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Acute Seizures Predict Epilepsy after Childhood Stroke

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Objective: To determine incidence rates and predictors of epilepsy after childhood stroke and compare these to published estimates of 3 to 5% cumulative epilepsy incidence by 5 years poststroke in adults.

Methods: In a retrospective population-based study of children with stroke (29 days–19 years) in an integrated health care system (1993–2007), poststroke seizures were identified through electronic searches and confirmed by chart review. Stroke and seizure characteristics were abstracted from medical records. Survival analysis was used to determine rates and predictors of remote seizures and active epilepsy (anticonvulsant treatment for remote seizure within prior 6 months) at last follow-up.

Results: From a population of 2.5 million children, we identified 305 stroke cases. Over a median follow-up of 4.1 years (interquartile range = 1.8–6.8), 49 children had a first unprovoked remote seizure. The average annual incidence rate of first remote seizure was 4.4% (95% confidence interval [CI] = 3.3–5.8) with a cumulative risk of 16% (95% CI = 12–21) at 5 years and 33% (95% CI = 23–46) at 10 years poststroke. The cumulative risk of active epilepsy was 13% (95% CI = 9–18) at 5 years and 30% (95% CI = 20–44) at 10 years. Acute seizures at the time of stroke predicted development of active epilepsy (hazard ratio = 4.2, 95% CI = 2.2–8.1). At last follow-up, 1/3 of the children with active epilepsy had a recent breakthrough seizure despite anticonvulsant usage.

Interpretation: Unlike adults, children are uniquely vulnerable to epilepsy after stroke. Children with acute seizures at the time of stroke are at particularly high risk.

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Stroke occurs in an estimated 3.8 per 100,000 children annually,^{1–3} and is an important cause of childhood brain injury and epilepsy. Estimates of seizure incidence after childhood stroke vary widely, in part due to variation in study referral populations and limitations of scope, sample size, and length of follow-up.^{4–9} In adults, remote seizures after stroke are relatively infrequent, and studies have suggested that stroke type and location influence their likelihood.^{10–12} Despite a growing body of literature on childhood stroke, epidemiologic data regarding the frequency, severity, and predictors of remote seizures and epilepsy due to stroke in childhood are limited.

Currently, the frequency of remote seizures and epilepsy after stroke in children may be underestimated by neurologists because of extrapolation from stroke studies

demonstrating that few adults develop poststroke epilepsy. Accurate estimates of poststroke seizure incidence and measurements of epilepsy severity in children are needed to offer accurate prognoses to families, assess the magnitude of the problems posed by poststroke seizures to society, and design effective health care and service programs for children afflicted by stroke.¹³ Furthermore, characterizing the children at greatest risk is important so that potentially vulnerable children can be targeted for closer follow-up and future studies of epileptogenesis and epilepsy prevention.

We hypothesized that children frequently develop remote seizures and epilepsy after a stroke, and that clinical factors such as age, stroke type, stroke location, and acute seizures at the time of stroke affect their risk. We examined a large, population-based childhood stroke

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cohort to measure the incidence rate for first remote seizure poststroke and determined clinical predictors. We also examined children with active epilepsy at last follow-up and described the severity of epilepsy in those children.

Patients and Methods

Study Design, Setting, and Population

We conducted a retrospective study of remote seizures and epilepsy within a population-based cohort of children with stroke enrolled at Kaiser Permanente Northern California (KPNC). All study procedures were approved by the institutional review boards at KPNC and the University of California, San Francisco. KPNC is an integrated health care system that cares for about 1/3 of the population in Northern California. KPNC electronic medical records include all outpatient and inpatient visits; encounters at outside facilities are also captured through the billing process. Electronic medical record coding is performed by the treating physician (for outpatient visits) or by professional coders reviewing admission records. All medications prescribed and filled are recorded in the KPNC electronic pharmacy database.

The study population included all children through 19 years of age enrolled at KPNC, January 1993 to December 2007. From this population base, a cohort of children diagnosed with symptomatic stroke was identified in the Kaiser Pediatric Stroke Study (KPSS). Methods of case identification and characteristics of the cohort, including stroke etiology, have been previously described.^{14–17} The criteria for stroke were: (1) documented clinical presentation consistent with stroke, such as a sudden onset focal neurological deficit, headache, or seizure; and (2) computed tomography or magnetic resonance imaging showing a focal ischemic infarct or hemorrhage in a location and of a maturity consistent with the neurological signs and symptoms. KPSS excluded cases of subdural and epidural hematomas and strokes that occurred outside of the study period. For the current seizure study, neonatal strokes (strokes that occurred before 29 days of life) and children who died during their stroke hospitalization were excluded.

