Incidence and predictors of epilepsy after pediatric arterial ischemic stroke

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ABSTRACT

Objective: To determine the cumulative incidence and clinical predictors of remote symptomatic seizures and epilepsy after pediatric arterial ischemic stroke (AIS).

Methods: We performed a retrospective analysis of 218 participants with neonatal AIS (NAIS), presumed perinatal AIS (PPAIS), and childhood AIS (CAIS) from a single-center prospective consecutive cohort enrolled from 2006 to 2014. Medical records were reviewed for timing, semiology, and treatment of acute symptomatic seizures, remote symptomatic seizures (RSS), and epilepsy. Cumulative incidence of RSS and epilepsy were assessed using survival analysis.

Results: Acute symptomatic seizures occurred in 94% of NAIS ($n = 70/74$) and 17% of CAIS ($n = 18/105$). Younger children were more likely to present with seizures at stroke ictus, and acute symptomatic seizures were predictive of later RSS and epilepsy in CAIS. Median follow-up for the entire cohort was 34 months, interquartile range 44.9 months (16.3–61.2). Estimated cumulative incidence of RSS at 2 years was 19% in NAIS, 24% in PPAIS, and 7% in CAIS. Estimated cumulative incidence of epilepsy at 2 years was 11% in NAIS, 19% in PPAIS, and 7% in CAIS. The median time to these outcomes was <2 years in all stroke subtypes. Among participants developing epilepsy ($n = 34$), seizures were often well-controlled at last follow-up with median Engel class of ≤ 2 (<1 seizure/month).

Conclusions: RSS and epilepsy are important neurologic sequelae of pediatric AIS. Children with perinatal stroke and CAIS with acute symptomatic seizures are at increased risk of these outcomes. These cohorts need further study to identify biomarkers and potential therapeutic targets for epileptogenesis. *Neurology*® 2017;88:630–637

GLOSSARY

AIS = arterial ischemic stroke; **CAIS** = childhood arterial ischemic stroke; **CHOP** = Children's Hospital of Philadelphia; **CI** = confidence interval; **HR** = hazard ratio; **IQR** = interquartile range; **KW** = Kruskal-Wallis; **NAIS** = neonatal arterial ischemic stroke; **PPAIS** = presumed perinatal arterial ischemic stroke; **RSS** = remote symptomatic seizures; **WRS** = Wilcoxon rank-sum.

Many children with arterial ischemic stroke (AIS) present with acute symptomatic seizures^{1–4} and survivors frequently develop remote symptomatic seizures (RSS) and epilepsy. However, the incidence of these sequelae is unclear, with prior studies of pediatric AIS populations reporting ranges of 13%–67%, varying by age at stroke onset.^{2,5–11} Moreover, few data are available regarding the risk factors for RSS and epilepsy after pediatric AIS. An improved understanding would help guide family counseling and support the development of approaches to prevent poststroke epilepsy. In this study, we assessed the cumulative incidence and predictors for the development of RSS and epilepsy in infants and children after neonatal AIS (NAIS), presumed perinatal AIS (PPAIS), and childhood-onset AIS (CAIS). This is the first study to directly compare these outcomes across the 3 pediatric AIS subtypes.

METHODS This was a retrospective analysis of a single-center prospective consecutive cohort at the Children's Hospital of Philadelphia (CHOP).

Supplemental data
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Standard protocol approvals, registrations, and patient consents. The institutional review board approved the study. Informed consent was obtained for all participants.

Inclusion criteria. The study population comprised 3 groups that presented to CHOP with AIS and were enrolled in the institutional Pediatric Stroke Registry between January 1, 2006, and October 31, 2014. NAIS was diagnosed in term neonates (≥ 37 weeks gestation at birth) with acute neonatal encephalopathy (seizures, altered mental status, or focal neurologic deficits) at ≤ 28 days old with acute infarction in an arterial territory on brain MRI (figure 1). PPAIS was diagnosed in children with normal perinatal neurologic histories who developed neurologic deficits or seizures at >28 days old and had remote focal infarction in an arterial territory on MRI.¹² CAIS was diagnosed in children >28 days old with new neurologic deficits or seizures attributable to acute infarction in an arterial territory on MRI or CT. Case ascertainment was thought to be near complete due to an institutional protocol involving stroke service consultation on all AIS cases presenting in both the acute and outpatient care settings. All patients were logged and approached for consent at first point of contact and later at follow-up outpatient visits if consent was not initially obtained. Estimated consent rate was $>95\%$ of all participants approached.

