Risk of Later Seizure After Perinatal Arterial Ischemic Stroke: A Prospective Cohort Study

WHAT'S KNOWN ON THIS SUBJECT: Acute symptomatic seizures are common after perinatal arterial ischemic stroke, but published data regarding incidence and timing of seizures after hospital discharge are limited.

WHAT THIS STUDY ADDS: The Kaplan-Meier probability of remaining seizure-free at 3 years after acute perinatal arterial ischemic stroke was 73% in this study. Larger stroke size on MRI was significantly associated with development of later seizures.

AUTHORS: Courtney J. Wusthoff, MD,[a] Sudha Kilaru Kessler, MD,[a,b] Arastoo Vossough, MD, PhD,[c] Rebecca Ichord, MD,[a,b] Sarah Zelonis, BA,[a] Aviva Halperin, BA,[a] Danielle Gordon, BA,[a] Gray Vargas, BA,[a] Daniel J. Licht, MD,[a,b] and Sabrina E. Smith, MD, PhD[a,b]

[a]Division of Neurology, Department of Pediatrics, and [c]Department of Radiology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and [b]Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

KEY WORDS
neonates, stroke, seizure, MRI, risk factors

ABBREVIATIONS
AIS—arterial ischemic stroke
EEG—electroencephalogram
ASPECTS—Alberta Stroke Program Early Computed Tomography Score
CT—computed tomography
modASPECT—modified Alberta Stroke Program Early Computed Tomography
MCA—middle cerebral artery
CI—confidence interval
AED—antiepileptic drug

All authors have contributed substantially to this research, and all authors approved the manuscript as submitted.

Funded by the National Institutes of Health (NIH).

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1577

doi:10.1542/peds.2010-1577

Accepted for publication Feb 17, 2011

Address correspondence to Sabrina E. Smith, MD, PhD, Division of Neurology, The Children's Hospital of Philadelphia, Colket Translational Research Building, 10th Floor, 3501 Civic Center Blvd, Philadelphia, PA 19104. E-mail: smithsa@email.chop.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

abstract

OBJECTIVE: Although acute seizures are common among neonates with arterial ischemic stroke (AIS), the incidence of subsequent seizures is unknown. The goals of this study were to determine the incidence of seizures following hospital discharge after perinatal acute AIS, and to assess lesion characteristics associated with later seizure occurrence.

METHODS: Neonates with confirmed acute AIS on MRI were identified through a prospective stroke registry. Clinic visits and telephone follow-up identified occurrence of seizures after hospital discharge. MRI scans were graded for size and characteristics of infarct, and associations with seizures after stroke were analyzed.

RESULTS: At a mean (SD) follow-up of 31.3 (16.1) months, 11 of 46 (23.9%) patients with perinatal AIS had at least 1 seizure. Five patients had a single episode of seizure, and 6 developed epilepsy. The Kaplan-Meier probability of remaining seizure-free at 3 years was 73%. Stroke size on MRI was significantly associated with development of later seizures, with an incidence rate of later seizures 6.2 times higher among those with larger stroke size.

CONCLUSIONS: Seizures occurred in <25% of patients during initial follow-up after perinatal AIS. Of those with seizures, nearly half had a single episode of seizure and not early epilepsy. Larger stroke size was associated with higher risk of seizure. These data suggest that prolonged treatment with anticonvulsant agents may not be indicated for seizure prophylaxis after perinatal AIS. These findings may help guide clinicians in counseling families and could form the basis for much-needed future research in this area. *Pediatrics* 2011;127:e1550–e1557

