Symptomatic Neonatal Arterial Ischemic Stroke: The International Pediatric Stroke Study

WHAT'S KNOWN ON THIS SUBJECT: Neonatal arterial ischemic stroke is a common cause of cerebral palsy and other lifelong neurologic disabilities. Studies to date have been limited by modest sample sizes of regional and heterogeneous populations, limiting advances in understanding and treatment.

WHAT THIS STUDY ADDS: Results from this sample of nearly 250 newborns with neonatal AIS provide a novel global view of clinical presentations, potential risk factors, current investigational and treatment practices, and early outcomes. Important directions for future research were also identified.

abstract

BACKGROUND: Neonatal arterial ischemic stroke (AIS) has emerged as a leading cause of perinatal brain injury, cerebral palsy, and lifelong disability. The pathogenesis is poorly understood, which limits the development of treatment and prevention strategies. Multicenter studies must define epidemiology, risk factors, treatment practices, and outcomes to advance clinical trials and improve the adverse outcomes suffered by most survivors.

METHODS: The International Pediatric Stroke Study is a global research initiative of 149 coinvestigators (30 centers in 10 countries). Patients with clinical and neuroimaging confirmation of symptomatic neonatal AIS were enrolled (2003–2007). Standardized, Web-based data entry collected clinical presentations, risk factors, investigations, treatments, and early outcomes. We examined predictors of infarct characteristics and discharge outcome by using multivariate logistic regression.

RESULTS: Two hundred forty-eight neonates were studied (57% male, 10% premature). Most of them presented with seizure (72%) and nonfocal neurologic signs (63%). MRI was completed for 92% of the infants, although <50% had vascular imaging. Infarcts preferentially involved the anterior circulation and left hemisphere and were multifocal in 30%. Maternal health and pregnancies were usually normal. Neonates often required resuscitation (30%) and had systemic illnesses (23%). Cardiac and prothrombotic abnormalities were identified in <20% of the infants. Antithrombotic treatment was uncommon (21%) and varied internationally. Half (49%) of the infants had deficits at discharge, and data on their long-term outcomes are pending.

CONCLUSIONS: Newborns with AIS are often systemically sick, whereas their mothers are usually healthy. Definitive causes for most neonatal AISs have not been established, and large-scale case-control studies are required to understand pathogenesis if outcomes are to be improved. *Pediatrics* 2011;128:e1402–e1410

AUTHORS: Adam Kirton, MD,[a] Jennifer Armstrong-Wells, MD,[b] Taeun Chang, MD,[c,d] Gabrielle deVeber, MD,[e] Michael J. Rivkin, MD,[f] Marta Hernandez, MD,[g] Jessica Carpenter, MD,[d] Jerome Y. Yager, MD,[h] John K. Lynch, DO,[i] and Donna M. Ferriero, MD,[j] for the International Pediatric Stroke Study Investigators

[a]Departments of Pediatrics and Clinical Neuroscience, University of Calgary and Alberta Children's Hospital, Calgary, Alberta, Canada; [b]Section of Neurology, Department of Pediatrics, University of Colorado and Children's Hospital Colorado, Denver, Colorado; [c]Neurophysiology and Epilepsy, [d]Department of Neurology, Children's National Medical Center, Washington, DC; [e]Division of Neurology, Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario, Canada; Departments of [f]Neurology, Psychiatry, and Radiology, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts; [g]Departamento de Pediatrica, Pontificia Universidad Catolica de Chile, Santiago, Chile; [h]Pediatric Neurosciences, Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada; [i]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; and [j]Newborn Brain Research Institute, University of California San Francisco, UCSF Benioff Children's Hospital, San Francisco, California

KEY WORDS
stroke, newborn, perinatal stroke

ABBREVIATIONS
AIS—arterial ischemic stroke
IPSS—International Pediatric Stroke Study
OR—odds ratio
CI—confidence interval
CT—computed tomography

All listed authors made substantive intellectual contributions to this study, including conception and design, acquisition of data, and/or analysis and interpretation of data; drafting and/or revising of the article for important intellectual content; and final approval of the version to be published. All listed authors qualify for authorship and have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-1148

doi:10.1542/peds.2011-1148

Accepted for publication Aug 15, 2011

Address correspondence to Adam Kirton, MD, Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary, Alberta, Canada T3B 6A8. E-mail: adam.kirton@albertahealthservices.ca

