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Early Recurrence of First Unprovoked Seizures in Children

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Abstract

Objectives—The risk of early seizure recurrences after first unprovoked seizures in children is largely unknown. We aimed to determine the rate of seizure recurrence within 14 days of first, unprovoked seizures in children and identify associated risk factors. Secondarily, we aimed to determine the risk of recurrence at 48 hours and 4 months.

Methods—We conducted a secondary analysis of a multicenter cohort study of children 29 days-18 years with first, unprovoked seizures. Emergency department (ED) clinicians completed standardized histories and physical examinations. The primary outcome, recurrent seizure at 14 days, and the secondary outcomes, recurrence at 48 hours and 4 months, were assessed by telephone follow-up and medical record review. For each recurrence time point, we excluded those patients for whom no seizure had recurred but chronic antiepileptic drugs (AEDs) had been initiated.

Results—475 patients were enrolled in the parent study. Of evaluable patients for this secondary analysis, 26/392 (6.6%, 95% CI: 4.4–9.6%) had recurrences within 48 hours of the incident seizures, 58/366 (15.8%; 12.3–20.0%) had recurrences within 14 days, and 107/340 (31.5%; 26.6–

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36.7%) had recurrences within 4 months. On logistic regression analysis, age younger than 3 years was independently associated with a higher risk of 14-day recurrence (adjusted OR 2.1, 95% CI 1.2, 3.7; p=0.01). Having had more than 1 seizure within the 24 hours prior to ED presentation was independently associated with a higher risk of seizure recurrence at 48 hours (adjusted OR 4.3, 95% CI 1.9, 9.8; p<0.001).

Conclusions—Risk of seizure recurrence 14 days after first unprovoked seizures in children is substantial, with younger children at higher risk. Prompt completion of an EEG and evaluation by a neurologist is appropriate for these children.

Keywords

Seizure; child; recurrence

Introduction

Annually, 25,000 to 40,000 children in the United States present to emergency departments (EDs) with first seizures that lack a clear precipitant such as head trauma, fever, or meningitis (referred to as “unprovoked seizures”).[1–3] Prior studies have most often assessed the risk of seizure recurrence 6 months or longer after first (incident) unprovoked seizures.[4–7] Estimates of seizure recurrence in prospective studies have ranged from 25–46% at 1 year.[4–7] Risk factors from patient history and physical examination associated with recurrence at 1 year include seizure onset at younger age, history of prior central nervous system insults (e.g. head trauma requiring hospitalization), partial seizures, and focal abnormalities on neurological examination after the incident seizure.[4–9]

Studies assessing the risk of, and risk factors associated with, early seizure recurrence (e.g. within 14 days of incident seizure) are sparse. One small cohort study noted a 14% risk of recurrence at 1 month.[7] Understanding the risk of early seizure recurrence would help determine the appropriate timing for completion of an electroencephalogram [EEG] and magnetic resonance imaging [MRI]), the results of which alter prognosis.[10–14] Presently, completion of an EEG is considered a standard-of-care after a first unprovoked seizure, although the optimal timing for its completion is unclear.[14] Therefore, we aimed to determine the rate of seizure recurrence within 14 days of first, unprovoked seizures in children and to identify associated risk factors. We hypothesized that seizure recurrence at 14 days was relatively common and risk factors available at ED presentation would be associated with the risk of recurrence. Secondarily, we aimed to determine the risk of recurrence 48 hours and 4 months after incident seizures.

Patients and Methods

Study Design and Setting

We performed a secondary analysis of data from a prospective cohort study of children who presented with seemingly unprovoked seizures to any of 6 urban, university-affiliated pediatric EDs in the US between March 2005 and September 2007. The parent study assessed the risk of intracranial abnormalities in children with first unprovoked seizures.[15] Each center’s Institutional Review Board approved the study. At each center, we obtained

written informed consent from the child's guardian or a waiver of written informed consent, as required.