Childhood arterial ischemic stroke (AIS) has its highest incidence in the neonatal period, occurring in ~1 per 4000 term births.[1,2] Among neonates with stroke, seizures are the most common presenting sign.[3] Conversely, among neonates with seizures, up to 15% have had ischemic stroke. [4]Most neonates start anticonvulsant treatment at the time seizures are diagnosed or even suspected. Traditionally, phenobarbital has been the first-line medication, although doses, blood levels, and duration of treatment may vary widely. In a retrospective review of practice in 5 ICU nurseries, 75% of neonates with seizures from any cause continued anticonvulsant treatment after hospital discharge; this practice ranged from 57% to 92% between sites.[5] Similarly, physicians self-reported shorter duration of phenobarbital treatment after neonatal seizures compared with 15 years ago, although practices vary widely.[6] No empiric data have been published to suggest the appropriate duration of anticonvulsant therapy after acute perinatal stroke. The clinician must balance competing, poorly defined risks in choosing whether and for how long to treat seizures after neonatal infarct.[7,8] On the one hand, in animal studies and in clinical observations, ongoing seizures are thought to be harmful to the developing brain, even beyond the causative insult itself.[9–11] At the same time, prolonged exposure to anticonvulsant medications such as phenobarbital may also be harmful.[12–14] A number of experts advise stopping anticonvulsant medications soon after the control of symptomatic neonatal seizures.[15,16] However, there is a paucity of data regarding the frequency of early seizure recurrence after the neonatal period. The present study prospectively followed up a cohort of neonates with confirmed acute AIS to determine the occurrence of seizures in the months after hospital discharge. A secondary goal was to determine if lesion characteristics were risk factors for subsequent seizures.

METHODS

Potential subjects were identified from an institutional prospective pediatric stroke registry including patients treated at the Children's Hospital of Philadelphia at the time of acute stroke and patients initially treated at another facility but subsequently seen in the hospital's outpatient stroke clinic. Inclusion criteria were birth at ≥37 weeks' gestational age between January 1, 2004, and October 31, 2009, and acute perinatal AIS within the first 28 days of life, confirmed by brain MRI results demonstrating restricted diffusion within a known arterial vascular territory. Patients brought to clinical attention after the first month of life (presumed perinatal stroke) were excluded. Only patients with at least 6 months of follow-up information were included. Parental consent was required for participation in the registry, and the protocol was approved by the Children's Hospital of Philadelphia Institutional Review Board.

Clinical information obtained at the time of initial patient assessment included details of the pregnancy and birth history, clinical signs and symptoms leading to the stroke diagnosis, and stroke risk factors. Per institutional protocol, most patients with suspected AIS underwent brain and vascular imaging with MRI, echocardiogram, and thrombophilia studies. Based on the results of these studies, stroke risk factors were classified as cardiac, vascular, hematologic, none, or other. Acute seizures were defined as paroxysmal clinical events considered seizures by the primary team during hospitalization. Clinical intervention, such as choice of anticonvulsant agent, was not controlled and was given at the discretion of the treating physician. Similarly, video-electroencephalogram (EEG) monitoring was used at the discretion of the primary team to identify electrographic seizures, and results reported by the interpreting clinical neurophysiologist are noted. After identification from the registry, a stroke neurologist (Dr Smith) screened neuroimaging studies to determine eligibility for this study, and to classify the involved vascular territory. A pediatric neuroradiologist (Dr Vossough), blinded to clinical outcome, then reviewed neuroimaging studies from included patients, noting the presence of acute AIS, hemorrhage, periventricular white matter injury, or additional injury suggestive of an arterial watershed mechanism.

Lesion size was described using a modified version of the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), a semiquantitative system for scoring early ischemic changes on head computed tomography (CT) in adult stroke patients.[17] This has also been applied to MRI diffusion-weighted imaging in adult stroke patients.[18–20] In our modified version (modASPECT), lesion size was assessed using diffusion-weighted imaging. The highest possible score was 16 per hemisphere, with a total score of 32. The cortex was divided into smaller regions corresponding to different vascular territories. For each hemisphere, there were 2 possible points in the cortical anterior cerebral artery region, 7 possible points in the cortical middle cerebral artery (MCA) region, and 2 possible points in the cortical posterior cerebral artery region. Detailed delineation of these regions is provided in Barber et al.[17] In addition, involvement of caudate, internal capsule, lentiform nuclei, thalamus, and cerebellum was assigned 1 point per hemisphere for each involved region. The 2 MRI slices best matching the CT slices described by Barber et al were