Data Abstraction

A single pediatric nurse professional medical record analyst abstracted demographic and clinical data from electronic and traditional medical records. For children with a confirmed remote seizure, the same analyst abstracted additional data pertaining to seizures. All abstracted data were reviewed for accuracy by a pediatric neurologist.

Remote Seizure Ascertainment

To determine the primary outcome of remote seizure, we first electronically searched for International Classification of Diseases, ninth revision codes related to seizure and epilepsy in inpatient or outpatient databases, and searched the pharmacy database for prescriptions of anticonvulsant medications filled >1 month after stroke. Two child neurologists then independently reviewed all potential cases to confirm the remote seizure.

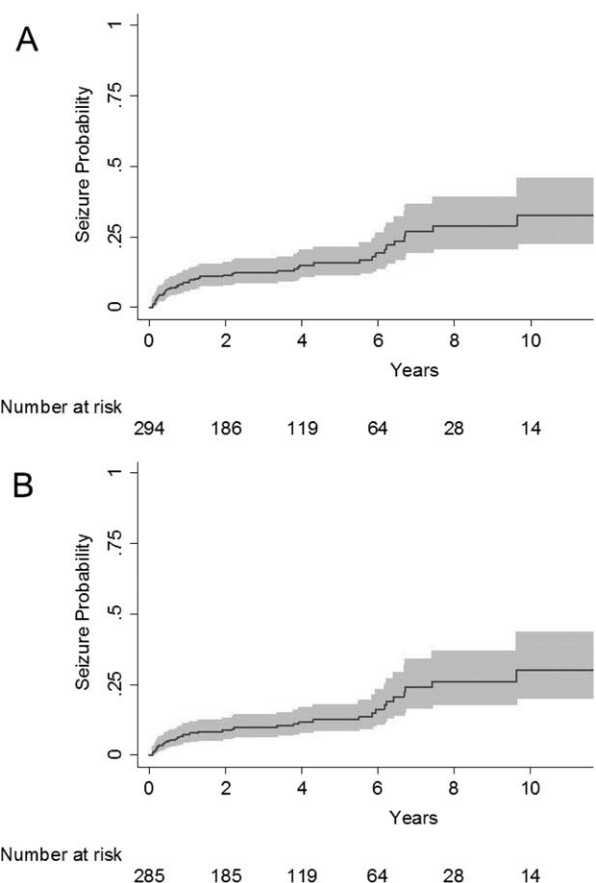


FIGURE 1: Among children with stroke enrolled at Kaiser Permanente Northern California, 1993–2007, Kaplan–Meier plot demonstrating failure function (solid lines) and 95% confidence intervals (gray shading) for (A) first remote seizure and (B) first remote seizure among those with active epilepsy at last follow-up. The x-axis is time from 30 days poststroke.

A third neurologist adjudicated in case of reviewer disagreement.

Definitions

Remote seizure was defined as at least 1 documented unprovoked seizure occurring >30 days after stroke. In 2 cases of acute ischemic strokes, the event date was not clear from the medical record, so the date of evaluation was used for the date of stroke onset. Unprovoked seizures were seizures that were not in close temporal association or attributable to an acute systemic, metabolic, or toxic insult (such as fever, hypoglycemia, or other electrolyte disturbances) or an acute central nervous system insult (such as a recurrent stroke) after chart review by a neurologist. We defined *active epilepsy* as at least 1 unprovoked remote seizure and either ongoing anticonvulsant treatment or <6 months seizure-free off of anticonvulsant agents at the time of the last follow-up. This is consistent with the International League Against Epilepsy definition of active epilepsy as “a person who is either currently being treated for epilepsy or whose most recent seizure has occurred within a time interval usually defined as the past 2 or 5 years... but the time should be specified.”¹³

Predictors

Age (in years) was analyzed as a continuous variable. *Acute seizure* was defined as the presence of a clinical seizure documented at the time of stroke presentation. *Neurologic deficit at hospital discharge* was defined as any neurologic deficit documented at the time of the patient's discharge from the acute stroke hospitalization. *Location* was defined by documentation in radiology reports. These categories were not mutually exclusive; a single stroke case could have multiple locations. *Stroke type* indicated stroke classification after chart review by a vascular neurologist (H.J.F.) into mutually exclusive categories: any intraparenchymal hemorrhage, subarachnoid hemorrhage/intraventricular hemorrhage (SAH/IVH), arterial ischemic stroke, or venous sinus thrombosis. *Laterality* classified side of stroke (left, right, bilateral, or none) documented in radiology reports. Pure SAH/IVH and some venous sinus thromboses were listed as "none" if no lateralizing components of the stroke were identified.