Exclusion criteria. Participants with the following comorbidities were excluded: prestroke epilepsy, prematurity (<37 weeks gestation at birth), in utero stroke (detected prenatally or finding of encephalomalacia on MRI at ≤ 10 days of age), intracerebral hemorrhage not attributable to hemorrhagic transformation of AIS, cerebral sinovenous thrombosis, periventricular venous infarction, moderate to severe hypoxic-ischemic encephalopathy, congenital

hydrocephalus, PHACES, Sturge-Weber syndrome, neonatal moyamoya vasculopathy, cranial surgery, or brain tumor-related infarctions (figure 1).

Data collection. Medical record data were reviewed and entered into a Research Electronic Data Capture database.¹³ These included (1) participant demographic and clinical characteristics, (2) time of onset of acute symptomatic seizures, remote symptomatic seizures, and epilepsy, (3) seizure semiology, and (4) antiseizure medication use and duration.

Definitions. An acute symptomatic seizure was defined as any clinically evident seizure observed by a parent/guardian or medical provider or any electrographically evident seizure occurring ≤ 7 days after stroke ictus identified by routine EEG or continuous EEG. Clinical seizures in neonates were classified as subtle, clonic, or tonic.¹⁴ An electrographic seizure was defined as any abnormal paroxysmal event different from the EEG background with a temporal-spatial evolution in morphology, frequency, and amplitude, and an electrographic field >10 seconds.¹⁵ An electroclinical seizure was defined as any electrographic seizure associated with observed clinical change. A subclinical seizure was defined as any electrographic seizure that was not associated with observed clinical change. Subacute symptomatic seizures were defined as any seizure occurring between 8 and 29 days after stroke ictus. RSS were defined as any seizure occurring ≥ 30 days after stroke ictus. These were classified as provoked seizures, probable epilepsy, or definite epilepsy. Provoked seizures were defined as any seizure occurring with fever or infection. Probable epilepsy was defined as one unprovoked seizure plus one of the following: (1) EEG with epileptiform abnormalities (sharp waves, spike and slow waves) or (2) initiation of treatment

Figure 1 Participant inclusion/exclusion flow diagram

AIS = arterial ischemic stroke; CAIS = childhood arterial ischemic stroke; HIE = hypoxic ischemic encephalopathy; NAIS = neonatal arterial ischemic stroke; PPAIS = presumed perinatal arterial ischemic stroke.

with an antiseizure medication. Definite epilepsy was defined as ≥ 2 unprovoked seizures occurring ≥ 24 hours apart. Status epilepticus in a neonate was defined as a single clinical or electrographic seizure lasting ≥ 30 minutes or multiple electrographic or electroclinical seizures totaling ≥ 30 minutes of a 60-minute EEG recording.¹⁶ Status epilepticus in a child was defined as any clinical or electrographic seizure lasting > 5 minutes.¹⁷ A modified form of the Engel classification^{5,18} was determined for all participants with probable or definite epilepsy where class 0 = seizure-free off anticonvulsants ≥ 6 months, class 1 = seizure-free ≥ 6 months on medication or seizure-free off medication for < 6 months, class 2 = < 1 seizure/month, class 3 = 1–4 seizures/month, class 4 = 5–30 seizures/month, and class 5 = > 30 seizures/month.

Clinical and radiographic data. The investigators (L.L.B., R.N.I.) reviewed diagnostic neuroimaging and associated reports for infarct characteristics. Participants with NAIS and PPAIS underwent echocardiogram and thrombophilia profile per the institutional protocol and physician preference. All participants with CAIS had comprehensive evaluation for stroke etiology including cranial and cervical vascular imaging, echocardiogram with bubble study, and thrombophilia profile. Primary CAIS subtype classification was assigned according to the Childhood AIS Standardized Classification and Diagnostic Evaluation criteria.¹⁹

