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Prolonged or recurrent acute seizures after pediatric arterial ischemic stroke are associated with increasing epilepsy risk

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*See Appendix S1 (online supporting information) for Seizures in Pediatric Stroke (SIPS) sites and investigators.

This article is commented on by Rivkin on page 6 of this issue.

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ABBREVIATIONS

AIS	Arterial ischemic stroke
SIPS	Seizures in Pediatric Stroke

AIM To determine epilepsy risk factors after pediatric stroke.
METHOD A cohort of children with arterial ischemic stroke (birth–18y) was enrolled at 21 centers and followed for 1 year. Acute seizures (≤7d after stroke) and active epilepsy (at least one unprovoked remote seizure plus maintenance anticonvulsant at 1y) were identified. Predictors were determined using logistic regression.
RESULTS Among 114 patients (28 neonates and 86 children) enrolled, 26 neonates (93%) and 32 children (37%) had an acute seizure. Acute seizures lasted longer than 5 minutes in 23 patients (40%) and were frequently recurrent: 33 (57%) had 2 to 10 seizures and 11 (19%) had more than 10. Among 109 patients with 1-year follow-up, 11 (10%) had active epilepsy. For each year younger, active epilepsy was 20% more likely (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.6–0.99, p=0.041). Prolonged or recurrent acute seizures also increased epilepsy risk. Each additional 10 minutes of the longest acute seizure increased epilepsy risk fivefold (OR 4.7, 95% CI 1.7–13). Patients with more than 10 acute seizures had a 30-fold increased epilepsy risk (OR 30, 95% CI 2.9–305).
INTERPRETATION Pediatric stroke survivors, especially younger children, have a high risk of epilepsy 1 year after stroke. Prolonged or recurrent acute seizures increase epilepsy risk in a dose-dependent manner.

Arterial ischemic stroke (AIS) is a leading cause of childhood brain injury. Many survivors suffer from permanent disability and epilepsy, although a subset recover without significant deficits. One of the critical differences of pediatric stroke compared with stroke in adults is that children frequently experience acute symptomatic seizures. Only 2% to 4% of adults with stroke have an acute seizure.[1] In contrast, an estimated 75% to 90% of neonates and 20% to 30% of children with AIS have acute seizures.[2–7] Convulsions at stroke presentation are more likely in young children.[8,9] Although determinants of epilepsy after pediatric AIS are poorly understood, emerging data suggest early seizures may be associated.[6,10–12] Therefore, the high incidence of acute seizures after pediatric AIS is worrisome. However, we know little about the characteristics of children who have acute seizures, or the mechanisms by which acute seizures are associated with epilepsy.

Large, prospective studies of neonates and children are critical to understand which patients are at greatest risk of epilepsy, and how acute seizures or other factors might influence that risk. Moreover, accurate prediction of epilepsy risk will allow providers to appropriately counsel patients and families and guide future research. We aimed to prospectively determine incidence rates and risk factors of acute seizures and epilepsy after pediatric AIS. We hypothesized that age at the time of a stroke is an important determinant both of acute symptomatic seizures and of later development of post-stroke epilepsy. Further, we hypothesized that the duration and frequency of acute seizures during the first week after stroke modify epilepsy risk.

METHOD

Seizures in Pediatric Stroke (SIPS) investigators at 21 sites (Appendix S1, online supporting information) enrolled

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newborns who were born at or after 37 weeks' gestation and children no older than 18 years within 14 days of stroke onset from March 2011 to August 2012 using the infrastructure of the International Pediatric Stroke Study, a multicenter pediatric stroke consortium. All sites obtained approval from their local institutional review board and written informed consent from guardians. For all participants, a child neurologist (GD or CKF) adjudicated brain imaging (computed tomography or magnetic resonance imaging) to confirm AIS with supplemental neuroradiologist review as needed. Inclusion criteria were: (1) acute focal neurological deficit or seizure consistent with stroke; and (2) arterial infarct on computed tomography or magnetic resonance imaging consistent with clinical symptom location and timing.