Analysis

We used summary statistics to describe characteristics of the stroke cohort and compare groups stratified by onset of remote seizures, with nonparametric tests for age and length of follow-up. We used survival analysis to determine incidence rates and cumulative risk of remote seizure and active epilepsy, with time at risk beginning 30 days after stroke ictus. The first remote seizure was the failure event; children were also censored from the analysis at death or the last clinical follow-up in the KPNC system. We also used the first remote seizure as the failure event in analyses of active epilepsy. Children with a history of seizure prior to stroke were excluded from the survival analyses. Cox proportional hazards models were used to determine univariate predictors of children with remote seizures and active epilepsy due to stroke, using the log-rank test for statistical significance. Our multivariate model included univariate predictors of remote seizure with $p < 0.2$, as well as predetermined demographic factors (sex and race). An interaction variable of "acute seizure" and "age at stroke" was used to examine independence of these clinical predictors of remote seizure and active epilepsy, but was not included in the final multivariate models because the interaction term did not reach significance (defined as $p < 0.2$).

Results

Description of Stroke Cohort

From a study base of 2.5 million children (11.5 million person-years at risk), we identified 322 children with a non-neonatal stroke (2.9 strokes per 100,000 person-years). Of these, 17 died during the acute hospitalization, leaving 305 for inclusion in our final study cohort: 140 ischemic and 165 hemorrhagic strokes. Median age at the time of the stroke was 13.1 years (interquartile range [IQR] = 6–17.1); the cohort was 41% Caucasian and 57% male. At stroke presentation, 27% (80 of 293, 12 missing) of the cases had an acute seizure and 60% (183 of 303, 2 missing) had a neurologic deficit documented

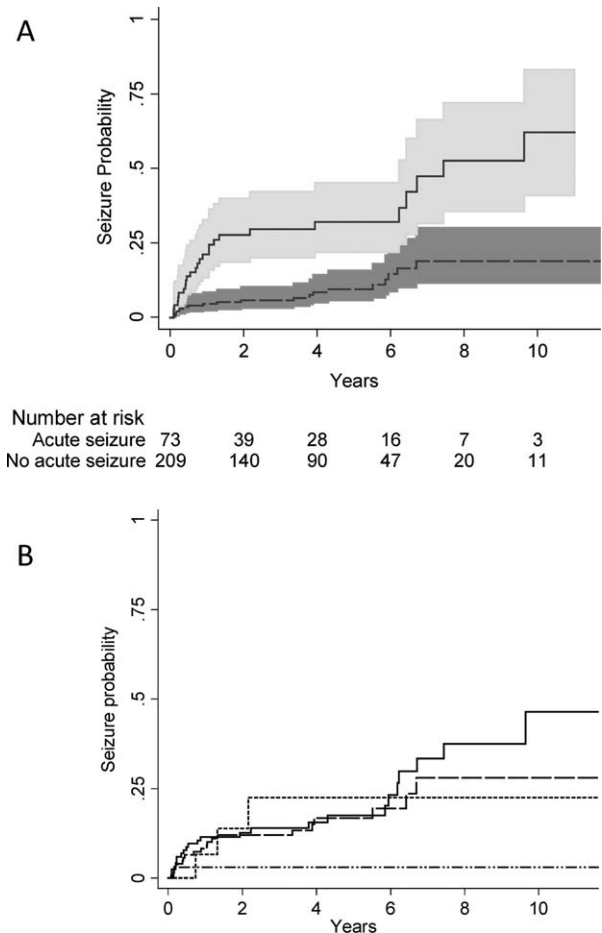


FIGURE 2: Among children with stroke enrolled at Kaiser Permanente Northern California, 1993–2007, Kaplan–Meier plots demonstrating (A) a 4-fold (hazard ratio = 4.1, 95% confidence interval = 2.3–7.3) increased risk of remote seizure among children with acute seizures (solid line, 95% confidence interval in light gray shading) compared to children without acute seizures (dashed line, 95% confidence interval in dark gray shading); and (B) the cumulative incidence of remote seizure stratified by stroke type: arterial ischemic stroke (solid line), intraparenchymal hemorrhage (large dashes), venous sinus thrombosis (small dashes), and subarachnoid hemorrhage/intraventricular hemorrhage (dash and dots). The x-axis is time from 30 days poststroke.