Statistical analysis. STATA version 12.0 (Stata Corporation, College Station, TX) was used for all analyses.²⁰ Fisher exact tests were used to analyze associations for categorical variables. The Wilcoxon rank-sum (WRS) test was used to determine the difference in age of those with and without acute symptomatic seizures in the CAIS cohort. The Kruskal-Wallis (KW) test was used to determine whether follow-up duration, time to RSS among those with RSS, and time to epilepsy among those with epilepsy were different across the CAIS, PPAIS, and NAIS groups. Subsequent pairwise comparisons were performed with the WRS test if the *p* value for the KW test was significant. The Kaplan-Meier estimate of survival was calculated to determine the RSS-free survival and epilepsy-free survival. Censor time was defined as the time between stroke ictus and last follow-up date for those without RSS or epilepsy (probable and definite) and was the time between stroke ictus and date of the first RSS for those with RSS or epilepsy. Date of stroke ictus was presumed to be date of birth for NAIS and PPAIS. The log-rank test was used to compare Cox proportional hazard ratios (HRs) and evaluate relative risk. A 2-sided probability value of ≤ 0.05 was considered statistically significant for all analyses.

RESULTS Overall cohort. A total of 285 Pediatric Stroke Registry cases were examined for eligibility

Table 1 Demographic and radiographic characteristics

	Total (n = 218)	NAIS (n = 74)	PPAIS (n = 39)	Fisher exact, p value ^a	CAIS (n = 105)
Male, n (%)	140 (64)	41 (55)	23 (59)		76 (72)
Age at stroke diagnosis, y (IQR) ^b		2 d (1–3.7)	0.9 y (0.7–1.5)		7.4 y (2–13.6)
Race/ethnicity, n (%)					
Caucasian	141 (65)				
African American	42 (19)				
Hispanic	11 (5)				
Asian	7 (3)				
Infarct location, n (%)					
Anterior circulation	154 (71)	60 (81)	36 (92)	0.17	58 (55)
Posterior circulation	45 (21)	4 (5)	1 (3)	0.65	40 (38)
Both	19 (9)	10 (14)	2 (5)	0.21	7 (7)
Infarct number, n (%)					
Unifocal	142 (65)	51 (69)	36 (92)	0.005	55 (52)
Multifocal	76 (35)	23 (31)	3 (8)	0.005	50 (48)
Laterality, n (%)					
Left	103 (47)	38 (51)	24 (62)	0.33	41 (39)
Right	66 (30)	21 (28)	13 (33)	0.67	32 (31)
Bilateral	49 (22)	15 (20)	2 (5)	0.05	32 (30)
Infarct location, n (%)					
Cortex	157 (72)	70 (95)	33 (85)	0.09	54 (51)
Basal ganglia	97 (44)	30 (41)	28 (72)	0.003	39 (37)
Brainstem	12 (6)	3 (4)	1 (3)	> 0.99	8 (8)
Cerebellum	21 (10)	4 (5)	0	0.30	17 (16)

Abbreviations: CAIS = childhood arterial ischemic stroke; IQR = interquartile range; NAIS = neonatal arterial ischemic stroke; PPAIS = presumed perinatal arterial ischemic stroke.

^a Comparing NAIS and PPAIS.

^b Age at neuroimaging confirmation of stroke.

and 67 had exclusionary diagnoses. A total of 218 participants were analyzed: 74 with NAIS, 39 with PPAIS, and 105 with CAIS. Demographic and radiographic characteristics are provided in table 1. The majority of infarcts in all 3 groups were unifocal and within the anterior circulation. No participant had subacute symptomatic seizures.

Neonatal AIS (n = 74). Seventy participants with NAIS (95%) had acute symptomatic seizures detected at <12 hours of life in 18 (26%), at 12–24 hours in 28 (40%), at 25–48 hours in 17 (24%), and at >48 hours in 7 (10%). Most presented with either subtle or multifocal clonic seizures (table e-1 at Neurology.org). Routine or continuous EEG was performed within 8 days of life in 67/70 (96%) patients, 57/67 (85%) of whom received antiseizure medications before the EEG. Electrographic seizures were detected in 36/67 (54%) and these were subclinical in 30/67 (45%) and electroclinical in 19/67 (28%). Nine neonates (12%) had either clinical or electrographic status epilepticus.