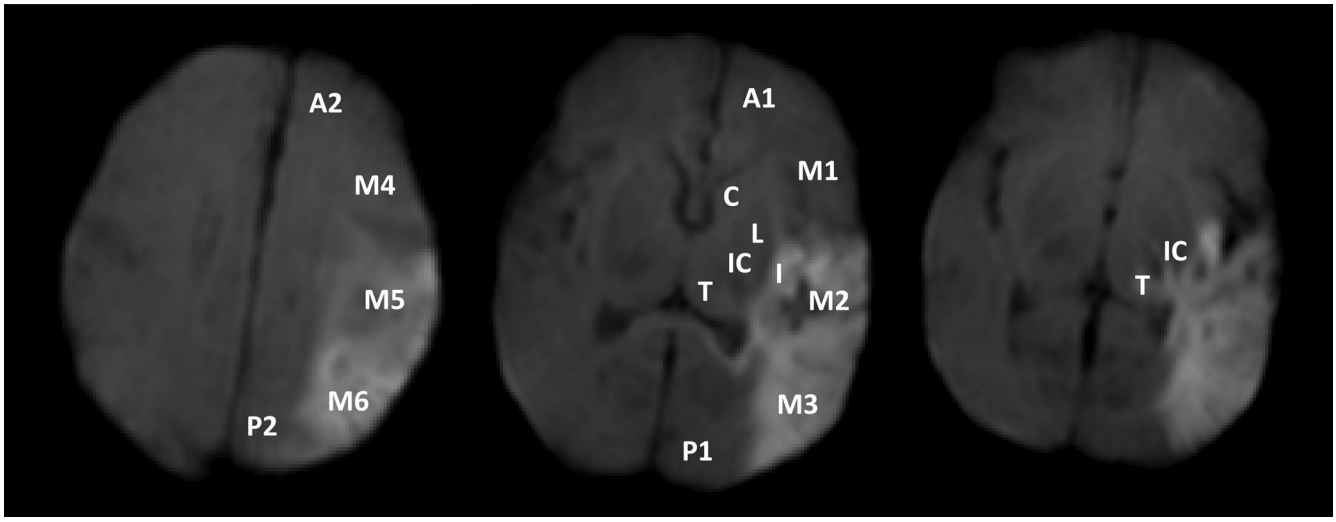

FIGURE 1
Diffusion-weighted axial MRI slices from a single patient. Labels indicate regions included in modASPECT score: anterior cerebral artery (A1–A2), MCA (M1–M6), insula (I), posterior cerebral artery (P1–P2), caudate (C), lentiform nuclei (L), internal capsule (IC), and thalamus (T). Total modASPECT score here is 7 for involvement of M2, M3, I, M5, M6, IC, and T.

used for analysis. Areas of restricted diffusion not captured on these 2 slices were scored 1 point in the ASPECT score region nearest the area of abnormality (Fig 1).

The primary outcome was time to seizure occurrence after hospital discharge. Occurrence of seizures was assessed at each follow-up outpatient neurology visit; for those with infrequent visits, this information was obtained through telephone contact with the patient's caregivers. Differences in baseline characteristics between patients with seizure occurrence after hospital discharge and those without seizures were assessed using 2-sample binomial comparisons (Fisher's exact tests) for dichotomous variables and Student's *t* tests of independent samples for continuous variables. Kaplan-Meier survival estimates were generated for the whole cohort, and separately for those with high (≥9) and those with low (≤8) modASPECT scores. A univariate comparison of seizure-free survival time was made between these 2 groups using the log-rank test. Additional univariate analyses using Cox proportional hazards methods were conducted to evaluate the modASPECT score as a continuous variable, as well as unilateral versus bilateral stroke, and ischemic stroke alone versus stroke with other mechanism of injury. Because of the small number of patients with each lesion location, we did not analyze specific stroke location as a risk factor for later seizure. This study was not adequately powered for additional multivariable regression analyses. *P* values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the 46 patients included in this study are described in Table 1. Two additional patients were not included because <6 months of follow-up data were available (1 was lost to follow-up, 1 was aged <6 months at time of the present study). Forty-one patients were diagnosed with seizures in the neonatal period. Clinical signs leading to stroke diagnosis in those without seizure were

TABLE 1 Patient Characteristics of Neonates With AIS Without and With Seizures After Hospital Discharge