at hospital discharge. Children who had a seizure at the time of the stroke were younger, with a median age of 8.4 years (IQR = 1.3–16.2) compared to 13.6 years (IQR = 7.8–17.3) among those who did not have an acute seizure ($p < 0.003$). Median length of poststroke follow-up was 4.1 years (IQR = 1.8–6.8), with a total of 1,111 person-years at risk for remote seizures.

Poststroke Incidence of Remote Seizure and Active Epilepsy

Seven children with remote seizures had a history of seizures prior to stroke and were excluded from survival analyses. We identified remote seizures in 49 children with no history of seizure prior to stroke. Of these, 40 children

TABLE 1. Unadjusted HRs for Remote Seizure after a Stroke among Children Enrolled at Kaiser Permanente Northern California, 1993–2007

Characteristic	No remote seizure, n/N (%)	Remote Seizure, n/N (%)	Unadjusted, HR [95% CI]	Log-Rank <i>p</i>
Age at stroke, median years {IQR}	13.4 {7.0–17}	9.8 {1.0–17}	0.96 [0.92–0.99]	<0.0001 ^a
Male sex	141/249 (57)	32/49 (65)	1.4 [0.8–2.6]	0.2
Caucasian race	99/249 (40)	20/49 (41)	0.9 [0.5–1.6]	0.8
Acute seizure	48/239 (20)	26/47 (55)	4.1 [2.3–7.3]	<0.0001 ^a
Neurologic deficit at discharge	144/247 (58)	36/49 (73)	1.7 [0.9–3.2]	0.1
Location				
Frontal	84/249 (34)	17/49 (35)	1.1 [0.6–1.9]	0.8
Parietal	70/249 (28)	20/49 (41)	1.7 [1.0–3.0]	0.1
Temporal	54/249 (22)	13/49 (27)	1.4 [0.7–2.7]	0.3
Occipital	33/249 (13)	10/49 (20)	1.6 [0.8–3.3]	0.2
Cerebellum	20/249 (8)	2/49 (4)	0.6 [0.1–2.5]	0.5
Stroke type			1.1 [0.9–1.3]	0.1
Intraparenchymal hemorrhage	108/249 (43)	20/49 (41)		
Arterial ischemic stroke	96/249 (39)	24/49 (49)		
SAH/IVH	32/249 (13)	1/49 (2)		
Venous sinus thrombosis	13/249 (5)	4/49 (8)		
Laterality			1.2 (0.8–1.6)	0.4
Left	91/245 (37)	21/49 (43)		
Right	76/245 (31)	18/49 (37)		
Bilateral	40/245 (16)	5/49 (10)		
None	38/245 (16)	5/49 (10)		

Location categories were not mutually exclusive.
^aStatistically significant.
 CI = confidence interval; HR = hazard ratio; IQR = interquartile range; SAH/IVH = subarachnoid hemorrhage/intraventricular hemorrhage.

had active epilepsy at the time of last follow-up. The average annual incidence rate of a first remote seizure post-stroke was 4.4% (95% confidence interval [CI] = 3.3–5.8), with a 5-year cumulative risk of 16% (95% CI = 12–21) and 10-year cumulative risk of 33% (95% CI = 23–46; Fig 1A). The average annual incidence rate of first remote seizure among those with active epilepsy at last follow-up was 3.6% (95% CI = 2.6–4.9), with a 5-year cumulative risk of 13% (95% CI = 9–18) and a 10-year cumulative risk of 30% (95% CI = 20–44; see Fig 1B).