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.*

Perinatal stroke has emerged as a common cause of lifelong neurologic disability. Neonatal arterial ischemic stroke (AIS) is a common variety and is defined as acute symptomatic, focal cerebral infarction in an arterial territory between birth and 28 days of life that is confirmed by neuroimaging.[1,2] Most survivors suffer neurologic morbidity, and perinatal stroke is the leading cause of hemiplegic cerebral palsy.[2] Many infants with AIS incur additional sequelae including impairments in language, cognition, and behavior and epilepsy.[3–5] Case-control data are limited, and little is understood regarding pathophysiology.[2,6] That adverse outcomes last for decades amplifies the impact of neonatal AIS on patients, their families, and society.

Studies of neonatal AIS have been limited by sample size and inconsistent terminology, data collection, and risk-factor evaluations. The International Pediatric Stroke Study (IPSS) was established to standardize approaches to childhood stroke research on a global scale. Treatment options remain to be established, and practice patterns seem widely discrepant.[7] Consensus-based guidelines for pediatric stroke[8–10] offer little direction in neonatal AIS, and global practices regarding identification, investigation, and management must be established to facilitate systematic studies and clinical trials.

We examine here the presentations, clinical associations, investigations, treatments, and early outcomes of a large, global population of neonates with AIS.

METHODS

International Pediatric Stroke Study

The IPSS was established in 2003 by 11 coinvestigators including pediatric neurologists, hematologists, and epidemiologists. The long-term goal of the prospective registry was to develop and execute international clinical trials (https://app3.ccb.sickkids.ca/cstrokestudy/). Prospective enrollment extended from January 1, 2003, to July 1, 2007 (149 coinvestigators, 30 centers, 10 countries) and included symptomatic neonatal AIS but not presumed perinatal ischemic strokes. The IPSS office (Hospital for Sick Children) managed Web-based data entry and the master database. Consensus-based definitions for diagnosis, investigations, outcomes, and treatment were applied. Study identification numbers were assigned at enrollment. Data were deidentified and entered into a password-protected, Web-based system. Clinical care was not prescribed by the IPSS. Methods were approved by site research ethics boards with informed consent. The complete IPSS methodology is described elsewhere.[11]

Population

Cases were enrolled by site investigators using established clinical and radiographic criteria[5] including (1) acute neurologic deficit or seizure and (2) radiographic confirmation of acute focal cerebral infarction(s) within arterial territories corresponding to clinical manifestations. Infants with the following conditions were excluded: neonatal cerebral sinovenous thrombosis,[12] presumed perinatal ischemic stroke, intracranial hemorrhage, global hypoxic-ischemic injury, periventricular leukomalacia, and metabolic injury.

Data Abstraction

Investigators collected data—demographics (age, gender, race/ethnicity, location), clinical presentations, imaging, potential risk factors and evaluations, treatments, and discharge outcomes—by using standardized forms. Age at diagnosis was expressed by postnatal week (ethical restrictions on birth dates). Neonates born at ≤36 or ≥41 weeks' gestation were considered to be premature or postmature, respectively. Investigational sites were grouped according to region (Europe, Canada, United States, South America, Asia, or Australia). Birth weight was trichotomized (<2500, 2500–4000, or >4000 g). Season of event was adjusted according to hemisphere.

Potential risk factors were classified into consensus IPSS categories based on case-control studies and theoretical considerations only including cardiac, prothrombotic, acute and chronic illnesses, arteriopathy, and neonatal (maternal, pregnancy, neonatal, and obstetric). Neonates with systemic illness or significant resuscitation were classified as having "acute neonatal illness." Prothrombotic testing and investigator interpretation varied across institutions, hence the term "possible" prothrombotic abnormality. Treatment categories included antithrombotic, anticonvulsant, and other. Outcomes, discharge destination, and causes of death were recorded.

Analysis

Numerators were expressed over the available population unless otherwise stated. For each outcome of interest, variables predefined on evidence were compared (χ^2 analysis, dichotomous; t tests, continuous) and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). To determine independent predictors, multivariate logistic regression models incorporated univariate P values of ≤ .1 with testing for colinearity. Stata 10.0 (College Station, TX) was used for statistical calculations.

