Prospective study of new-onset seizures presenting as status epilepticus in childhood

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ABSTRACT

Objective: To characterize children with new-onset seizures presenting as status epilepticus at a tertiary care children’s hospital.

Methods: Prospectively collected data were reviewed from a database derived from a mandated critical care pathway. A total of 1,382 patients presented with new-onset seizures between 2001 and 2007.

Results: A total of 144 patients presented in status epilepticus. The average age was 3.4 years. The majority of seizures (72%) lasted between 21 and 60 minutes. The majority of patients had no significant past medical history; one-fourth had a family history of epilepsy. Five (4%) patients with EEGs had electrographic seizures during the study, captured only with prolonged monitoring. The most common etiology was febrile convulsion, followed by cryptogenic. The most common acute symptomatic cause was CNS infection; the most common remote symptomatic cause was cerebral dysgenesis. Combined CT and MRI provided a diagnosis in 30%. CT was helpful in identifying acute vascular lesions and acute edema, whereas MRI was superior in identifying subtle abnormalities and remote symptomatic etiologies such as dysplasia and mesial temporal sclerosis.

Conclusions: Children who present in status epilepticus that is not a prolonged febrile convulsion should undergo neuroimaging in the initial evaluation. For any child who presents in status epilepticus and has not yet returned to baseline, the possibility of nonconvulsive status epilepticus should be considered. Although CT is often more widely accepted, especially in the urgent setting, strong consideration for MRI should be given when available, due to the superior yield.

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GLOSSARY

CSE = convulsive status epilepticus; HCT = head CT; NCSE = nonconvulsive status epilepticus; SE = status epilepticus.

Status epilepticus (SE) is one of the most common life-threatening medical emergencies in children, with an annual incidence ranging from 10 to 73 per 100,000. The highest incidence is in the less than 2 years of age group, ranging from 135 to 156/100,000, with the greatest peak in the first year of life. If febrile SE is excluded, the incidence is decreased by 25%–40%. The mortality rate in pediatric SE ranges from 0% to 7%. Acute or remote symptomatic convulsive SE (CSE) is associated with the highest mortality during hospitalization. Death due to SE is most often due to the underlying cause, such as CNS infection or severe neurologic disabilities. However, some children die from SE regardless of the underlying etiology.

Although the most recent revision of the International League Against Epilepsy definition does not specify a temporal meaning, the traditional view of the duration is greater than 30 minutes. As the molecular basis for the advantages of early seizure cessation has begun to be elucidated, more recent literature advocates that there be a revised definition of SE, lasting no longer than 10 minutes or even 5 minutes.

Extensive epidemiologic studies have evaluated SE in the adult population; however, few have investigated the characteristics of pediatric patients presenting in SE, especially those who present in...
SE as their first identified seizure. In a large prospective study, seizure duration in children with a first unprovoked seizure lasted $>20$ minutes in 16% of children, and $>30$ minutes in 12%. The longer a seizure lasts, the less likely it is to stop within the next few minutes. In this prospective study, we aimed to characterize children with new-onset seizures presenting as SE at a tertiary care children’s hospital, in order to elucidate the demographics and etiology of SE, as well as the utility of laboratory, EEG, and imaging studies.

METHODS Patients were identified from a prospective database that collects demographic information, including seizure characteristics and duration, medical and family history, physical examination, basic chemistry and blood panel, EEG, and head CT (HCT) on all children presenting with new-onset seizures at a tertiary care pediatric hospital (appendix e-1 on the Neurology® Web site at www.neurology.org).

Standard protocol approvals, registrations, and patient consents. The work was conducted as part of quality assurance monitoring for the new-onset seizure clinical care pathway. The institutional review board deemed the protocol met requirements for a limited data set and thus waived requirements for individual consent and assent.

RESULTS Between January 1, 2001, and December 31, 2007, 1,382 infants and children with new-onset seizures were identified: 144 (10%) presented in SE. Fifty-six percent were male. The average age at presentation was 3.4 years, the median 2.0 years, the mode under 1 year. Excluding the 46 (32%) patients with febrile SE, the median age of the remaining 98 patients was the same (figure 1). Most patients (62%) had no significant past medical history, 13% had a history of non-neurologic medical problems, 8% had a history of a prior febrile seizure, and 17% of patients had a history of developmental delays. Thirty-six (25%) patients had a family history of seizures and/or epilepsy. In the majority of patients ($n = 103$ or 72%), seizure duration was 21–60 minutes; for 41 patients (28%), SE lasted for greater than 1 hour.