Predictors of Remote Seizure and Active Epilepsy

On univariate analysis, children who had an acute seizure at the time of stroke were 4X as likely to have a remote

seizure compared to children who did not have a seizure at the time of their stroke (hazard ratio [HR] 4.1, 95% CI 2.3, 7.3) (Figure 2A, Table 1). The average annual incidence rate of remote seizure among children who had an acute seizure was 10.6% compared to 2.5% for those without acute seizure, for an incidence rate difference of 8.1% (95% CI 3.8%, 12.2%). Among children with acute seizures, the cumulative risk of active epilepsy was 25% (95% CI 16%, 38%) by five years. Younger age also predicted remote seizures: for each 1 year increase in age at the time of stroke onset, the hazard ratio decreased by 4.3% (HR 0.96, 95% CI 0.92, 0.99). The cumulative incidence of first remote seizure was lowest among children with SAH/IVH (Figure 2B), although estimates stratified by stroke type had wide confidence intervals

TABLE 2. Adjusted HRs for Remote Seizure after a Stroke among Children Enrolled at Kaiser Permanente Northern California, 1993–2007

Characteristic	HR (95% CI)	<i>p</i>
Age at stroke, yr	1.0 (0.9–1.0)	0.5
Male sex	1.6 (0.9–2.9)	0.1
Caucasian race	1.1 (0.6–2.1)	0.7
Acute seizure	3.5 (1.9–6.6)	< 0.001 ^a
Neurologic deficit at discharge	1.5 (0.8–2.9)	0.2
Parietal location	1.5 (0.8–2.7)	0.2
Stroke type	1.0 (0.8–1.2)	0.9

The adjusted model included univariate predictors of remote seizure with *p* < 0.2 and predetermined demographic factors (sex and race).
^aStatistically significant.
 CI = confidence interval; HR = hazard ratio.

and the difference in estimates did not reach statistical significance. Excluding children with SAH/IVH, the cumulative incidence of first remote seizure was 4.9% (95% CI 4%, 7%) at 1 year, 17% (95% CI 13%, 24%) at 5 years and 37% (95% CI 26%, 51%) at 10 years.

In our multivariate model, the hazard ratio for acute seizure was slightly attenuated (HR 3.5, 95% CI 1.9, 6.6) but remained a strong independent predictor of remote seizure, while age did not (Table 2). Younger age (HR 0.95, 95% CI 0.9, 1.0) and acute seizures (HR 4.1, 95% CI 2.1, 7.8) were also univariate predictors of active epilepsy, but only acute seizures predicted active epilepsy (HR 3.5, 95% CI 1.7, 7.1) in our multivariate model.

Younger age (HR = 0.95, 95% CI = 0.9–1.0) and acute seizures (HR = 4.1, 95% CI = 2.1–7.8) were also univariate predictors of active epilepsy, but only acute seizures predicted active epilepsy (HR = 3.5, 95% CI = 1.7–7.1) in our multivariate model. Among children with acute seizures, the cumulative risk of active epilepsy was 25% (95% CI = 16–38) by 5 years.

Measures of Epilepsy Severity

Among the 49 children with a remote seizure, 34 were seen in an emergency department at least once and 21 had multiple emergency encounters for seizure (Fig 3A). Fifteen children had been admitted to a hospital for a seizure, and 4 had been intubated and admitted to an intensive care unit because of an episode of status epilepticus. All children with remote seizures after stroke were ultimately treated with an anticonvulsant medication. Most had been treated with at least 2 different

anticonvulsant agents (range = 1–7) during the follow-up period (see Fig 3B). At last follow-up, 9 children were on polytherapy with >1 concurrent anticonvulsant agent. Despite anticonvulsant usage, 13 (33%) of the children with active epilepsy had at least 1 breakthrough seizure in the month prior to the last follow-up and 8 were having multiple seizures per month.

Discussion

In this population-based childhood stroke cohort, 1 of 6 children suffering from stroke had a remote seizure by 5 years, and this increased to 1 of 3 children by 10 years poststroke. Prior pediatric stroke studies have reported proportions of children with remote seizures or epilepsy ranging from 7 to 29%, although these studies were limited by variable duration of follow-up or losses to follow-up, and were not population-based.^{5–9,18,19} A recent study of perinatal and childhood intracerebral hemorrhage found 13% of children developed epilepsy by 2 years.¹⁹ Several large population-based studies of