Study Population

Details of the parent cohort study have been published previously.[15] For this secondary analysis, we included children ages 29 days to 18 years who presented to the ED for evaluation following first seemingly unprovoked seizures (i.e. incident seizures). As in the parent cohort, we excluded patients with head trauma or fever in the 24 hours prior to presentation or known metabolic disorders predisposing to seizures. We also excluded patients with any of the following: syncope or a presumed breath-holding episode, altered mental status without seizure symptoms, neurological disorders that inhibited the ability to conduct a neurological examination (e.g. hypoxic ischemic encephalopathy with generalized hypertonia), or absence seizures.

Patients for whom chronic AEDs were initiated prior to recurrences and patients lost to follow-up, for whom recurrences at particular time points could not be assessed, were excluded from analyses. Additionally, we excluded from the 48-hour recurrence outcome analysis those patients for whom a one-time bolus of phenobarbital, phenytoin, or valproic acid was administered in the ED. We also excluded patients from the analysis of seizure recurrence at 4 months if 4-month follow-up was not completed and the patient had not had a recurrence noted on prior follow-up (e.g. at 14 days). Finally, we excluded patients from analysis if, at the time of the initial follow up call (detailed below), it became clear that the event was not a seizure, the patient experienced an absence seizure, there was a clear seizure precipitant, or the seizure was not an incident event.

Study Protocol Measurements

In the ED, a clinician (attending physician, fellow, resident physician, nurse practitioner, or physician assistant) performed a detailed patient history and physical examination and recorded the findings on a standardized case report form. Site investigators conducted one hour in-service training sessions with faculty and fellow physicians to educate them on study procedures.

To determine seizure recurrence outcomes, we reviewed the medical records for patients hospitalized at the time of the incident seizure and conducted follow-up telephone calls for all patients. Trained research coordinators or site investigators completed all telephone follow-up calls. The first telephone follow-up was completed 14 days-2 months after the seizure and the second was completed at 4–6 months. If we were unable to reach the legal guardian by telephone, we conducted mail surveys in which we asked the same questions. For the first recurrent seizure, we asked the exact date of recurrence or the number of days the seizure occurred since leaving the ED.

During the first telephone follow-up, we also determined whether the child had a history of febrile seizures and obtained further, detailed narrative information about the seizure event for which the child presented to the ED. Due to clinicians' time constraints, they were not asked to complete such narratives at the index visit in the ED. At least 1 epileptologist or the lead investigator, blinded to patient outcomes, evaluated the description of the initial seizure

assessments in order to determine whether a seizure actually occurred, whether there was a clear precipitant, and whether it was an incident seizure.

Study Outcome Measures

Our primary outcome was seizure recurrence within 14 days of the incident seizure. We chose this primary outcome as it was thought to reflect a reasonable timeframe to complete appropriate diagnostic testing (i.e. EEGs). Secondary outcomes included recurrence within 48 hours (to assess acute recurrences) and 4 months (to allow comparison to prior research). For our main analysis, we excluded patients who had not had a recurrence but for whom chronic AEDs were initiated prior to the time at which that outcome would be assessed. We compared patients for whom chronic AEDs were and were not started prior to the 14-day recurrence assessment (and whose seizures had not recurred) in order to assess for any biases this would potentially create in the recurrence estimates.

For all recurrence time points (48 hour, 14 day, and 4 months), we determined both low and high estimates of recurrence risk. We determined the low estimate of risk for each time point based on those patients for whom the date or exact timing of the recurrence was provided by the parent or was identified in the medical record. We calculated a high estimate for each time point that included all patients with recurrence for whom either: a) the timing was clearly within the outcome timeframe, or b) the exact timing of the recurrence was not available but the date of follow-up was available. For those with only the date of follow-up available, we included them in the high estimate for a specific time point if the follow-up was: a) within 21 days of the index seizure (to assess 14-day recurrence) or b) within 5 months of the index seizure (to determine 4-month recurrence). For the low (but not high) estimate of the 48-hour recurrence, we excluded those patients who were hospitalized from ED, had a seizure recurrence in the hospital, but it was unclear if the seizure occurred before a chronic AED was initiated.