Seizure type. Seizure type was classified according to clinical history, physical examination, EEG, and imaging. The most common was generalized tonic-clonic SE ($n = 57$, 39.6%), followed by complex partial SE ($n = 49$, 34%), partial with secondary generalization ($n = 34$, 23.7%), simple partial SE ($n = 3$, 2%), and myoclonic SE ($n = 1$, 0.7%). Two patients with secondary generalization were later diagnosed with benign epilepsy of childhood with centrotemporal spikes.

EEG findings. EEG was performed within 24 hours of presentation, after medical treatment. Of 139 patients (97%) who had an EEG, 115 (83%) had routine 30-minute EEGs, 6 (4%) had multiple routine EEGs, and 18 (13%) had prolonged digital video
recordings. Stage II sleep was captured in 84 (73%) of the routine EEGs, in all patients with multiple EEGs, and in 14 (78%) of the prolonged EEGs. Those who did not have evidence of sleep architecture were sedated, encephalopathic, comatose, or had electrographic seizures without a clinical correlate. Fifty-six patients (40%) had normal EEGs; 26 (19%) showed focal epileptiform activity, 9 (6%) showed focal slowing, 13 (9%) showed generalized slowing, and 5 (4%) had electrographic seizures during the study. Ten patients had focal epileptiform activity and focal slowing, 9 with beta activity, and the remaining 11 patients had a combination of patterns. In all patients with electrographic seizures, the events were captured with prolonged monitoring; 4 patients had no recognizable sleep architecture and were in nonconvulsive SE.

Laboratory abnormalities. All patients had full electrolyte panels including glucose, sodium, calcium, and magnesium. Two patients (1%) had clinically significant hyponatremia, sodium <125 mEq/L. A total of 139 patients (97%) had complete blood counts, 11 (8%) with a serum leukocyte count >20,000, half of whom were afebrile. Urine toxicology screens were performed in 61 patients (42%) and all were negative, although one patient reported a toxic ingestion.

Lumbar puncture was performed in 89 patients (62%), including 57 of 66 febrile patients (86%) and 32 afebrile children. The average CSF leukocyte count was 7.3 cells/μL, with 16 patients (18%) with a leukocyte count >5 cells/μL. Although all CSF bacterial cultures were negative, 13 patients were diagnosed with a primary CNS infection, based upon the clinical symptoms, CSF pleocytosis, EEG, and imaging findings. Nine of the 66 patients with fever (14%) did not have a lumbar puncture because a clear source of fever was identified, the patient returned quickly to baseline, or a remote symptomatic etiology was identified.

**Neuroimaging studies.** All patients had neuroimaging: 143 (99%) had HCT and 45 (31%) had MRI. Of the HCTs, 115 (80%) were normal; 14 (10%) showed acute abnormalities; 14 (10%) showed relevant chronic abnormalities. Forty-four patients had both HCT and MRI. Seventeen patients had normal MRI and HCT, and 11 patients had abnormal MRI and HCT. MRI detected abnormalities not identified by HCT in 14 of 30 normal HCTs (47%) (fig-

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![Figure 2 Summary of diagnostic imaging findings, HCT compared to MRI](image)

<table>
<thead>
<tr>
<th>Normal HCT</th>
<th>Normal MRI</th>
<th>Abnormal HCT</th>
<th>Abnormal MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal MRI</td>
<td>Normal (6)*</td>
<td>Abnormal (14)</td>
<td>Abnormal (11)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Focal signal</td>
<td>Abnormal</td>
<td>Metabolic</td>
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<tr>
<td>Metabolic</td>
<td>abnormalities</td>
<td>MRI</td>
<td>abnormalities</td>
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<tr>
<td>Metabolic</td>
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<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MTS*</td>
<td>2</td>
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<td>2</td>
</tr>
<tr>
<td>Vascular</td>
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</tr>
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<td>Edema</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dysgenesis</td>
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<tr>
<td>Encephalomalacia</td>
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</tr>
</tbody>
</table>

* - number of patients with febrile status epilepticus (≥38.0°C) and normal neuroimaging. HCT = head CT; MTS = mesial temporal sclerosis.
Etiology of new-onset pediatric status epilepticus