Acute symptomatic seizures were treated in 66/70 (94%), and more than one antiseizure medication was required to terminate clinical or electrographic seizures in 23/66 (35%). Fifty-five of 70 (79%) were discharged on an antiseizure medication for a median

duration of 2.4 months (interquartile range [IQR] 1.2, 2–3.1). Phenobarbital was used in 46/55 (66%) and levetiracetam in 19/55 (34%).

RSS occurred in 17 participants (23%), all of whom had acute seizures. Five participants (7%) developed provoked seizures and one child had an unprovoked seizure at 6.3 years but did not have EEG results available. Eleven participants (15%) developed epilepsy (table 2), in whom 6/11 (55%) had focal epilepsy with or without secondary generalization and 5/11 (45%) had infantile spasms. At time of last follow-up, the median Engel class was 2, and 2/11 participants with epilepsy (18%) had Engel class 0.

Presumed perinatal AIS (n = 39). Thirty-six participants with PPAIS (92%) were diagnosed due to emerging neurologic signs in infancy. Three were identified after developing RSS: one each with focal seizures, infantile spasms, and status epilepticus. None received an antiseizure medication prior to stroke diagnosis.

RSS occurred in 17/39 participants (44%). Three participants had provoked seizures at 16, 20, and 25 months of age, respectively, and none was treated with antiseizure medication. Fourteen participants (36%) developed definite epilepsy, of whom 11 (79%) had

Table 2 Remote symptomatic seizures and epilepsy

	NAIS (n = 74)	PPAIS (n = 39)	CAIS (n = 105)	Entire cohort (n = 218)
Median time (IQR)				
Follow-up	3.4 y (1.5–5.8)	5.3 y (2.5–7.5)	2 y (1–3.5)	34 mo (16.3–61.2)
To first RSS, mo	16.3 (7.8–27.6)	20 (7.1–53.3)	10 (7–30.4)	
To epilepsy onset, mo	12.2 (5.8–48.4)	21.7 (6.3–67.7)	12.2 (7.6–30.4)	
Median Engel class at last follow-up	2	1	2	
RSS, n (%)^a				
All RSS	17 (23)	17 (44)	10 (10)	44 (20)
Provoked seizures only	5 (7)	3 (8)	1 (1)	9 (4)
Single unprovoked seizure	1 (1)	0	0	1 (1)
All epilepsy	11 (15)	14 (36)	9 (9)	34 (16)
Definite epilepsy	11 (15)	14 (36)	7 (7)	32 (15)
Probable epilepsy	0	0	2 (2) ^b	2 (1)
Epilepsy characteristics, n (%)^{c,d}				
Focal epilepsy	6 (54)	11 (79)	8 (89)	25 (74)
Infantile spasms	5 (45)	3 (21)	1 (11)	9 (26)
Engel class 1 or 2	5 (45)	9 (64)	6 (67)	20 (59)
Engel class 0	2 (18)	2 (14)	0	4 (12)

Abbreviations: CAIS = childhood arterial ischemic stroke; IQR = interquartile range; NAIS = neonatal arterial ischemic stroke; PPAIS = presumed perinatal arterial ischemic stroke; RSS = remote symptomatic seizure.

^aPercent in stroke subgroup.

^bOne participant had asymmetric background slowing and low voltage ipsilateral to the infarct and was started on antiseizure medication after a single RSS. Another had frequent focal spike and wave discharges ipsilateral to the infarct and was not started on antiseizure medication after a single RSS.

^cDefined for those with definite and probable epilepsy only.

^dPercent with epilepsy.

focal epilepsy with or without secondary generalization and 3 (21%) had infantile spasms. At time of last follow-up, the median Engel class was 1 and 2/14 participants with epilepsy (14%) had Engel class 0.

Childhood AIS (n = 105). Primary CAIS subtype was classified as intracranial vasculopathy in 37 (35%), extracranial vasculopathy in 29 (28%), cardiogenic in 19 (18%), indeterminate in 15 (14%), and multifactorial in 2 (2%). Eighteen participants (17%) had acute symptomatic seizures. Fourteen of 18 participants with CAIS (78%) with acute seizures were <6 years old and none was >12 years old. Acute seizures were treated in 17/18 (94%), and more than one antiseizure medication was required to terminate clinical or electrographic seizures in 8/17 (47%). Thirteen of 18 participants with acute seizures (72%) were discharged on an antiseizure medication for a median duration of 3.8 months (IQR 2.9, 2.5–5.4). Levetiracetam was used in 8/13 (62%), phenobarbital in 6/13 (46%), oxcarbazepine in 1/13 (8%), and phenytoin in 1/13 (8%). Three participants (23%) were discharged on more than 1 antiseizure medication.