Characteristic	Without Seizures (*n* = 35)	With Seizures (*n* = 11)	*P*
Male sex, *n* (%)	19 (57)	9 (73)	.35
Gestational age, mean (SD), wk	39.43 (1.18)	39.07 (1.20)	.38
Cesarean delivery, *n* (%)	20[a] (63)	8 (73)	.72
Apgar score,[b] median (range)			
At 1 min	8 (1–9)	8 (2–9)	.74
At 5 min	9 (3–9)	9 (7–10)	.16
Neonatal seizures as presenting sign of stroke, *n* (%)	33 (94)	8 (73)	.08
Identified stroke risk factors,[c] *n* (%)			
None	25 (71)	7 (64)	.71
Cardiac	7 (20)	2 (18)	1.0
Hematologic	2 (6)	2 (18)	.09
Vascular	2 (6)	1 (9)	1.0
Other	2 (6)	1 (9)	1.0

[a] Delivery method not identified for 3 patients.
[b] Apgar scores unavailable for 3 neonates without later seizures and 1 with later seizures.
[c] Patients may have >1 risk factor. See text for details of stroke risk factors.

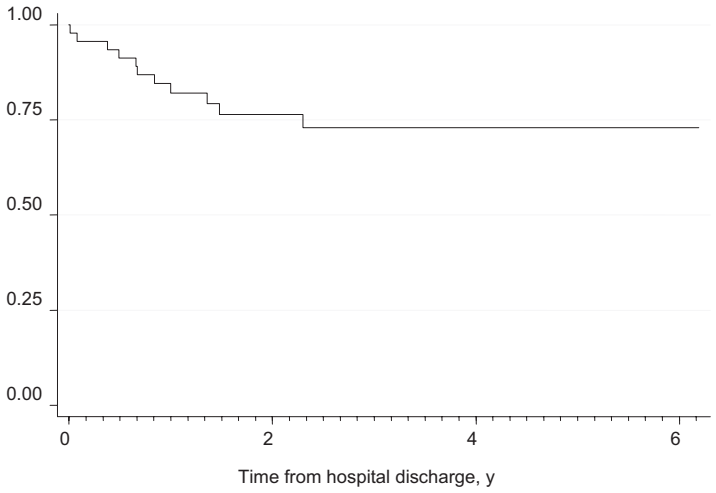

FIGURE 2
Kaplan-Meier curve of seizure-free survival following hospital discharge after perinatal AIS. At 3 years, the estimate for seizure freedom was 73%.

apnea ($n = 2$), lethargy ($n = 1$), and incidental finding on neuroimaging ($n = 2$). In 1 patient, stroke was found during evaluation for Sturge-Weber syndrome, and in the other case, the MRI was done subsequent to an abnormal head ultrasound in a child with congenital heart disease.

Forty-one patients were treated with an anticonvulsant agent in the neonatal period. One patient who had a clinical seizure was not treated with an anticonvulsant because the EEG did not capture ongoing seizures, and 1 patient who did not have seizures received phenobarbital for postoperative sedation after cardiac surgery. All treated patients received phenobarbital. Ten patients received concomitant treatment with phenytoin and 2 received levetiracetam, and 1 patient received all 3 anticonvulsant agents during the initial hospitalization. An EEG was conducted in the neonatal period in 45 patients (routine EEG only, $n = 28$; continuous video- EEG monitoring, $n = 17$). As noted in the 43 available clinical reports, 15 patients had electrographic seizures, and these seizures were subclinical in 13 patients. All patients with electrographic seizures were treated with an anticonvulsant agent. An additional 22 patients had focal epileptiform discharges without seizures on EEG.

Mean (SD) duration of follow-up for the whole cohort was 31.3 (16.1) months. Overall, 11 patients (23.9%) had seizures during the observation period, at a median age of 8 months (interquartile range: 4.6–16.3). At an age of 3 months, which was just beyond the median duration of antiepileptic drug (AED) treatment, only 1 of 41 patients had recurrence of seizures, and 1 of 5 patients without seizures at stroke diagnosis had a single episode suspicious for seizure. The cumulative probability of remaining seizure-free by 3 years was 73%, as shown in the Kaplan-Meier survival curve (Fig 2). No patients in this cohort experienced a first seizure after 27.6 months.