RESULTS

Patient Population

A total of 1194 patients were enrolled in the IPSS, 347 (29%) of which were

neonates. Neonates with AIS totaled 248 and represented our population (71% of all neonates, 21% of all AISs). Median gestational age was 39.0 weeks (mean: 39.0 ± 1.9; range: 31–42). Birth weight was considered normal (86%) or small (10%) or large (4%) for gestational age, and 55% had birth weights lower than the median for gestational age. Multiple (twin) gestations were uncommon (3 [1%]). Nineteen of the infants were born prematurely (8%), and another 20 (10%) were born postmaturely. Gender was discrepant; 140 (57%) were male (detailed analysis described elsewhere).[11] Geographic origin of the patients was United States (51%), Europe (19%), Canada (16%), South America (6%), Australia (6%), or Asia (3%) (Fig 1).

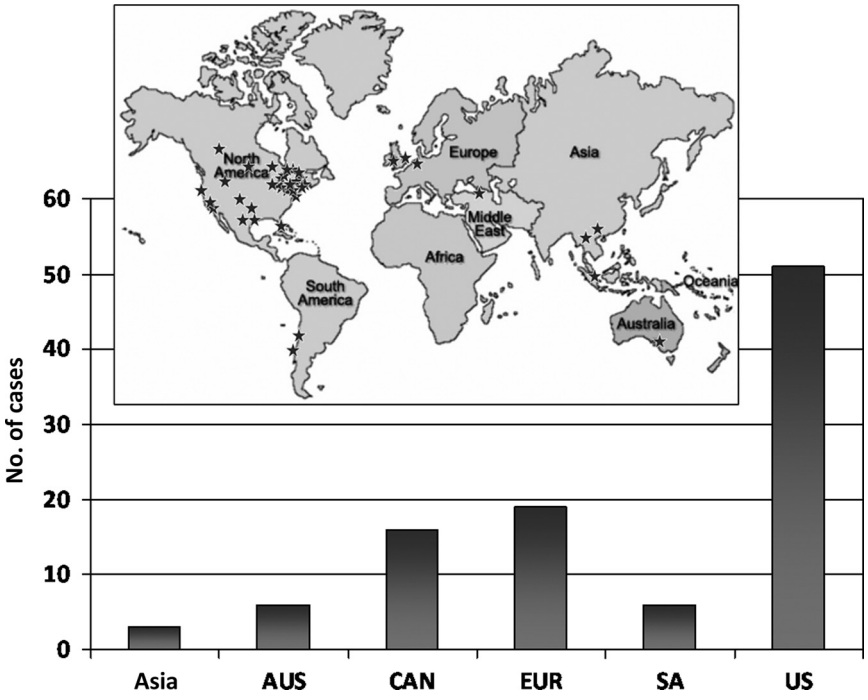

FIGURE 1

International distribution of neonatal AIS cases. During the period of prospective enrollment (January 1, 2003, through July 1, 2007), the IPSS included 149 coinvestigators at 30 centers in 10 countries. According to geographic category, the United States constituted the largest share of patients, and approximately two-thirds of them were enrolled in North America. LOC indicates level of consciousness.

Clinical Presentations

Most patients presented in the first week of life (87%). Seizures were common at presentation (178 [72%]), as were diffuse neurologic signs (157 [63%]); the most common sign was abnormal tone (38%) or level of consciousness (39%). A minority of the patients demonstrated focal neurologic signs (30%), the majority of which were lateralizing hemiparesis (95%). Systemic findings included respiratory (26%) and feeding (24%) difficulties (Fig 2).

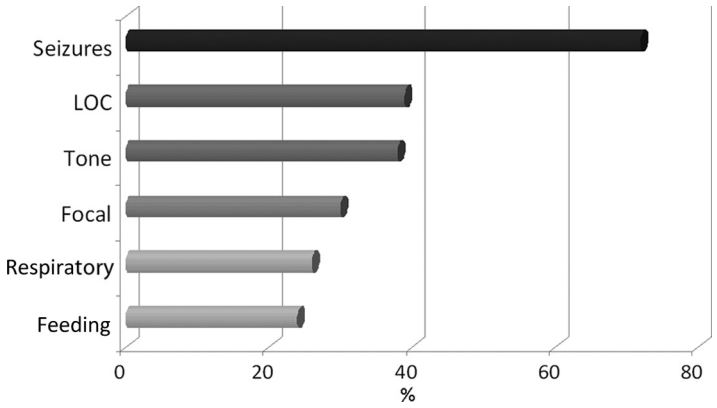

FIGURE 2

Clinical presentations of neonatal AIS. Most neonates presented with seizures (dark), although diffuse neurologic signs (altered level of consciousness or tone) and systemic abnormalities (respiratory or feeding difficulties) were frequent. Fewer than 30% of the newborns were described as having focal neurologic deficits. AUS indicates Australia; CAN, Canada; SA, South America.