RSS occurred in 10/105 participants (10%), with definite epilepsy in 7, probable epilepsy in 2, and a provoked seizure in 1. Seven of 10 with RSS (70%) had acute seizures and 5/10 with RSS (50%) were <2 years old at stroke ictus. Epilepsy was focal with or without secondary generalization in all participants except one with infantile spasms. At time of last follow-up, the median Engel class was 2 and no participant had Engel class 0.

Group comparisons. Acute symptomatic seizures were more common in NAIS than CAIS, $p < 0.001$, Fisher exact test. There were similarly high rates of EEG use in both groups (96% vs 83%; $p = 0.10$, Fisher exact) and in those with EEG, no differences were found in numbers with electrographic seizures (54% vs 33%, $p = 0.26$, Fisher exact test). Moreover, both groups were equally likely to present in status epilepticus, $p = 0.68$, Fisher exact test.

Acute seizures could not be analyzed as a predictor of RSS or epilepsy in NAIS as they were present in 95%. In CAIS, those with acute seizures were younger ($n = 18$, median age 1.3 years, IQR 5.3, 0.6–5.9) than those without ($n = 87$, median age 9.3 years, IQR 9.9, 4.8–14.6, $p < 0.0001$, Wilcoxon rank sum) and they were 7 times more likely to develop RSS (HR 6.95, 95% confidence interval [CI] 1.94–24.91, $p = 0.003$) and 9 times more likely to develop epilepsy (HR 9.26, 95% CI 2.29–37.44, $p = 0.002$). Younger age at stroke ictus in CAIS did not predict RSS risk (HR 0.94, 95% CI 0.83–1.06, $p = 0.31$) or epilepsy risk (HR 0.93, 95% CI 0.81–1.06, $p = 0.29$).

Median follow-up time was 3.4 years (IQR 1.5–5.7 years) for NAIS, 5.3 years (IQR 2.5–7.5) for PPAIS, and 2 years (IQR 1–3.5) for CAIS, ($p = 0.0001$, KW). All subsequent pairwise comparisons were significant with correction for multiple comparisons (not shown). There was no difference among the 3 groups for time to first RSS ($p = 0.42$, KW) or epilepsy onset ($p = 0.65$, KW).

Kaplan-Meier survival curves for all 3 groups are presented in figure 2. Estimated cumulative incidence of RSS at 2 years was 19% in NAIS, 24% in PPAIS, and 7% in CAIS (table 3). Estimated cumulative incidence of epilepsy at 2 years was 11% in NAIS, 19% in PPAIS, and 7% in CAIS. PPAIS was more likely than CAIS to develop RSS (HR 3.02, 95% CI 1.35–6.72, $p = 0.007$) and epilepsy (HR 2.5, 95% CI 1.05–5.95, $p = 0.0038$). NAIS showed a trend toward greater risk for RSS than CAIS (HR 2.09, 95% CI 0.95–4.57, $p = 0.07$) but not for a greater risk of epilepsy (HR 1.35, 95% CI 0.55–3.28, $p = 0.50$).

DISCUSSION While most newborns with NAIS and many children with CAIS have clinical seizures at stroke ictus, we found that RSS and epilepsy later

Figure 2 Kaplan-Meier analysis

(A) Remote symptomatic seizure-free survival. (B) Epilepsy-free survival. CAIS = childhood arterial ischemic stroke; NAIS = neonatal arterial ischemic stroke; PPAIS = presumed perinatal arterial ischemic stroke.