MRI findings are detailed in Table 2. Unilateral MCA stroke was the most common vascular distribution, and a high number of infarcts involved multiple territories. Original images were available for additional analysis in 40 patients. Median modASPECT score was 7 (interquartile range: 4–11). Additional, nonstroke MRI lesions were present in 26 subjects (65%), with some patients having >1 type of additional lesion. Stroke size, as estimated by modASPECT score, was associated with the risk of later seizures. When comparing patients with high (≥9) versus lower (≤8) modASPECT scores, there was a statistically significant dif-

TABLE 2 MRI Features in Neonates With AIS and Without and With Seizures After Hospital Discharge

Feature	Total ($N = 46$)	Without Seizures ($n = 35$)	With Seizures ($n = 11$)	P[d]
AIS location,[a] *n* (%)				
Unilateral anterior cerebral artery	0 (0)	0 (0)	0 (0)	—
Unilateral MCA	23 (50)	17 (49)	6 (55)	.50
Unilateral posterior cerebral artery	1 (2)	1 (3)	0 (0)	.76
Multiple territories	22 (48)	17 (49)	5 (45)	.56
Bilateral MCA only	7 (15)	4 (11)	3 (27)	.21
MCA + other	14 (30)	12 (34)	2 (18)	
Multiple territories without MCA	1 (2)	1 (3)	0 (0)	.27
Bilateral involvement,[a] *n* (%)	17 (37)	12 (34)	6 (55)	.20
Stroke size according to modASPECT score, mean (SD)[b,c]	7.7 (4.7)	6.7 (3.9)	11 (5.8)	.01
Hemorrhage,[b] *n* (%)				
None	29 (72.5)	24 (77)	5 (56)	.22
Punctate	7 (17.5)	4 (13)	3 (33)	.32
Confluent	4 (10)	3 (10)	1 (11)	1.0
Additional white matter disease,[b] *n* (%)	8 (20)	7 (23)	1 (11)	.65
Additional arterial watershed injury,[b] *n* (%)	12 (30)	5 (16)	7 (78)	.10

[a] Location as determined by changes on diffusion weighted imaging at the time of presentation.
[b] Original images not available for further analysis in 6 patients.
[c] See Methods for details on modified ASPECTS calculation.
[d] *P* values for binomial variables calculated using Fisher's exact test; *P* value for comparison of mean stroke size calculated using Student's *t* test of independent variables.

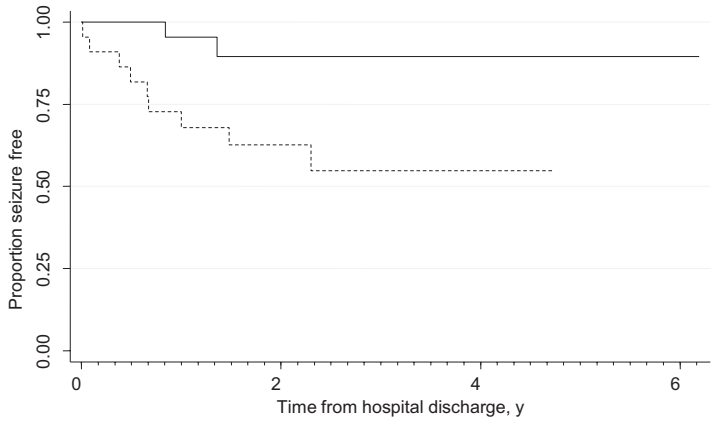

FIGURE 3

Kaplan-Meier curve of seizure-free survival following hospital discharge after perinatal AIS, according to size of stroke using modASPECT score. Three-year seizure freedom was 89% (95% CI: 64%–97%) in low modASPECT score (≤8) group (solid line) and 55% (95% CI: 30%–74%) in high modASPECT Score (≥9) group (dashed line) ($P = .01$).

ference in survival estimates, as illustrated in Fig 3, with an incidence rate of seizures in the high score group 6.2 times higher than in the low score group ($P = .01$). In the low modASPECT score group, the cumulative probability of remaining seizure-free at 3 years was 89% (95% confidence interval [CI]: 64%–97%), and 55% (95% CI: 30%–74%) in the high modASPECT score group ($P = .01$). The highest area under the receiver operating characteristic curve was achieved with the cutoff of 8, indicating the best sensitivity and specificity for predicting seizures.