Local site investigators determined acute seizures on a clinical basis or by electroencephalography (EEG) performed for clinical indications, documented the number of acute seizures as an ordinal categorical variable (single, 2–10 seizures, or >10 seizures), and the duration of the longest acute seizure in minutes. Infarct characteristics were collected from clinical reports. At hospital discharge, guardians were given seizure diaries with instructions to document remote seizures. Longitudinal follow-up data including anticonvulsant use and characteristics of seizures after hospital discharge were obtained by review of health records, standardized telephone or in-person parental questionnaires at 3 months, and in-person investigator visit 1 year after stroke. All data were abstracted onto standardized case record forms.

Definitions

Neonatal stroke was defined as a stroke presenting from birth to 28 days old; childhood stroke was defined as a stroke presenting at age 29 days to 18 years old. Acute seizures were defined as a seizure at stroke onset or within the subsequent 7 days.[13] Remote seizure was defined as a seizure more than 7 days after stroke and excluded seizures provoked by fever, transient ischemic attack, or stroke recurrence.[13] Active epilepsy was defined as treatment with a maintenance anticonvulsant at the 1-year follow-up in a child who had at least one remote seizure.[14]

Statistical analysis

Statistical analyses were performed using Stata 14 (StataCorp, College Station, TX, USA). Summary statistics were used to describe the cohort demographics and baseline clinical characteristics. Proportions were compared by χ^2 testing. We described the onset time of acute seizures in children but not in neonates, because the exact time of stroke onset for neonates is generally not known. Acute seizure predictors were determined by logistic regression. We first estimated the probability of acute seizure by age in a linear model. Because the association of acute seizures and age had evidence of nonlinearity, we then depicted the association graphically as a cubic spline to allow variation across age. We considered variables with marginal outcome associations significant at the $p<0.1$ for inclusion in multivariable analysis of acute seizure predictors. In the final model, we included age in years but not neonatal stroke to avoid overfitting. Survival analysis methods were used to estimate remote seizure incidence rates. Time at risk began 7 days after stroke; in neonates, stroke onset was assumed to be on the day of birth. Patients were right-censored at the last observed seizure-free date. We present Kaplan–Meier plots stratified by acute seizure (yes/no) and acute seizure frequency. Predictors of active epilepsy at 1-year follow-up were determined by logistic regression. We performed a test for trend to determine whether acute seizure frequency (categorized as none, single, 2–10, or more than 10 seizures) was associated with higher epilepsy risk. For sensitivity analyses, we repeated predictor testing, applying the assumption that patients with an acute seizure but incomplete data for duration or frequency had only brief (30s) or a single acute seizure to provide conservative estimates. We did not report a multivariable model for epilepsy predictors because of the limited number of outcomes.

What this paper adds

- Younger children are at higher risk of acute seizures and epilepsy after stroke.
- One year after pediatric stroke, 10% of survivors are treated for epilepsy.
- Each 10-minute increase in acute seizure duration increases epilepsy risk fivefold.
- Children with more than 10 acute seizures after stroke have a 30-fold increased epilepsy risk.

RESULTS

We enrolled 114 patients (73% of the eligible sample; 28 neonates and 86 children) (Fig. 1). Median age of neonates at the time of AIS symptom onset was day of life 0 (range 0–20d). Median age for children was 6 years 1 month (interquartile range 1y 5mo–12y). Baseline demographics and clinical characteristics of the participants are shown in Table I. An acute seizure was identified in 26 (93%) neonates and 32 (37%) children. Neonates were more likely to have recurrent acute seizures compared with older children (88% vs 66% of those with an acute seizure, $p=0.043$), but recurrent acute seizures were common overall. Acute seizures were often prolonged (Fig. 2a). Among the 32 children with an acute seizure, 12 (38%) were seizing upon arrival to the emergency department. Onset of the first seizure was delayed by at least 8 hours after stroke presentation in another 12 (38%). Seizures were classified as focal motor in 21 (81%) neonates, with the remainder classified as generalized. Among children, the seizures were classified as focal motor ($n=23$; 72%), complex partial ($n=5$; 16%), simple partial ($n=3$; 9%), and bilateral convulsive ($n=2$; 6%). At the end of the stroke hospitalization, 23 neonates (82% of neonates in the cohort) and 25 children (29% of all children in the cohort) were discharged on an anticonvulsant medication, including two neonates and three children who did not have an acute seizure.