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. of patients</th>
<th>% Total</th>
</tr>
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<tr>
<td>Acute symptomatic</td>
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<td></td>
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<tr>
<td>Febrile status epilepticus</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td>CNS infection</td>
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<td>9</td>
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<tr>
<td>Electrolyte imbalance</td>
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<td>1.4</td>
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<tr>
<td>Trauma</td>
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<td>1.4</td>
</tr>
<tr>
<td>Vascular</td>
<td>5</td>
<td>3.4</td>
</tr>
<tr>
<td>Toxin</td>
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<td>1.4</td>
</tr>
<tr>
<td>Remote symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral dysgenesis</td>
<td>8</td>
<td>5.6</td>
</tr>
<tr>
<td>Mesial temporal sclerosis</td>
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<td>1.4</td>
</tr>
<tr>
<td>Remote infection</td>
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<td>1.4</td>
</tr>
<tr>
<td>Remote vascular</td>
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<td>2.8</td>
</tr>
<tr>
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<td>Benign epilepsy with centrotemporal spikes</td>
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<tr>
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<tr>
<td>Primary generalized epilepsy</td>
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<td>0.7</td>
</tr>
</tbody>
</table>

aStrong family history of complex partial epilepsy.
bStrong family history of generalized epilepsy.

The etiology of new-onset pediatric SE. The etiology of SE was based on a combination of history, presentation, and laboratory testing, along with EEG and neuroimaging (table 1). Forty-six patients (32%) had true febrile SE, with a source of infection outside the CNS, and aged between 6 months and 5 years, as adapted from the NIH consensus statement.\(^1\) However, fever, defined as $\geq38.0^\circ$C, was present in 20 other patients at the time of presentation. Twenty-four patients had acute symptomatic etiologies: all required urgent treatment in addition to seizure control. The majority of the acute symptomatic etiologies was primary CNS infection, followed by vascular, electrolyte imbalance, trauma, and toxin (one patient with alcohol intoxication and one patient treated with antihistamines). Twenty-six patients had remote symptomatic etiologies, with cerebral dysgenesis and inborn errors of metabolism being the most common, followed by remote vascular and mesial temporal sclerosis, remote infection, and chromosomal abnormalities.

The remaining patients were classified as cryptogenic ($n=42; 29\%$) or idiopathic ($n=6; 42\%$). The cryptogenic group\(^1\) included patients with localization-related seizures (based on history, EEG, and/or imaging findings, $n=22$), developmental delay ($n=12$), and patients with no clear etiology, without a compelling family history, whose studies were all normal ($n=8$). The idiopathic group encompassed patients with benign epilepsy of childhood with centrotemporal spikes and those with a possible hereditary predisposition with epilepsy present in multiple family members. Nine of the 145 patients previously experienced unrecognized and undiagnosed seizures and thus had newly diagnosed epilepsy.

Compared to the distribution of seizure type in published studies of adults,\(^10\)\(^15\) primarily generalized seizures occurred more often in children, while simple partial and secondarily generalized seizures occurred more often in adults ($\chi^2 = 120.77, p < 0.001$). Our sample had fewer incidents of SE longer than 1 hour ($\chi^2 = 9.31, p < 0.01$), and no cases of mortality in the acute period, whereas 3% of the pediatric North London cases resulted in death.\(^1\) Grouping etiology to 5 categories (prolonged febrile convolution, acute symptomatic, remote symptomatic, cryptogenic, idiopathic) to match previously published studies,\(^1\) our sample had similar rates of prolonged febrile convolution and acute symptomatic, but fewer cases due to remote and idiopathic etiologies and more cases of cryptogenic etiology ($\chi^2 = 87.22, p < 0.001$) (table 2).

DISCUSSION Ten percent of children and adolescents with a first seizure presented in SE, comparable to prior studies.\(^1\)\(^3\)\(^16\) The most common etiology was prolonged febrile convolution, followed by cryptogenic. The most common acute symptomatic cause was CNS infection, and the most common remote symptomatic cause was cerebral dysgenesis. Combined CT and MRI provided a diagnosis in 30% and directed acute management in 24%.

Hypoglycemia and hypocalcemia can be triggers for seizures. In our population, these abnormalities were rare, which may be attributed to the probability that serum electrolytes were checked after the administration of IV fluids with glucose. Although all patients with lumbar punctures had negative CSF cultures, many had CSF pleocytosis, indicating a primary CNS infection. However, postictal pleocytosis
new-onset status epilepticus. Compared to the North London study, which may confer a different patient selection bias. Compared to the North London tertiary care hospital, which may confer a different patient selection bias. The patients in our study, however, were community-based in which patients were identified by telephone interviews, cards, and chart reviews, but not by routine hospital admission. The North London study has the advantage of being community-based in which patients were identified by telephone interviews, cards, and chart reviews, but is a retrospective design. The patients in our study were prospectively identified upon presentation to a tertiary care hospital, which may confer a different selection bias. Compared to the North London study, our group had fewer cases of prolonged SE, no cases of mortality, and different rates of cryptogenic and idiopathic etiologies. The lower rates of mortality and SE greater than 1 hour at our institution may be representative of out-of-hospital treatment patients receive in the United States en route to the hospital and the early transfer to a tertiary care center. Compared to the pediatric cohort in the Richmond study, our group had a similar age distribution, but varied in seizure type with a lower mortality. Compared to a large multicenter study in children, our group had a similar distribution of age, but the younger age group varied in etiology, with cryptogenic and acute symptomatic being more common than remote symptomatic causes, especially in those less than 2 years of age.