In a univariate Cox proportional hazards analysis, the risk of earlier seizures was increased by 14% for every single point increase in modASPECT score (hazard ratio: 1.14; $P = .02$). No statistically significant relationships were found between occurrence of seizures and other MRI features, including bilateral versus unilateral involvement, and ischemic stroke alone compared with stroke with other pathologic conditions.

Table 3 provides details for the 11 patients with seizures after hospital discharge. Six patients developed epilepsy during follow-up, and 5 had single episodes of seizure only. One of these patients had an underlying disorder, Sturge-Weber syndrome, known to be associated with epilepsy independent of stroke risk. Another had coexisting moyamoya disease, diagnosed soon after birth. There were no diagnoses of Sturge-Weber syndrome or moyamoya disease among those who did not go on to develop later seizures. Twenty-nine patients had subsequent EEG after hospital discharge. Of those who developed epilepsy, all 6 had follow-up EEGs with epileptiform discharges. Of those with a single episode of seizure, 2 had normal results on EEG, 2 had focal slowing and epileptiform discharges, and 1 did not have an EEG. Of those patients who did not have subsequent seizures, 19 had follow-up EEGs. EEG results were normal in 13 and abnormal in 6.

Other than stroke size, there were no appreciable differences in baseline characteristics between patients with and without later seizures, except treatment with an AED in the neonatal period (7 of 11 patients with later seizures versus 34 of 35 patients without later seizures; $P = .01$). Median dura-

TABLE 3 Patients With Seizures After Hospital Discharge

Patient	Acute Seizures[a]	AED Duration (mon)[b]	Age at First Seizure (mon)[c]	Seizure Details	Other Neurologic Diagnoses
1	None	NA	1.0	Single seizure with fever, none in subsequent 21 mo	NA
2	Present	2.0	8.0	Two focal seizures in 1 day, none in subsequent 11 mo	NA
3	Present	2.2	16.3	Single episode of eye deviation lasting 1 minute, no other suspicious events in subsequent 18 mo	NA
4	Present	1.7	17.8	Single seizure with fever, none in subsequent 12 mo	NA
5	Present	6.0	27.6	Single seizure with fever, none in subsequent 10 mo	NA
6	Present	16.9[d]	NA	Epilepsy; never seizure-free	Moyamoya disease
7	Present	2.5	4.6	Epilepsy	NA
8	Present	NA[e]	5.9	Epilepsy	NA
9	None	NA	7.9	Epilepsy (infantile hemi-spasms)	NA
10	None	NA	10.1	Epilepsy	Sturge-Weber syndrome
11	Present	6.7	12	Epilepsy	NA

NA indicates not applicable.

[a] Seizures during hospitalization for acute perinatal stroke.

[b] Duration of initial course of AED treatment after presentation with stroke. NA indicates patient did not receive AED during hospitalization for acute perinatal stroke.

[c] First seizure after discharge from hospital.

[d] Equal to duration of follow-up for this patient.

[e] Single clinical seizure in the neonatal period but no AED administered because EEG results showed no ongoing seizures.

tion of treatment was 2 months (interquartile range: 0.6–2.5 months), with no significant difference in duration of AED treatment between those with later seizures (2 months) and those without (1.6 months; $P = .38$). Patient 6 continued to have seizures in the setting of moyamoya disease and recurrent strokes, and therefore remained on AEDs continuously from presentation throughout follow-up.

DISCUSSION

This study showed that neonates with acute AIS have a low rate of seizure after hospital discharge, with a cumulative probability of seizure freedom of 73% at 3 years. Estimated rates of childhood epilepsy after neonatal stroke range from 0% to 67%.[1,21,22] Our data were most consistent with the lower end of this range. Some of the higher estimates were obtained retrospectively from clinic populations and may inaccurately reflect true rates of seizure. A strength of the present study is that incidence of seizures was evaluated prospectively, avoiding selection and recall biases that may affect retrospective studies. Of note, our goal was not to capture epilepsy rates but only seizure occurrence in the first months and years of life. Epilepsy might emerge at higher rates with longer follow-up. However, for the clinician, seizure of any kind may be the most immediate concern when deciding whether to continue anticonvulsant medication at the time of hospital discharge. Given the high rate of seizure freedom in the first months and years after perinatal AIS, it may be a reasonable strategy to select early discontinuation of anticonvulsant agents on hospital discharge, rather than prolonged prophylaxis. Additional research is needed to evaluate outcome after early anticonvulsant discontinuation.