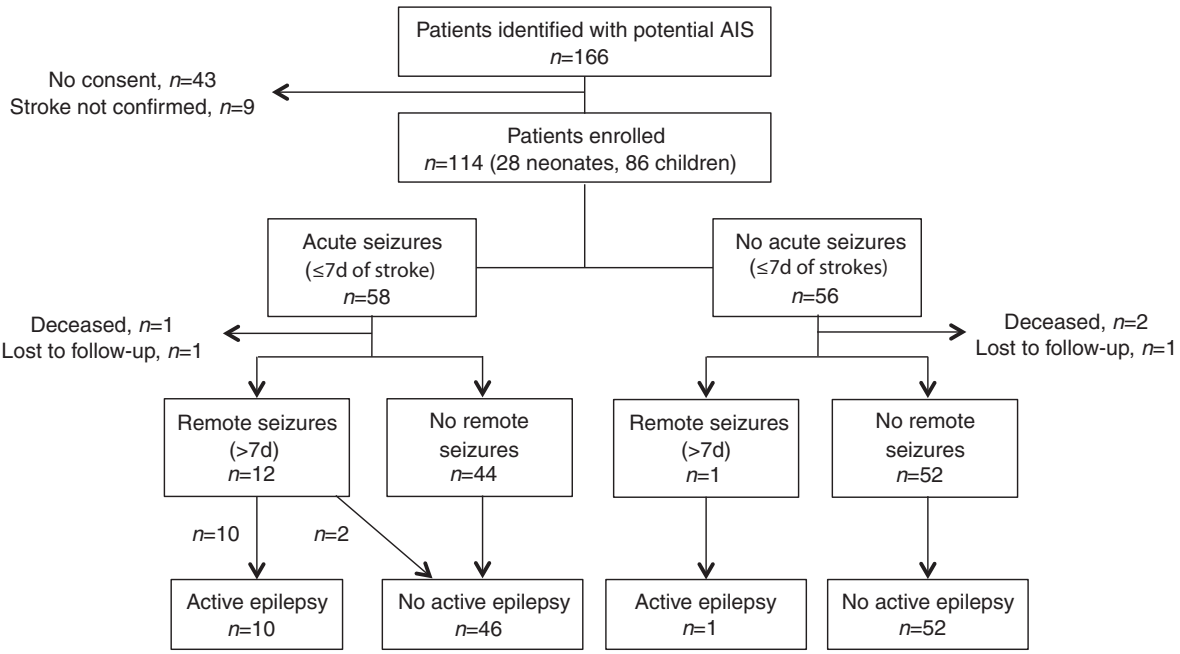

Figure 1: Flow diagram of pediatric stroke cohort demonstrating seizures and epilepsy during the first year after stroke. The final cohort included 114 participants. Among these, 109 completed 1-year follow-up for a measurement of active epilepsy. AIS, arterial ischemic stroke.