Diagnosis and Neuroimaging

A brain MRI was obtained from nearly all of the infants (92%). Computed tomography (CT) scans were obtained for 119 (48%) infants. AIS lesions were single in 70% and isolated to the anterior circulation (71%), posterior circulation (9%), or both (20%). Strokes were more commonly left-sided (left alone in 51%, right alone in 25%), whereas bilateral lesions were observed in 24%. In those with only anterior circulation strokes, a strong left-sided preference was seen (73%).

Multiple vascular territory AIS was common (30%). In univariate analysis, associations with multiple-territory infarcts included neonatal resuscitation (OR: 4.58; $P < .0001$), maternal hypertension (OR: 4.29; $P = .006$), and acute systemic illness (OR: 2.13; $P = .03$). In multivariate analysis, only neonatal resuscitation was independently associated with multiple-territory infarction (OR: 5.5; $P < .0001$) (Table 1).

Intracranial hemorrhage in 56 neonates (23%) was reported. Most of

TABLE 1 Predictors of Infarct Characteristics

	Univariate			Multivariate		
	OR	*P*	95% CI	OR	*P*	95% CI
Predictors of multiple infarcts						
Significant neonatal resuscitation	4.58	<.0001	20.9–10.02	5.5[a]	<.0001[a]	2.30–13.17[a]
Maternal hypertension	4.29	.006	1.52–12.07	2.91	.09	0.84–10.10
Neonatal acute systemic illness	2.13	.03	1.09–4.13	0.8	.66	0.29–2.18
Predictors of hemorrhagic infarct						
Neonatal acute systemic illness	18.78	.008	2.13–165.74	8.72	.07	0.81–93.76
Neonatal sepsis	21.5	.002	3.01–153.5	6.69	.22	0.32–141.07
Neonatal acidosis	17.1	.004	2.52–116.2	0.63	.77	0.03–14.58
Bilateral lesions	20.29	.007	2.29–179.21	15.54[a]	.03[a]	1.28–189.09[a]

The variables tested were week of event, region, gender, presentation (focal deficit[s], hemiparesis, diffuse neurologic signs, abnormal tone, altered level of consciousness, seizure, feeding difficulties, respiratory difficulties), imaging completed (CT, MRI, computed tomography angiography, magnetic resonance angiography), lesion features (anterior circulation, posterior circulation, both anterior and posterior circulations, multiple vascular territories, left any/only, right any/only, bilateral, hemorrhage [any/inside lesion/outside lesion]), cardiac risk (congenital heart disease, other heart disease, related to surgery, related to catheterization [diagnostic or interventional]), arteriopathy, prothrombotic state, neonatal acute systemic illness, neonatal sepsis, neonatal acidosis, birth weight, gestational age, prematurity, postmaturity, maternal age, natural conception, low Apgar score (at 1 or 5 minutes), maternal hypertensive disorder, maternal diabetes, prolonged rupture of membranes, vaginal birth, any assisted delivery, urgent cesarean delivery, significant neonatal resuscitation, treatment (any antithrombotic, any anticoagulant, unfractionated heparin, low molecular weight heparin, acetylsalicylic acid, anticonvulsants).

[a] Factor was independently associated with outcome on multivariate analysis (see text).

