority of our patients, supporting the diagnosis of epileptic seizures. A neurological consultation and EEG evaluation for patients in the PICU are of the utmost importance to help rule in or out epileptic disorders in emergency situations (Kothare *et al.* 2005).

One pitfall of the study is that patients of different ages have been included. Therefore, the conclusions need to be interpreted with caution. Further prospective studies including enough patients in different age groups are warranted. □

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