On univariate analyses, younger age and stroke involving the middle cerebral artery territory predicted acute seizures (Table II). Overall, acute seizures were 20% more likely (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.7–0.9, $p<0.001$) for each year of age below age 18 at the time of AIS. However, the risk was nonlinear, with greater probability of acute seizures under 4 years of age (Fig. 2b). The magnitude of risk and shape of the curve were similar when neonates were excluded from the model, except that 95% CIs were wider at the youngest ages (Fig. S1, online supporting information). We did not find an association between acute seizures and hemorrhagic conversion or cortical infarct location. In a multivariable model including age in years, the presence of an arteriopathy, and middle cerebral artery territory infarct, estimates of association were younger age (OR 0.8, 95% CI 0.7–0.9, $p<0.001$), arteriopathy (OR 0.3, 95% CI 0.1–0.8, $p=0.022$), and middle cerebral artery territory infarct (OR 3.3, 95% CI 1.2–9.1, $p=0.021$).

Follow-up was available for 109 children (three were deceased, two were lost to follow-up) at a median of 12.3 months (interquartile range 11.6–13) after stroke. All 13 of the children with a remote seizure had been discharged on an anticonvulsant after their stroke hospitalization. Children with an acute seizure had a 2% (95% CI 1.1–3.4%) average monthly incidence rate of a first remote seizure with 18% (95% CI 10–31%) cumulative incidence at 1 year after stroke (Fig. 2c). At 1 year, 11 patients (10%, 95% CI 4–16%) had active epilepsy, including three with neonatal stroke (11%) and eight with childhood stroke (10%; $p=0.854$ for difference between neonates and children). Epilepsy severity varied. Over the year, seven of the children with epilepsy had more than one remote seizure and three reported at least 100 seizures (Table SI, online supporting information). Eight of the children had been treated with multiple anticonvulsants, and four of the children had ongoing treatment with concurrent anticonvulsants.

For each year younger than 18 at the time of stroke, active epilepsy risk increased 20% (OR 0.8, 95% CI 0.6–0.99, $p=0.041$); this relationship was similar when neonatal strokes were excluded (OR 0.7, 95% CI 0.5–0.96, $p=0.027$). Acute systemic illness and acute seizures were also risk factors for active epilepsy (Table II). Greater duration or frequency of acute seizures elevated epilepsy risk in a dose-dependent manner. Each additional 10-minute duration of the longest acute seizure increased active epilepsy risk fivefold (OR 4.7, 95% CI 1.7–13.1). Children with a higher number of recurrent acute seizures had greater probability of a first remote seizure (Fig. 2d). Patients with more than 10 acute seizures had 30-fold increased risk of active epilepsy at 1 year compared with patients without an acute seizure (Table II). EEG characteristics were only available for the subset of children in which EEG was clinically performed ($n=51$). In this subset, abnormal slowing on the acute EEG was associated with 10-fold increased risk of active epilepsy (OR 9.7, 95% CI 1.1–84, $p=0.036$) at 1 year, but we did not find an association with the presence of epileptiform discharges (OR 2.9, 95% CI 0.7–13, $p=0.172$). In sensitivity analyses, acute seizure duration was unknown in 10 out of 109 (8%); four patients had at least one acute seizure with an unknown

Table I: Demographics and characteristics of 114 neonates and children with arterial ischemic stroke