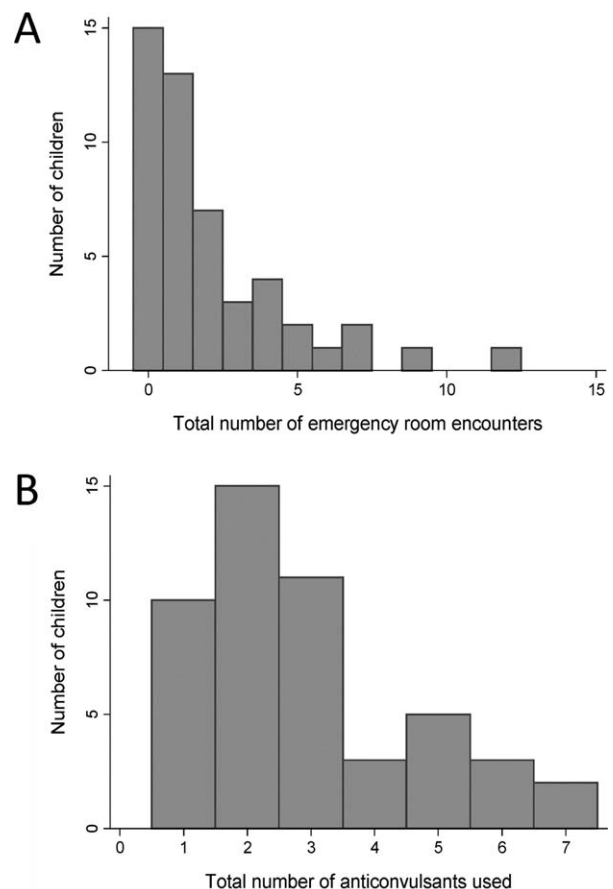


FIGURE 3: Histogram plots demonstrating measures of epilepsy severity among 49 children with remote seizure after stroke. Children were stratified by: (A) the number of emergency room encounters for seizure during the follow-up period, and (B) the number of separate anticonvulsant medications prescribed during the follow-up period.

TABLE 3. Comparison of Incidence Rate Estimates of Remote Seizure after Stroke from the Current and Previously Published Population-Based Studies

Authors	Stroke Study, N	Mean Age, yr (range)	Estimated Incidence Rate	Seizure Outcome
Kammersgaard & Olsen, 2005 ¹⁰	Copenhagen Stroke Study, N = 1,195	73 (all ages)	1% by 3 years	Recurrent seizures after stroke + AED
Chen 2012 ²⁰	Taiwan Health Insurance Database, N = 4,126	63 (20–80)	3% by 5 years	2 ICD-9 diagnoses in ambulatory care claims
Lossius 2005 ²¹	Askershus Stroke Study, N = 484	76 (>60)	3% by 1 year	1 seizure > 1 week after stroke
			3% by 7 years	Recurrent seizures > 1 week after stroke
Burn 1997 ¹¹	Oxfordshire Community Stroke Project, N = 675	72 (all ages)	4% by 5 years	1 seizure > 1 month after stroke
			4% by 2 years	Recurrent seizures > 24 hours after stroke
So 1996 ²²	Rochester, Minnesota, N = 535	72 (all ages)	5% by 5 years	1 seizure > 1 week after stroke
			4% by 5 years	Recurrent seizures > 1 week after stroke
Viitanen 1998 ²³	Umea, Sweden, N = 409	72 (all ages)	5% at 5 years	Recurrent seizures > 1 month after stroke + AED
Current	Kaiser Pediatric Stroke Study, N = 305	11 (0.1-19)	16% by 5 years	1 seizure > 1 month after stroke
			13% by 5 years	1 seizure > 1 month after stroke + AED

In some studies, >1 seizure outcome was reported.
AED = anticonvulsant agent; ICD-9 = International Classification of Disease, ninth revision.

poststroke seizures in adults have used survival analysis techniques; despite varying definitions of late seizures and poststroke epilepsy, the range of 3 to 5% cumulative incidence by 5 years^{10,11,20–23} is relatively consistent (Table 3). Although different definitions across studies might influence incidence rates, all of the comparable definitions result in lower estimates in the adult studies, suggesting that the developing brain may be more susceptible than the mature brain to remote seizures and epilepsy after an injury.

We found that children with acute seizures at the time of stroke represent a particularly vulnerable subgroup, with 4× the risk of remote seizures; 1/4 of these children develop active epilepsy within 5 years. The greatest risk for a first remote seizure was within the first year after stroke, which may suggest a time period that warrants close clinical follow-up for seizure. Our findings are consistent with 2 adult stroke studies^{10,11} and a recent childhood stroke study, which defined *epilepsy* as a seizure after discharge and treatment with an anticonvulsant agent; at 6 months after stroke, epilepsy was found

in 5 of 21 children who presented with acute seizures and none of the 44 children without acute seizures.⁴

Studies that have examined age at the time of stroke in adults as a predictor of poststroke epilepsy report conflicting results. Younger age was associated with poststroke epilepsy in the Copenhagen Stroke Study, but the Askershus Stroke Study found no association.^{10,21} We found that younger age was associated with remote seizures after childhood stroke on univariate analysis, but was no longer significant in multivariate analysis. This is likely due to younger age being highly correlated with risk of acute seizure at time of stroke in our cohort; therefore, adjustment for acute seizure in multivariate analysis removed the age effect.