Table 3 Remote symptomatic seizure (RSS) and epilepsy-free survival

Time, mo	NAIS (n = 74)			PPAIS (n = 39)			CAIS (n = 105)		
	No. at risk	No. of failures	RSS-free survival (95% CI)	No. at risk	No. of failures	RSS-free survival (95% CI)	No. at risk	No. of failures	RSS-free survival (95% CI)
3	71	1	99 (91-99)	39	0	100	100	1	99 (93-99)
6	67	3	94 (86-98)	37	3	92 (78-97)	91	1	98 (92-99)
12	54	3	90 (80-95)	34	3	85 (69-93)	76	3	95 (88-98)
18	45	5	81 (69-89)	31	1	82 (66-91)	62	1	93 (86-97)
24	39	0	81 (69-89)	28	2	76 (59-87)	51	1	92 (83-96)
36	32	1	76 (63-85)	19	0	70 (53-82)	31	2	87 (76-93)
48	25	0	76 (63-85)	17	1	66 (48-80)	21	0	87 (76-93)
60	16	0	70 (54-81)	15	0	62 (43-76)	12	0	87 (76-93)
Time, mo	No. at risk	No. of failures	Epilepsy-free survival (95% CI)	No. at risk	No. of failures	Epilepsy-free survival (95% CI)	No. at risk	No. of failures	Epilepsy-free survival (95% CI)
3	72	0	100	39	0	100	100	1	99 (93-99)
6	68	3	96 (87-99)	37	3	92 (78-97)	92	0	99 (93-99)
12	56	2	93 (83-97)	34	3	85 (69-93)	76	3	96 (89-98)
18	50	2	89 (78-95)	32	0	85 (69-93)	62	1	94 (87-98)
24	43	0	89 (78-95)	30	1	82 (65-91)	51	1	93 (84-97)
36	37	1	87 (75-93)	22	0	79 (62-89)	31	2	88 (76-94)
48	29	0	87 (75-93)	19	1	75 (56-86)	21	0	88 (76-94)
60	19	0	80 (66-90)	17	0	70 (51-83)	12	0	88 (76-94)

Abbreviations: CAIS = childhood arterial ischemic stroke; CI = confidence interval; NAIS = neonatal arterial ischemic stroke; PPAIS = presumed perinatal arterial ischemic stroke.

develop in much smaller, though noteworthy proportions. The highest rates of these outcomes were observed in PPAIS, followed by NAIS and CAIS, suggesting that focal neonatal brain injury has a greater propensity for remote seizures than insult later in childhood. While infarcts in NAIS and PPAIS are presumed to occur at the same time perinatally, children with PPAIS are identified after the neonatal period when they present with moderate to severe neurologic deficits or seizures.^{12,21} Those with no or mild impairments may not be diagnosed with stroke or referred to a pediatric stroke service. For these reasons, PPAIS is a stroke subtype participant to clinical referral bias and enriched for adverse neurologic outcomes.

Among perinatal AIS, infarcts in NAIS were more likely to be multifocal and bilateral and PPAIS infarcts more commonly involved the basal ganglia. These findings may suggest that perinatal infarcts with multifocal cortical involvement are more likely to produce acute, clinically detected seizures and that concomitant involvement of cortex and basal ganglia is more likely to result in RSS and epilepsy.²² Future studies designed to evaluate radiographic predictors of poststroke epilepsy are needed.

Strengths of our study include a well-characterized pediatric AIS cohort without medical comorbidities

affecting RSS and epilepsy outcome, prospective and consecutive participant enrollment, rigorous RSS and epilepsy definitions, and inclusion of all 3 pediatric AIS subtypes, allowing for direct comparisons. Our retrospective analysis was limited by single-center participant recruitment, short follow-up, and the small number of children developing RSS and epilepsy. Despite our modest cohort size, this is the largest study reporting RSS and epilepsy outcomes in pediatric AIS. Prior retrospective studies of perinatal AIS with longer follow-up durations have shown higher rates of epilepsy,^{6,11} though one included preterm participants¹¹ and another included only children with moderate to severe neuromotor impairments.⁶ A recent prospective study of 80 participants with NAIS reported 11% active epilepsy at 7 years poststroke, similar to our NAIS rate at 2 years.²³

The frequency of acute seizures we observed in NAIS and CAIS was similar to previous reports.^{1,4,9} Overall, acute seizures were much more common in NAIS than in CAIS, and those with acute seizures at CAIS ictus were younger than those without, highlighting the tendency of the younger brain to seize with brain insult. While 85% of our NAIS cohort received antiseizure medication prior to EEG recording, 45% had subclinical seizures. This finding supports the notion that many neonatal seizures are

subclinical²⁴ and illustrates the phenomenon of neonatal electroclinical dissociation.²⁵ While we anticipated a high rate of subclinical seizures in NAIS, we were surprised to find that a quarter of CAIS with EEG recording also had subclinical seizures. This observation may support closer encephalographic monitoring of children after stroke.