	Neonates (*n*=28) *n* (%)	Children (*n*=86) *n* (%)
Demographics		
Male	15 (54)	51 (59)
North American	20 (71)	60 (70)
Hispanic parent	6 (21)	15 (17)
Stroke risk factors		
Arteriopathy	1 (4)	33 (38)
Cardiac disease	7 (26)	22 (26)
Acute illness	6 (22)	21 (24)
Underlying chronic disease	2 (7)	24 (28)
Head trauma at time of stroke	0 (0)	7 (8)
No risk factor identified	14 (50)	15 (17)
Clinical characteristics		
Prolonged acute seizure (≥5min)	8 (29)	11 (13)
History of seizure before stroke	0 (0)	5 (6)
Family history of epilepsy	1 (4)	0 (0)
Discharged home	24 (86)	70 (81)
Infarct description		
MCA territory stroke	23 (82)	53 (62)
ACA territory stroke	2 (7)	12 (14)
PCA territory stroke	3 (11)	18 (21)
Cortical stroke location	10 (36)	15 (17)
Multifocal infarcts	8 (29)	29 (34)
Any hemorrhage	4 (14)	3 (3)
EEG done	27 (96)	35 (41)
Routine EEG (<30min)	10 (36)	14 (16)
Prolonged EEG (30min–2h)	8 (29)	13 (15)
Continuous EEG (>2h)	9 (32)	7 (8)
Acute seizure	26 (93)	32 (37)
Clinical seizure	19 (69)	26 (30)
Electrographic seizure	8 (29)	3 (3)
Electroclinical seizure	10 (36)	4 (5)
Seizure frequency		
None	2 (7)	54 (63)
Single seizure	3 (11)	7 (8)
2–10 seizures	18 (64)	15 (17)
>10 seizures	5 (18)	6 (7)
Unknown frequency	0 (0)	4 (5)

Except for seizure frequency, categories were not mutually exclusive, so do not sum to 100%. MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; EEG, electroencephalography.

number of additional seizures. Assuming that patients with unknown acute seizure duration had brief (30s) seizures, each additional 10 minutes in longest acute seizure duration still increased active epilepsy risk (OR 3.5, 95% CI 1.4–8.8, p=0.009). Assuming that the patients with an acute seizure but unknown frequency had only a single seizure did not substantially change the estimate or magnitude of the association of seizure frequency and active epilepsy (OR 30, 95% CI 2.9–305, p=0.004 for children with more than 10 acute seizures compared with those with no acute seizures).

DISCUSSION

In this prospective study, we demonstrated that a significant proportion of pediatric stroke survivors later develop epilepsy. Among children who had an acute symptomatic seizure, the incidence rate of a first remote seizure is about 2% each month during the year after stroke. By 1 year after stroke, 10% of all neonates and children were on a maintenance medication for active epilepsy. Nearly half of the children in our cohort had been discharged from the stroke hospitalization on maintenance anticonvulsants. Ongoing anticonvulsant treatment during the first year after stroke may have prevented a first remote seizure, resulting in an underestimation of the natural history of epilepsy development. Importantly, we did not find a leveling off of the remote seizure incidence rate by 1 year, and speculate that the risk probably persists well beyond the first year, resulting in higher incidence of post-stroke epilepsy over time.

The incidence rate of epilepsy in our study is higher than that reported among children in the population-based Kaiser Pediatric Stroke Study, in which 3.6% of children developed active epilepsy annually, with a cumulative incidence of 13% at 5 years.[6] Our higher incidence rates may be explained by age differences between the stroke cohorts; our cohort included neonates with stroke. Among neonates in the Kaiser Pediatric Stroke Study, the cumulative incidence of an unprovoked remote seizure was similar to our cohort, at 20% by 1 year of age.[10] Another reason for our higher incidence rate could be that our cohort, enrolled at pediatric stroke centers that are generally regional tertiary care facilities, may have preferentially included children with more severe strokes or greater medical illness, who were then more likely to go on to develop epilepsy. Finally, the Kaiser Pediatric Stroke Study was dependent on electronic database searches to identify patients with epilepsy, and may have underestimated epilepsy incidence rates.

We found that younger age and middle cerebral artery territory strokes predict acute seizures. The incidence of acute seizures after neonatal AIS should be considered with detection bias in mind because very young infants may not show other clinical signs of stroke. In neonates with AIS, an estimated 80% of seizures identified on continuous EEG may be clinically unsuspected.[15] Systematic continuous EEG monitoring in all patients would be a better way to identify and quantify all seizures but was beyond the scope of our study. Yet, the magnitude and shape of the curve of acute seizure probabilities does not change for children when neonates were excluded, suggesting that this potential bias does not account for the observed association with young age. Younger age also predicts epilepsy at 1 year after stroke; this was unchanged when neonates were excluded.