Several of the children were treated with multiple anticonvulsant medications, which we speculate was likely to be related to either poor seizure control or unacceptable medication side effects. A third of the children who were on treatment with an anticonvulsant agent at last follow-up had a seizure within the month prior to last follow-up, suggesting treatment-refractory epilepsy. The multiple

emergency room visits and hospitalizations for poststroke epilepsy among the children in our cohort are further evidence of the heavy burden of disease that poststroke epilepsy places on both individual families and society.

The cumulative risk and timing of remote seizures in our cohort are comparable to the patterns of remote seizures found after traumatic brain injury in children^{24,25} and adults.^{26,27} Studies of traumatic brain injury in children suggest that in this group, early seizures and younger age may also predict remote epilepsy.^{24,28,29} Post-traumatic epilepsy has recently received increasing attention because of its high incidence and its delayed but possibly predictable onset, suggesting a potential window for intervention and prevention.³⁰ Poststroke epilepsy in children appears to similarly manifest a delayed but predictable onset, presenting an opportunity for intervention if an agent to prevent epilepsy after acquired brain injury can be identified. The potential for intervention is important because even without a stroke, children with epilepsy are at an increased risk for comorbid physical, developmental, and behavioral problems.³¹ Furthermore, current literature suggests that children who develop epilepsy after a stroke are more likely to have poor neurodevelopmental outcomes compared with children who do not develop poststroke epilepsy,^{32–37} even after accounting for stroke location.³⁷ We do not know yet whether epilepsy is a marker for more severe initial brain injury or whether stroke recovery is impaired by seizures, interictal epileptiform discharges, or anticonvulsant treatment.

Our study had limitations. First, we were limited in assessing recurrent seizures because many of the children were treated with an anticonvulsant agent after the first remote seizure. We addressed this limitation by measuring active epilepsy, an outcome that should provide a more conservative estimate of epilepsy risk by limiting the outcome to those who had ongoing clinical treatment with an anticonvulsant agent. Second, because our initial screen for poststroke seizure outcomes used electronic data, it is possible that some outcomes may have been missed if no seizure or epilepsy diagnostic codes were given and anticonvulsant medications were not filled through the integrated health care pharmacy. Missed cases would result in underestimating the incidence rate of remote seizures. Finally, the sociodemographic and health characteristics of the adult Kaiser population base are comparable to the Northern California adult population, and data obtained from KPNC are considered generalizable to wider populations.³⁸ Although it is likely that this is also true for children enrolled at Kaiser, it is possible that the Kaiser pediatric population may not be similarly generalizable.

Despite these limitations, our study provides strong evidence that remote seizures and epilepsy are common

after stroke in children, particularly among children with acute seizures. The frequency of remote seizures after pediatric stroke has important implications both for public health and for individual families. These data highlight the urgency of understanding the neurocognitive implications of seizures and anticonvulsant medication usage after childhood stroke, and of searching for neuroprotective agents or other interventions to decrease epilepsy risk. Children with acute symptomatic seizures who are at higher risk may benefit from counseling and close monitoring for seizures in the outpatient setting, particularly during the first year poststroke.

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Potential Conflicts of Interest

C.K.F.: grants/grants pending, NIH-NINDS. S.S.: grants/grants pending, NIH, NHLBI, US FDA, AHA/UCSF, Garfield Memorial Foundation, NINDS, NIDDK/GHRI, Thrasher Foundation/UCSF, NINDS/UCSF, REAC-UCSF, NHLBI/University of Minnesota, AHA-FTF, NHLBI/Northwestern University; travel expenses, National Forum for Stroke and Heart and Stroke Disease Prevention, Multi-ethnic Study of Atherosclerosis (MESA), GRADE DSMB. D.H.L.: board membership, UCB Pharm, Upsher-Smith; grants/grants pending, NINDS. H.J.F.: grants/grants pending, NINDS.

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