In refining these estimates, we found a significant association between stroke size and risk of later seizure. To estimate stroke size, we used a simplified semiquantitative system based on a method validated in adult stroke patients.[17] Although there are techniques for accurately quantifying exact stroke volume, these are labor intensive and require specialized resources. Our goal was to use a method that might be useful to the majority of clinicians in routine practice. The ASPECT system of scoring has been applied to diffusion-weighted imaging views in adult stroke patients. This technique has good interrater reliability, correlates highly with ASPECT scoring using head CT results[19] and clinical status at admission,[18] and predicts later outcome.[20] Because no similar tool exists specifically for pediatric or neonatal stroke, we adapted this system for use with our patients. The modASPECT score can be applied quickly and without special software or training. Using this system, we found larger stroke size was associated with higher risk of seizures; this was true both as a continuous variable and when dichotomized into "small" and "large" stroke size. This information may guide clinicians as they discuss perinatal AIS with families: patients with smaller strokes had an estimated seizure freedom rate of ~90% at 3 years. Conversely, those with larger strokes are at higher risk and may need closer surveillance. Given the potential usefulness of the modASPECT score as an efficient semiquantitative system, additional research is needed to explore its applications in pediatric and neonatal stroke.

This study defined acute symptomatic seizures as diagnosed by the treating clinician in the neonatal period, but not all patients underwent an EEG as part of clinical care to confirm or rule out seizures. Although this definition of seizures is used widely in clinical practice, accurate recognition of seizures in neonates can be challenging. Rhythmic movements in the neonate may be misclassified as seizure, and subtle or subclinical seizures also occur frequently in this population.[23] Given this limitation, we interpret our findings regarding early neonatal seizures and AED use with caution. We found no significant association between symptomatic seizures after perinatal AIS and later seizures, but additional research is needed using systematic EEG to more definitively identify seizures in this population. An unexpected finding was the statistically significant association between treatment with an anticonvulsant in the acute period and no seizures after hospital discharge. There are several possible explanations for this result. Most likely this was a spurious result that would not be reproduced with a larger sample size. One of the 4 untreated patients with later seizures had Sturge-Weber syndrome, which is strongly associated with the development of epilepsy, and 1 had only a single seizure in the setting of fever. Another possibility is that some patients were undertreated (did not receive anticonvulsant agents) for unrecognized seizures during the neonatal period in cases in which video-EEG monitoring was not used, and this led to pathologic changes and later seizures during follow-up. Neonates with only subtle or subclinical seizures may have been less likely to receive anticonvulsants. Future studies using prospectively obtained video-EEG data are needed to better define the timing and incidence of electrographic seizures in this population. A third possible explanation is that there is a physiologic distinction among our heterogeneous population for those neonates who developed later seizures. It may be that while the most common clinical scenario after AIS is symptomatic neonatal seizures treated with anticonvulsants and no subsequent seizure, a

minority of patients have a different neurophysiologic response to stroke, presenting acutely with signs less likely to trigger administration of early anticonvulsants but manifesting more chronically with seizures later in life. Finally, we cannot rule out the possibility that anticonvulsant administration in the acute period had some protective effect against epileptogenesis for some patients. Additional study is needed to address these questions.

A unique strength of this study was the use of a prospective cohort to determine seizure incidence after discharge. This avoids the potential selection bias of making such estimates from a clinic population retrospectively. Likewise, we had follow-up well beyond 6 months for the majority of patients. More patients may have had seizures with longer follow-up. At the same time, the plateau of the Kaplan-Meier curves and the absence of new seizures after 27 months of age in any patient suggest this is less likely for most patients. Our study was limited by the nature of a prospective observational study. We did not standardize treatments administered in either the acute period or after hospital discharge, so there is some heterogeneity in care. Also, although a secondary goal of this study was to identify lesion characteristics that were risk factors for seizures after perinatal stroke, the size of our cohort may have limited power to analyze for differences between patients with and without later seizures. Nonetheless, the information from this study regarding seizure incidence may be useful for guiding power analysis and design of future research to address these questions in more detail.