Few previous studies have directly measured epilepsy after pediatric AIS across age groups. Younger children may have had different infarct characteristics than older children, which could influence epileptogenesis and the age-related epilepsy risk. Alternatively, characteristics of the immature brain that favor excitatory neurotransmitter systems could account for both a vulnerability to acute seizures and the transformation of a normal neuronal network into a hyperexcitable one after an ischemic infarct.[16,17] A third possibility is that acute seizures in the setting of

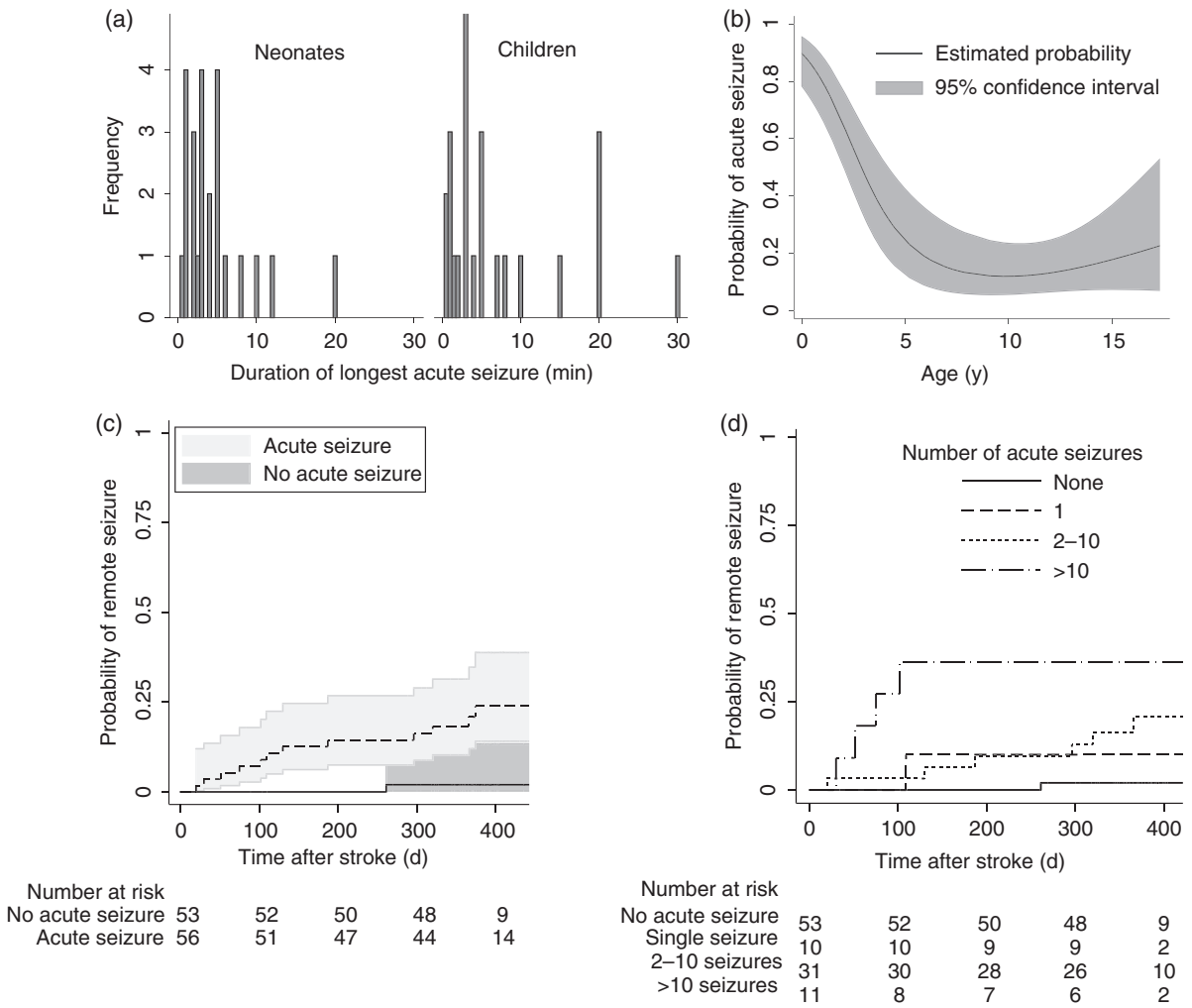

Figure 2: Acute and remote seizure characteristics and predictors after pediatric arterial ischemic stroke. (a) Durations of the longest acute seizure (≤7d after stroke) after arterial ischemic stroke. (b) Younger age predicted acute seizures (black line, estimated probability of acute seizure by age; shading, 95% confidence intervals [CI]); model includes neonates and children (all participants from birth to18y at the time of stroke). (c) Children with an acute post-stroke seizure had a 2% (95% CI 1.1–3.4%) average monthly incidence rate of a first remote seizure and 18% (95% CI 10–31%) cumulative incidence at 1 year after stroke. (d) Recurrent acute seizures were associated with increasing remote seizure risk. Reference group: patients with no acute seizures; single acute seizure: hazard ratio 5 (95% CI 0.3–84, p=0.2); 2–10 acute seizures: hazard ratio 10 (95% CI 1.2–85, p=0.03); >10 acute seizures: hazard ratio 26 (95% CI 2.9–230, p=0.004).