Risk Factors

We considered 4 types of risk factors for 14-day seizure recurrence: patient characteristics (e.g. age, sex), general medical history, incident seizure characteristics, and neurological examination findings in the ED. We examined age as a factor because patients younger than 3 years have been previously noted to have a higher seizure recurrence rate at 1 year compared to older children.[7] For general history, we considered as potential risk factors a history of febrile seizures and known central nervous system (CNS) anatomical or post-natal insults/abnormalities. We defined CNS insults/abnormalities as a history of any of the following: birth injury, brain malformation, meningitis or encephalitis, post-natal head trauma requiring hospitalization, motor or language delay, cerebral palsy, mental retardation, or stroke. In regard to the incident seizure itself, we considered sleep state (asleep vs. awake) at the time of the seizure, seizure focality, and longer seizure duration as potential risk factors.[5,7,9] Finally, we evaluated the association between 14-day recurrence and an abnormal neurological examination in the ED, defined as abnormal mental status or other abnormal neurological findings, after resolution of the seizure. Although abnormal findings on EEGs and neuroimaging (MRI or CT) are associated with higher likelihood of seizure recurrences, we purposefully did not include these risk factors in our analysis. These tests,

particularly EEG and MRI, are not routinely completed in the ED to inform clinical decision-making.

Statistical Analysis

We summarized categorical data using frequencies and proportions with 95% confidence intervals (CIs), where appropriate. We summarized continuous data using means with standard deviations or medians with interquartile ranges. We calculated relative risks with 95% CIs and conducted bivariable analyses to assess for potential associations between recurrence at 14 days and individual risk factors. For bivariable analyses, we used the chi-square or Fisher's Exact test for categorical data and the Mann-Whitney U test for continuous variables that were not normally distributed.

We performed a backward elimination multivariable logistic regression analysis to identify independent risk factors of seizure recurrence at 14 days. We considered variables for model inclusion based on prior literature suggestion that there was a potential association with seizure recurrence. Additionally, we only included potential risk factors with a bivariable association with seizure recurrence of $p < .1$. We planned to include no more than one covariate in the regression analysis for every 10 patients with seizure recurrences at 14 days. For the regression modeling, we only used categorical variables to facilitate clinical interpretation. Specifically, we analyzed models that included age <36 months as a category rather than as a continuous variable. We evaluated variance inflation factors to assess for multicollinearity and the Hosmer-Lemeshow statistic to determine model goodness-of-fit. To confirm the results of the backward elimination regression, we performed a forward stepwise logistic regression analysis, again entering all variables with $p < .1$. We conducted similar bivariable and logistic regression analyses to assess the association between risk factors and 48 hour recurrence. We performed all statistical analyses using SPSS version 23.0.

Results

We enrolled 475 of 625 (76.0%) eligible children (comparisons between those who were and not enrolled are detailed in parent manuscript).[15] Of the 475 patients, we excluded 27 patients from all analyses for the following reasons: a clear precipitant was present (n=12), the event was not a seizure based on follow-up telephone call (n=9), or the seizure was either an absence seizure or a prevalent (not incident) seizure (n=6). Overall, 392, 366, and 340 patients were analyzed for the 48-hour, 14-day, and 4-month seizure recurrence estimates, respectively. The Figure displays the flow diagram of patients included for the 14-day seizure recurrence estimates.