While acute seizures after NAIS could not be analyzed as a predictor of RSS or epilepsy, we did find that children with acute seizures at CAIS ictus were more likely to develop these outcomes. This parallels a retrospective study of mixed childhood ischemic and hemorrhagic stroke in which those with acute seizures were more likely to have active epilepsy at last follow-up.² How acute symptomatic seizures promote RSS and epilepsy in CAIS is unknown, though animal work suggests that seizures may exacerbate pre-existing ischemic brain injury.²⁶ This high-risk population warrants further study as pediatric patients with AIS may be suited to future studies of antiepileptogenic therapies.

Even though half of those developing RSS and epilepsy after CAIS were <2 years at stroke ictus, we did not find age at time of CAIS to predict later RSS or epilepsy, contrasting with prior work.² An explanation for this discrepancy may be that acute seizures at stroke ictus in CAIS are more important to RSS and epilepsy outcome than age per se, though we acknowledge our results may reflect the effect of our aforementioned study limitations on the analysis. Notably, the rate of epilepsy we observed after CAIS closely approximates that reported in young adults (18–50 years) after AIS.²⁷

Epileptogenesis after acquired brain injury appears to be a continuous process that is age-specific.^{28,29} We found the median time to onset of the first RSS or epilepsy to be similar among the perinatal and childhood AIS subtypes, with both occurring <2 years after stroke ictus in all 3 groups. This suggests that the cellular and molecular events comprising epileptogenesis follow a similar temporal course from infancy through childhood. In addition, these data imply that studies of antiepileptogenic therapies could be feasible in children since epilepsy appears to develop relatively quickly in some. Larger studies with longer follow-up durations are needed to fully understand the temporal course of epileptogenesis in childhood.

A long-term study of epilepsy in children with hemiplegic cerebral palsy due to NAIS and PPAIS found that the proportion of participants with active epilepsy declined over time and in many cases epilepsy resolved.⁶ At last follow-up, we found epilepsy to be well-controlled (Engel class 1 or 2) in most children ($n = 20/34$, 59%) and in a small number ($n = 4/34$, 12%), epilepsy was no longer active.

While these data support a favorable prognosis for epilepsy after pediatric stroke, the potential for negative consequences should be recognized. A recent study found that children with poststroke epilepsy reported worse health-related quality of life than those without,³⁰ a finding that underscores the urgent need for new therapies targeting epileptogenesis. Future study of radiographic and electrographic predictors of poststroke seizures and epilepsy may help identify children with a less favorable prognosis and those who will benefit most from clinical trials aimed at preventing acquired epilepsy.

AUTHOR CONTRIBUTIONS

Lori Billingham: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript for intellectual content. Lauren Beslow: analysis and interpretation of data, critical revision of manuscript for intellectual content. Nicholas Abend: study concept and design, acquisition of data, critical revision of manuscript for intellectual content. Michael Uohara: acquisition of data. Laura Jastrab: study concept and design, acquisition of data, critical revision of manuscript for intellectual content. Daniel Licht: critical revision of manuscript for intellectual content. Rebecca Ichord: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript for intellectual content.

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REFERENCES

1. Abend NS, Beslow LA, Smith SE, et al. Seizures as a presenting symptom of acute arterial ischemic stroke in childhood. *J Pediatr* 2011;159:479–483.
2. Fox CK, Glass HC, Sidney S, Lowenstein DH, Fullerton HJ. Acute seizures predict epilepsy after childhood stroke. *Ann Neurol* 2013;74:249–256.
3. Grunt S, Mazenauer L, Buerki SE, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. *Pediatrics* 2015;135:8.
4. Singh RK, Zecavati N, Singh J, et al. Seizures in acute childhood stroke. *J Pediatr* 2012;160:291–296.
5. Golomb MR, Garg BP, Carvalho KS, Johnson CS, Williams LS. Perinatal stroke and the risk of developing childhood epilepsy. *J Pediatr* 2007;151:409.
6. Wanigasinghe J, Reid SM, Mackay MT, Reddihough DS, Harvey AS, Freeman JL. Epilepsy in hemiplegic cerebral palsy due to perinatal arterial ischaemic stroke. *Dev Med Child Neurol* 2010;52:1021–1027.
7. Hsu CJJ, Weng WCC, Peng SS, Lee WTT. Early-onset seizures are correlated with late-onset seizures in children with arterial ischemic stroke. *Stroke* 2014;45:1161–1163.
8. Fitzgerald KC, Williams LS, Garg BP, Golomb MR. Epilepsy in children with delayed presentation of perinatal stroke. *J Child Neurol* 2007;22:1274–1280.