ischemia have an epileptogenic effect.[18] Acute post-stroke seizures were associated with epilepsy in our study and the Kaiser Pediatric Stroke Study.[6] Building on this association, we found that epilepsy risk appears to increase in a dose-related manner with an increasing number and duration of acute seizures. Children with more than 10 acute seizures had a 30-fold increased epilepsy risk compared with children who did not have an acute seizure.

Could acute seizures, observed more frequently in younger children, explain the age-related epilepsy risk? A high burden of acute seizures could potentially contribute to epileptogenesis directly by inducing neurobiological changes or indirectly by increasing metabolic demand in poorly perfused brain and worsening secondary injury. Current pediatric stroke guidelines do not recommend continuous EEG monitoring or routine prophylactic administration of antiepileptic medications after AIS before acute seizures.[19] Although acute seizures after pediatric AIS might be preventable, in practice anticonvulsants are typically only started after a seizure occurs. The most appropriate time for starting anticonvulsant treatment and the duration of treatment after acutely provoked seizures subside, especially in neonates and younger children, remain open questions. However, given the possibility that prolonged or recurrent acute seizures are detrimental, our data suggest an important theoretical opportunity for intervention. A significant proportion of children did not seize at stroke onset, suggesting a window of time to start an

Table II: After pediatric arterial ischemic stroke (n=114), unadjusted odds ratios and 95% confidence intervals (CI) for clinical factors associated with acute seizures (≤7d after stroke) and epilepsy at 1y (n=109 with 1y follow-up)