Table 1 demonstrates the comparisons between patients for whom clinicians did and did not initiate chronic AEDs prior to a 14-day recurrence. Across sites, initiation of AEDs prior to a 14-day recurrence ranged from 6.9%–12.7%. Patients placed on chronic AEDs prior to recurrent seizures at 14 days (n=43) were more frequently younger, had histories of CNS insults/abnormalities, experienced longer incident seizures, had more than one seizure in the prior 24 hours, had abnormal neurological examinations, or had focal aspects to their seizures. Additionally, the 43 patients were more likely to have been hospitalized at the time

of the ED visit and to have received an EEG or consultation by a neurologist prior to ED or hospital discharge.

Recurrence and Risk Factors for Recurrence

Table 2 displays the seizure recurrence risk for all outcome timeframes. Low and high estimates for each seizure recurrence time point (48 hour, 14-day, and 4-month) did not differ substantially. The higher estimate of 14-day recurrence varied from 9.5%–19.8% across sites. We conducted a sensitivity analysis to estimate the 14-day recurrence risk when including both those patients who had and had not been started on AEDs prior to seizure recurrence. When these two groups were combined, 64/408 (15.7%, 95% CI 12.3–20.0%) had a recurrence within 14 days. However, assuming all patients for whom AEDs were started would have had recurrences had AEDs not been started, the 14-day recurrence rate would be as high as 24.5% (100/408; 95% CI 20.4–30.0%).

Table 3 presents the risk of recurrence at 14 days based on the presence or absence of potential risk factors. Factors associated with 14-day recurrence on bivariable analysis included younger age and more than 1 seizure within 24 hours at the time of ED presentation. The median ages of those with and without 14-day recurrences were 33.6 months (IQR 8.3, 71.5) and 76.2 months (IQR 18.1, 134.2), respectively [$p<0.001$]. On multivariable analysis, only younger age (analyzed as < 36 months) remained statistically associated with 14-day recurrence (adjusted odds ratio 2.1, 95% CI 1.2, 3.7; $p=0.01$, Hosmer-Lemeshow statistic 0.99).

On bivariable analysis, the same 2 factors, younger age and more than 1 seizure within 24 hours at the time of ED presentation, were associated with seizure recurrence at 48 hours (Supplemental table). On multivariable analysis using these two variables, the only factor independently associated with recurrence at 48 hours was having had more than 1 seizure within 24 hours at the time of ED presentation (adjusted odds ratio 4.3, 95% CI 1.9, 9.8; $p<0.001$). Of patients with recurrences within 48 hours, 9/26 (34.6%) occurred at home, after discharge from the ED.

Discussion

In this cohort of patients with incident unprovoked seizures, recurrence at 14 days was relatively frequent. Younger patients were at higher risk of recurrence within this timeframe. As patients with previously identified risk factors for recurrence were often placed on chronic AEDs shortly after the incident seizure, the risk of 14-day recurrence is potentially higher than we report. Our results suggest that prompt follow-up, including completion of an EEG and evaluation by a neurologist appears appropriate for children with first unprovoked seizures, particularly younger children. Given the relatively high risk of seizure recurrence within 48 hours for patients with more than one seizure in the 24 hours prior to ED presentation, more timely completion of an EEG and an evaluation by a neurologist would be reasonable.

Although data are relatively lacking with which to compare our early recurrence estimates, one prior prospective cohort of 133 children with first unprovoked seizures noted a 1-month

risk of 14%, similar to the risk we noted at 14 days.[7] Beyond the inherent value of providing anticipatory guidance to parents, the relative frequency of early recurrences raises the question of whether this knowledge should affect practice in the acute setting. As practice parameters consider the completion of EEGs a standard for the neurodiagnostic evaluation of children with first unprovoked seizures, prompt completion of the EEG may allow for earlier, more informed individualized management.[10,14] EEGs aid in the determination of seizure type and the risk of recurrence. EEGs completed within 24 hours of the seizure may be more likely to identify abnormalities, although some of the abnormalities may be transient.[14,16]

Prior studies have found that the risk factors for recurrence 6–12 months after the incident seizure included family history of epilepsy, age younger than 3 years, patient sex, prior febrile seizure, sleep state at the time of the seizure, status epilepticus, abnormal neurological findings, and an abnormal EEG.[4–9] We only noted 2 factors (1 independently) associated with recurrence at 14 days: young age and more than 1 seizure in the prior 24 hours. However, patients with known risk factors for recurrence were frequently started on AEDs prior to recurrence.