9. Wusthoff CJ, Kessler SK, Vossough A, et al. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. *Pediatrics* 2011;127:7.
10. Suppiej A, Mastrangelo M, Mastella L, et al. Pediatric epilepsy following neonatal seizures symptomatic of stroke. *Brain Dev* 2016;38:27–31.
11. Lee J, Croen LA, Lindan C, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol* 2005;58:303–308.
12. Kirton A, Deveber G, Pontigon AMM, Macgregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann Neurol* 2008;63:436–443.
13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–381.
14. Volpe JJ. Neonatal seizures: current concepts and revised classification. *Pediatrics* 1989;84:422–428.
15. Abend NS, Gutierrez-Colina AM, Topjian AA, et al. Non-convulsive seizures are common in critically ill children. *Neurology* 2011;76:1071–1077.
16. Tsuchida TN, Wusthoff CJ, Shellhaas RAA, et al. American Clinical Neurophysiology Society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. *J Clin Neurophysiol* 2013;30:161–173.
17. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17:3–23.
18. Glass HC, Hong KJ, Rogers EE, et al. Risk factors for epilepsy in children with neonatal encephalopathy. *Pediatr Res* 2011;70:535–540.
19. Bernard TJ, Manco-Johnson MJ, Lo W, et al. Towards a consensus-based classification of childhood arterial ischemic stroke. *Stroke* 2012;43:371–377.
20. Stata Statistical Software: Release 12 [Computer Program]. College Station, TX: StataCorp LP; 2011.
21. Ghotra SK, Johnson JA, Qiu W, Newton A, Rasmussen C, Yager JY. Age at stroke onset influences the clinical outcome and health-related quality of life in pediatric ischemic stroke survivors. *Dev Med Child Neurol* 2015;57:1027–1034.
22. Okumura A, Hayakawa F, Kato T, Kuno K, Watanabe K. Epilepsy in patients with spastic cerebral palsy: correlation with MRI findings at 5 years of age. *Brain Dev* 1999;21:540–543.
23. Chabrier S, Peyric E, Drutel L, et al. Multimodal outcome at 7 years of age after neonatal arterial ischemic stroke. *J Peds* 2016;172:156–161.
24. Boylan GB, Kharoshankaya L, Wusthoff CJ. Seizures and hypothermia: importance of electroencephalographic monitoring and considerations for treatment. *Semin Fetal Neonatal Med* 2015;20:103–108.
25. Scher MS, Alvin J, Gaus L, Minnigh B, Painter MJ. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. *Pediatr Neurol* 2003;28:277–280.
26. Björkman ST, Miller SM, Rose SE, Burke C, Colditz PB. Seizures are associated with brain injury severity in a neonatal model of hypoxia-ischemia. *Neuroscience* 2010;166:157–167.
27. Arntz RM, Rutten-Jacobs LC, Maaijwee NA, et al. Post-stroke epilepsy is associated with a high mortality after a stroke at young age: follow-up of transient ischemic attack and stroke patients and unelucidated risk factor evaluation study. *Stroke* 2015;46:2309–2311.
28. Williams PA, White AM, Clark S, et al. Development of spontaneous recurrent seizures after kainate-induced status epilepticus. *J Neurosci* 2009;29:2103–2112.
29. Kadam SD, White AM, Staley KJ, Dudek FE. Continuous electroencephalographic monitoring with radio-telemetry in a rat model of perinatal hypoxia-ischemia reveals progressive post-stroke epilepsy. *J Neurosci* 2010;30:404–415.
30. Smith SE, Vargas G, Cucchiara AJ, Zelonis SJ, Beslow LA. Hemiparesis and epilepsy are associated with worse reported health status following unilateral stroke in children. *Pediatr Neurol* 2015;52:428–434.

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