	Acute seizures (n=58)		Epilepsy (n=11)	
	OR (CI)	p value	OR (CI)	p value
Demographics				
Male	0.8 (0.4–1.7)	0.549	1.4 (0.4–5.2)	0.571
North American	0.6 (0.3–1.4)	0.270	1.1 (0.3–4.5)	0.857
Hispanic parent	0.9 (0.3–2.2)	0.741	1.0 (0.2–5.0)	0.976
Neonatal stroke	21.9 (4.9–98.6)	<0.001	1.1 (0.3–4.6)	0.854
Age at stroke (y)[a]	0.8 (0.7–0.9)	<0.001	0.7 (0.5–0.96)	0.027
Stroke risk factors				
Cardiac disease	1.6 (0.7–3.7)	0.309	0.6 (0.1–3.2)	0.619
Arteriopathy	0.2 (0.1–0.6)	0.001	0.9 (0.2–3.6)	0.840
Acute illness	2.0 (0.8–4.8)	0.139	4.9 (1.2–17.6)	0.016
Underlying chronic disease	0.7 (0.3–1.6)	0.336	0.7 (0.1–3.5)	0.722
Head trauma	0.4 (0.1–2.0)	0.240	n/a	
Infarct description				
MCA territory	2.8 (1.2–6.3)	0.013	1.4 (0.3–5.4)	0.654
ACA territory	0.7 (0.2–2.1)	0.523	1.6 (0.3–8.3)	0.589
PCA territory	0.7 (0.3–1.8)	0.417	0.9 (0.2–4.6)	0.911
Cortical location	1.3 (0.5–3.2)	0.563	2.3 (0.6–9.0)	0.208
Multifocal	1.2 (0.6–2.6)	0.638	2.1 (0.6–7.4)	0.265
Hemorrhage	1.3 (0.3–6.1)	0.733	1.8 (0.2–17.4)	0.594
History of seizure before stroke	4.1 (0.4–37.6)	0.216	n/a	
Acute seizure (any)			11.5 (1.4–93.1)	0.022
No acute seizure			Reference	0.001[b]
Single acute seizure			6.0 (0.3–104.8)	0.229
2–10 acute seizures			7.7 (0.8–72.3)	0.074
>10 acute seizures			30.9 (3.0–316.7)	0.003

[a]Non-neonates. [b]Test for trend across ordinal categories. OR, odds ratio; n/a, odds ratios not applicable because no epilepsy outcomes; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; Reference, reference group for comparison of the other categorical variables

early anticonvulsant. Further, most patients with an acute seizure in our cohort went on to have multiple seizures during the first week. Perhaps after stroke, epilepsy risk could be modified through more aggressive acute seizure management or early detection with continuous EEG monitoring, but further research is required to determine whether this is possible.

Our study had limitations. First, the timing of onset, frequency, and duration of acute seizures were classified at the judgment of the site investigator using all available clinical and EEG data. Some patients may have had clinical or subclinical seizures that were not identified, resulting in an underestimation of acute seizure frequency or duration. Misclassification of exposure is generally thought to result in bias towards the null, so the strength of the association of epilepsy risk with acute seizure presence, frequency, and duration might be underestimated. Further, the estimated risks of epilepsy associated with acute seizure frequency were limited in precision, as reflected by large confidence intervals. Second, remote seizures could have been related to factors other than stroke in our cohort, such as head trauma or underlying neurodevelopmental disorders. However, only 6% of the patients had head trauma at the time of the AIS and none of these had active epilepsy at 1 year after stroke. While 5% of the cohort had a history of seizure before stroke, none of these children met our definition of active epilepsy at 1 year. Finally, the cohort was not population-based or a consecutively enrolled sample. Our estimates of acute seizure probability could have been skewed if investigators preferentially enrolled patients either with or without acute seizures.

Our study highlights that children have an increased and age-related propensity for stroke-related seizures compared with adults. Approximately one in five school-age children has an acute seizure related to AIS, and this proportion is even higher in younger children. Pediatric stroke survivors have a significant risk of developing epilepsy, particularly if they have experienced prolonged or multiple acute seizures. Young children and those with middle cerebral artery territory infarcts are important at-risk groups who could be targeted for closer EEG monitoring and rapid seizure management. Because acute seizures after stroke are a potentially modifiable risk factor, future studies should evaluate whether prevention of recurrent seizures with anticonvulsants can reduce the risk of later epilepsy in this vulnerable population.

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Seizures in Pediatric Stroke (SIPS) sites and investigators.

Figure S1: Predicted probabilities of an acute seizure (≤7d) after childhood arterial ischemic stroke in a model excluding patients who were neonates (birth–28d) at the time of the stroke.

Table SI: Seizure severity among 11 children with epilepsy 1 year after pediatric stroke

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