Limitations

Our study had several limitations. As a substantial proportion of patients had AEDs initiated prior to recurrences, our findings might underestimate the risk of early recurrence. Although our study was completed 10 years ago, the underlying risk of seizure recurrence likely has not changed during this period. The practice to initiate AEDs prior to seizure recurrence may have changed since study completion, with recent literature suggesting that neurologists do not typically recommend AEDs for most children who experience first unprovoked seizures.[10, 17] Although we did not collect EEG results, more patients for whom EEGs were obtained had chronic AEDs initiated, suggesting that the EEG results influenced practice and, again, that our rate of early recurrence may be an underestimate. We did not collect other clinical or patient-related factors that may have influenced use of AEDs prior to a recurrence, such as parental anxiety. We also did not collect data on family history of epilepsy so were unable to assess this as a factor influencing recurrence. Additionally, we were unable to complete the 14-day and the 4-month assessments for all patients, although we were able to complete these assessments for most. However, the clinical characteristics of patients lost to 14-day follow-up were similar to patients for whom follow-up was completed (data available on request). Finally, the exact dates of recurrence were not clear for a subset of patients, necessitating providing low and high estimates for each time point of seizure recurrence.

Conclusions

Risk of seizure recurrence at 14 days is substantial after a first unprovoked seizure in children, with younger children at higher risk. Prompt completion of an EEG and evaluation by a neurologist are appropriate to determine further management for these children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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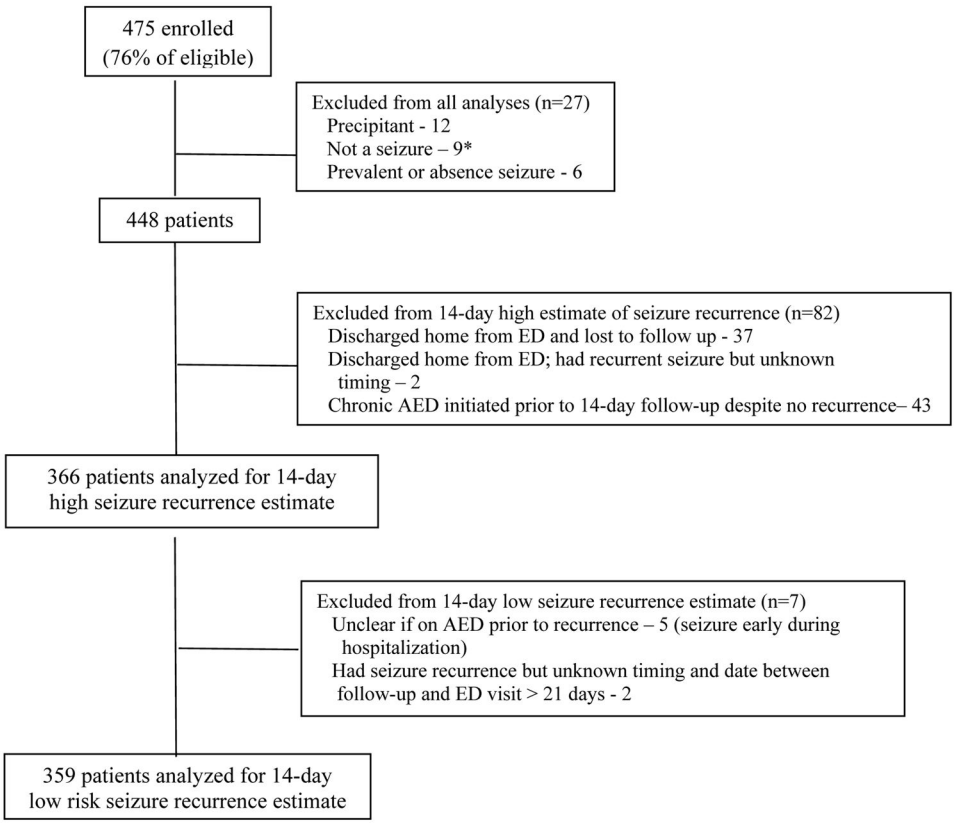