For the evaluation of any child with newly recognized seizures, the Subcommittee of the American Academy of Neurology, Child Neurology Society, and American Epilepsy Society recommends EEG as a standard part of diagnostic investigation, and neuroimaging is considered optional. Recent literature emphasizes the yield of prolonged video EEG monitoring in identifying nonconvulsive SE (NCSE), an important subtype of SE, yet difficult to identify and treat. The incidence of NCSE in pediatric patients undergoing long-term monitoring ranges from 16 to 32 percent. In patients who had an EEG for coma, 8% were found to be in NCSE, including 12% of children 18 years of age or younger. In our study, all patients with electrographic seizures were captured only with prolonged video monitoring; NCSE was captured in 22% of those with prolonged monitoring. Although this study was not intended to evaluate the yield of prolonged video EEG monitoring, patients in SE may benefit from monitoring, especially if there is a protracted impairment of consciousness, comatose state, or postictal behavior.

Several studies have addressed the utility of neuroimaging in patients who present with a first-time seizure, with the incidence of abnormalities ranging from 13% to 32%. Studies have concluded there is little evidence to support routine imaging for those who have no risk factors for epilepsy and that neuroimaging in these patients may not warrant a change in the acute management. These studies did not address imaging in the context of SE. In a large study of 613 children with newly diagnosed epilepsy, nearly 80% had neuroimaging, with relevant lesions in 13%. In our study evaluating neuroimaging in new-onset SE, CT was helpful in identifying acute vascular lesions and acute edema in patients, whereas MRI was superior, particularly in identifying subtle abnormalities and remote symptomatic etiologies.
The choice of imaging modality, often debated, depends on urgency, availability, and resolution. However, CT confers radiation exposure that may not be trivial especially for the youngest children. Although this study was not intended to directly compare imaging modalities, the results of our cohort of patients with a more severe presentation highlight the importance of neuroimaging to help establish an etiology, inform management, and provide information relevant to long-term prognosis.

Imaging abnormalities must be placed in the context of those of the normal population. The NIH Clinical Center study, one of few large-scale normative imaging studies, reported on 1,000 normal volunteers aged 3–83 years. Fifteen percent had incidental findings that did not require further follow-up or evaluation, 1% had findings that required urgent evaluation, and 1.8% had findings that required routine evaluation. In contrast, our study had incidental neuroimaging findings in 6%. It is possible in the NIH study that some patients may have entered the study to obtain an MRI for underappreciated reasons.

One limitation of this study is that with our standardized database SE was defined as a tonic, clonic, or tonic-clonic unremitting seizure lasting greater than 20 minutes, and did not include other definitions, of 2 or more such seizures between which consciousness was not regained (intermittent convulsive SE), or which lasted for at least 30 minutes. In one study, seizures of 20–29 minutes duration were more likely to stop spontaneously or with medical treatment and have a lower mortality than those ≥30 minutes. However, we could not evaluate distinctions based on this time frame.

Understanding the epidemiologic and etiologic basis of pediatric SE is important due to the significant risk of recurrent SE, which has been reported as 11%–16% at 1 year and 18% at 2 years. Our findings are similar to those outlined in a recent review of the evaluation of pediatric SE. This study adds to the literature the evaluation of a child with new-onset seizures that are SE. From this study, we cannot determine whether routine EEG is helpful in a patient with a known history of epilepsy or SE. For any child who presents in SE and who has not yet returned to baseline, the possibility of nonconvulsive SE should be considered; these patients may benefit from long-term video EEG monitoring. The use of long-term EEG in both populations merits further study.

We recommend imaging in this population, as a substantial proportion of children had abnormalities that helped establish etiology and direct therapy. The role for imaging in patients with known epilepsy and SE remains undefined. Access to imaging modality varies among institutions. CT is often more widely available, especially in the urgent setting, but may be falsely reassuring and exposes the patient to radiation. Due to the superior yield, strong consideration for MRI should be given when available.

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