CONCLUSIONS

Seizures occurred in a minority of these subjects with perinatal AIS in the months and early years after hospital discharge. Risk of seizures was lower in patients with smaller stroke size. Given the high rate of seizure freedom, early discontinuation of anticonvulsant agents rather than prolonged prophylaxis may be appropriate. Additional research is needed to clarify the relationship between early seizures, anticonvulsant use, and later seizures after perinatal AIS.

ACKNOWLEDGMENT

This work was supported by The Children's Hospital of Philadelphia Research Institute. Drs Smith and Kessler were supported by NIH K12 NS049453.

REFERENCES

1. Lee J, Croen LA, Lindan C, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol*. 2005; 58(2):303–308
2. Perlman JM, Rollins NK, Evans D. Neonatal stroke: clinical characteristics and cerebral blood flow velocity measurements. *Pediatr Neurol*. 1994;11(4):281–284
3. Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. *Stroke*. 2007;38(8):2234–2240
4. Tekgul H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. *Pediatrics*. 2006;117(4): 1270–1280
5. Bartha AI, Shen J, Katz KH, et al. Neonatal seizures: multicenter variability in current treatment practices. *Pediatr Neurol*. 2007; 37(2):85–90
6. Guillet R, Kwon JM. Prophylactic phenobarbital administration after resolution of neonatal seizures: survey of current practice. *Pediatrics*. 2008;122(4):731–735
7. Marsh ED, Brooks-Kayal AR, Porter BE. Seizures and antiepileptic drugs: does exposure alter normal brain development? *Epilepsia*. 2006;47(12):1999–2010
8. Glass HC, Wirrell E. Controversies in neonatal seizure management. *J Child Neurol*. 2009;24(5):591–599
9. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. *J Pediatr*. 2009; 155(3):318–323
10. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology*. 2000;55(4):506–513
11. Miller SP, Weiss J, Barnwell A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology*. 2002; 58(4):542–548
12. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci U S A*. 2002;99(23): 15089–15094
13. Sulzbacher S, Farwell JR, Temkin N, Lu AS, Hirtz DG. Late cognitive effects of early treatment with phenobarbital. *Clin Pediatr (Phila)*. 1999;38(7):387–394
14. Calandre EP, Dominguez-Granados R, Gomez-Rubio M, Molina-Font JA. Cognitive effects of long-term treatment with phenobarbital and valproic acid in school children. *Acta Neurol Scand*. 1990;81(6): 504–506
15. Ferriero DM. Neonatal brain injury. *N Engl J Med*. 2004;351(19):1985–1995
16. Hellström-Westas L,Blennow G, Lindroth M, Rosén I, Svenningsen NW. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period. *Arch Dis Child Fetal Neonatal Ed*. 1995; 72(2):F97–F101
17. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet*. 2000;355(9216): 1670–1674
18. Schaefer P, Mehta A, Camargo E, Schwamm L, Gonzalez RG, Lev M. Modified ASPECT Score (mASPECT) on Diffusion/Perfusion MRI Correlates Strongly with NIH Stroke Scale Score (NIHSS) in Acute Stroke. Presented at: Radiological Society of North America 91st Scientific Assembly and Annual Meeting; Chicago, IL; Nov 27–Dec 2, 2005
19. Barber PA, Hill MD, Eliasziw M, et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry*. 2005; 76(11):1528–1533
20. Kimura K, Iguchi Y, Shibazaki K, et al. Large ischemic lesions on diffusion-weighted im-

aging done before intravenous tissue plasminogen activator thrombolysis predicts a poor outcome in patients with acute stroke. *Stroke*. 2008;39(8):2388–2391

21. Golomb MR, Garg BP, Carvalho KS, Johnson CS, Williams LS. Perinatal stroke and the risk of developing childhood epilepsy. *J Pediatr*. 2007;151(4):409–413
22. Mercuri E, Rutherford M, Cowan F, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. *Pediatrics*. 1999;103(1):39–46
23. Clancy RR. Prolonged electroencephalogram monitoring for seizures and their treatment. *Clin Perinatol*. 2006;33(3):649–665, vi