Figure. Flow diagram for analysis of 14-day seizure recurrence estimates

ED – emergency department; AED – anti-epileptic drug

* Two examples of patients found on 14-day narrative follow-up screen not to have had seizures:

Patient 1 - vomiting and dehydrated. Had few episodes of arching which resolved when parents picked her up

Patient 2 - 18 month old crying, took deep breath, turned blue, then arched her back. She came out of it and was back to normal; had similar prior episodes

Table 1

Characteristics of patients for whom chronic AEDs were (N=43) and were not (N=366) initiated prior to recurrence at 14-day assessment *

Characteristic	Chronic AEDs not initiated prior to recurrence **	Chronic AEDs initiated prior to recurrence ***
Median age, mo (IQR)	63.8 (15.1–131.0)	53.5 (10.7–107.0)
Mean age, mo (SD)	76.3 (64.5)	70.1 (64.6)
Male, n/N (%)	191/366 (52.2%)	28/43 (65.1%)
Any CNS insult/abnormality by history, n/N (%) ****	22/366 (6.0%)	11/43 (25.6%)
Brain malformation	2/366(0.5%)	0/43 (0.0%)
Any meningitis/encephalitis	4/366 (1.1%)	1/43 (2.3%)
Birth brain injury	3/366 (0.8%)	4/43 (9.3%)
Post-natal head trauma requiring hospitalization	2/366 (0.5%)	0/43 (0.0%)
Motor or language delay, cerebral palsy, mental retardation	15/366 (4.1%)	6/43 (14.0%)
Stroke	1/366 (0.3%)	2/43 (4.7%)
Seizure specific history, n/N (%)		
More than 1 seizure in previous 24 hours	69/358 (19.3%)	14/40 (35.0%)
Longest seizure in previous 24 hours		
≥5 minutes	73/321 (22.7%)	13/38 (34.2%)
≥15 minutes	18/321 (5.6%)	8/38 (21.1%)
Any focal aspect to seizure *****	126/333 (37.8%)	21/38 (55.3%)
Neurologic examination, n/N (%)		
Abnormal mental status	62/355 (17.5%)	10/40 (25.0%)
Abnormal overall neurologic exam other than mental status	29/349 (8.3%)	9/39 (23.1%)
Any focal neurologic findings on exam	13/362 (3.6%)	1/41 (2.3%)
ED disposition, n/N (%)		
Discharged to home	278/366 (76.0%)	10/43 (23.3%)
Hospitalized	88/366 (24.0%)	33/43 (69.8%)
Intensive care	7/366 (1.9%)	3/43 (7.0%)
ED CT or MRI, n/N (%)	233/366 (63.7%)	32/43 (74.4%)
EEG prior to discharge from ED or hospital, n/N (%)	96/350 (27.4%)	29/38 (76.3%)
Neurology consult in ED or hospital, n/N (%)	227/362 (62.7%)	43/43 (100%)

* Excludes patients without 14-day follow up (n=37) and those with recurrence but of unclear timing (n=2)

** Includes patients for whom AEDs initiated but only after recurrence

*** Only includes patients who had not had recurrence

**** Defined as having a history of any of the following: birth injury, brain malformation, meningitis or encephalitis, post-natal head trauma requiring hospitalization, motor or language delay, cerebral palsy, mental retardation, or stroke; patients could have more than one CNS insult/abnormality

***** Defined as motor aspect 1-sided or head or eyes turned to 1 side at any point.

AED – antiepileptic drugs; IQR –interquartile range; CNS – central nervous system; ED – emergency department; CT – computed tomography; MRI – magnetic resonance imaging; EEG – electroencephalogram

Table 2

Risk of seizure recurrence after first unprovoked seizure

	Low estimate of seizure recurrence* n/N (%; 95% CI)	High estimate of seizure recurrence* n/N (%, 95% CI)
48-hour recurrence	21/387 (5.4%; 3.4–8.2%)	26/392 (6.6%; 4.4–9.6%)
14-day recurrence	51/359 (14.2%; 10.8–18.3%)	58/366 (15.8%; 12.3–20.0%)
4-month recurrence	102/335 (30.4%; 25.6–35.7%)	107/340 (31.5%; 26.6–36.7%)

* Low estimates at each time point include all patients who had a recurrence for whom the specific date of recurrence was known. High estimates at each time point include all patients who had a recurrence for whom either the specific date of recurrence was known or the date of follow-up was during hospitalization (for 48-hour recurrence), within 21 days of index seizure (for 14-day recurrence), or within 5 months of index seizure (for 4-month recurrence).

CI – confidence interval

Table 3

Risk factors associated with 14-day seizure recurrence on bivariable analysis (N=366) *

Risk factor	Risk of 14-day seizure recurrence if risk factor present	Risk of 14-day recurrence if risk factor absent	Relative Risk (95% CIs)
Age, n/N (%)			
<12 months	21/74 (28.4%)	37/292 (12.7%)	2.2 (1.4, 3.6) **
<36 months	32/147 (21.8%)	26/219 (11.9%)	1.8 (1.1, 2.9) **
Male, n/N (%)	36/191 (18.8%)	22/175 (12.6%)	1.5 (0.9, 2.4)
Prior medical history, n/N (%)			
Any CNS insult / abnormality predisposing to seizure ***	1/22 (4.5%)	57/344 (16.6%)	0.3 (0.04, 1.9)
Motor or language delay, cerebral palsy/mental retardation	1/15 (6.7%)	57/351 (16.2%)	0.4 (0.06, 2.8)
Prior febrile seizures	1/17 (5.9%)	50/298 (16.8%)	0.4 (0.05, 2.4)
Seizure specific history, n/N (%)			
More than 1 seizure in prior 24 hours	17/69 (24.6%)	40/289 (13.8%)	(1.1, 2.9) **
Longest seizure in prior 24 hours			
≥5 min	10/73 (13.7%)	42/248 (16.9%)	0.8 (0.4, 1.5)
≥15 min	1/18 (5.6%)	51/303 (16.8%)	0.3 (0.05, 2.3)
Any focal aspect to seizure ****	23/126 (18.3%)	32/207 (15.5%)	1.2 (0.7, 1.9)
Asleep (fully) at seizure onset	7/45 (15.6%)	40/238 (16.8%)	0.9 (0.4, 1.9)
Neurologic examination, n/N (%)			
Abnormal mental status	9/62 (14.5%)	45/293 (15.4%)	0.9 (0.5, 1.8)
Abnormal overall neurologic exam other than mental status	5/29 (17.2%)	48/320 (15.0%)	1.1 (0.5, 2.7)
Any focal neurologic findings on exam	4/13 (30.8%)	53/349 (15.2%)	2.0 (0.9, 4.8)

* Analysis based on high estimate for the 14-day seizure recurrence time point

** $p < 0.05$ on bivariable analysis; no other variables in table with $p < 0.1$ on bivariable analysis

*** Defined as having a history of any of the following: birth injury, brain malformation, meningitis or encephalitis, post-natal head trauma requiring hospitalization, motor or language delay, cerebral palsy, mental retardation, or stroke.

**** Defined as motor aspect 1-sided or head or eyes turned to 1 side at any point

CNS – central nervous system