TABLE 2 Predictors of Neurologic Deficit at Discharge

Predictor	Univariate		
	OR	*P*	95% CI
Delivery characteristics			
Vaginal delivery	1.87	.04	1.05–3.36
Urgent Cesarean delivery	0.41	.01	0.21–0.83
Presentation			
Hemiparesis[a]	1.29	<.0001	4.16–17.68
Tone/reflex abnormality[a]	4.56	<.0001	2.26–9.21
Any focal deficit	8.67	<.0001	4.29–17.50
Seizure	0.37	.001	0.20–0.67
Feeding difficulties	2.31	.01	1.19–4.48
Newborn risk factors			
Underlying chronic disease	2.32	.01	1.21–4.50
Prothrombotic state	2.24	.02	1.12–4.48
Vasculopathy	9.45	.036	1.16–76.91
Fever	3.77	.02	1.19–11.95
Acidosis	6.65	.08	0.79–56.21
Acute head/neck disorder	2.82	.09	0.86–9.29
Infarct characteristics			
Left-sided	0.39	.001	0.22–0.67
Right-sided	2.36	.008	1.24–4.47
Hemorrhage outside	0.32	.04	0.11–0.93

The variables tested were week of event, region, gender, presentation (focal deficit[s], hemiparesis, diffuse neurologic signs, abnormal tone, altered level of consciousness, seizure, feeding difficulties, respiratory difficulties), imaging completed (CT, MRI, computed tomography angiography, magnetic resonance angiography), lesion features (anterior circulation, posterior circulation, both anterior and posterior circulations, multiple vascular territories, left any/only, right any/only, bilateral, hemorrhage [any/inside lesion/outside lesion]), cardiac risk (congenital heart disease, other heart disease, related to surgery, related to catheterization [diagnostic or interventional]), arteriopathy, prothrombotic state, neonatal acute systemic illness, neonatal sepsis, neonatal acidosis, birth weight, gestational age, prematurity, postmaturity, maternal age, natural conception, low Apgar score (at 1 or 5 minutes), maternal hypertensive disorder, maternal diabetes, prolonged rupture of membranes, vaginal birth, any assisted delivery, urgent cesarean delivery, significant neonatal resuscitation, treatment (any antithrombotic, any anticoagulant, unfractionated heparin, low molecular weight heparin, acetylsalicylic acid, anticonvulsants).

[a] Factor was independently associated with outcome on multivariate analysis (see text).

them (62%) were classified as hemorrhage within the infarct (hemorrhagic transformation). In univariate analysis, associations with hemorrhagic transformation included acute systemic illness (OR: 18.78; $P = .008$), acidosis (OR: 17.7; $P = .004$), sepsis (OR: 21.5; $P = .002$), and bilateral lesions (OR: 20.29; $P = .007$). In multivariate analysis, only bilateral lesions remained an independent predictor (OR: 15.54; $P = 0.03$) (Table 1).

Arterial imaging was performed on 53% of the infants (magnetic resonance angiography in 49%). CT and conventional angiography were rare (4% and 3%, respectively). Abnormalities of arterial imaging were reported in 29 infants (12% overall, 22% of those imaged). Abnormal vascular imaging results included descriptions of arterial occlusion (9 [7%]) and possible arteriopathy (stenosis, dissection, or vasculitis) (10 [8%]), but further details were not available. No associations with abnormal arterial imaging were identified.

Potential Risk factors

Median maternal age was 29 years (mean: 29.8 ± 5.6; range: 16–43). Fifty-two percent of women were primiparous, and 15% were of advanced maternal age (≥35 years). History of previous miscarriage was recorded for 27 of the mothers (11%). Diagnosis was not associated with month or season of birth. The majority of pregnancies were conceived naturally (144 of 159 [91%]). Family-history data were incomplete, but not a single case of perinatal stroke in a sibling was reported. Maternal medical conditions

were uncommon with the exception of gestational hypertension and/or preeclampsia, reported in 10%. Factors such as gestational diabetes, oligohydramnios/polyhydramnios, and prenatal trauma, infections, or bleeding were each recorded in <1%.

Potential perinatal factors included maternal fever (9%), prolonged rupture of membranes (6%), and presence of meconium (23%). A prolonged second stage of labor was reported for 22%. Mode of delivery included emergent cesarean (26%), elective cesarean (15%), assisted vaginal (14%), and spontaneous vaginal (45%) delivery. Apgar scores were usually normal (score ≤ 5 at 1 minute [25%] and 5 minutes [6%]). Significant early neonatal resuscitation (assisted ventilation, chest compressions, intubation, medications) was documented in 30% of the cases. The term "birth asphyxia" was used in only 21 cases (8%). Data on placental abnormalities was recorded in only 20 cases (8%), but of these cases, 16 (80%) were classified as "abnormal." Details of placental pathologic findings were not recorded. Cooccurrence with acute systemic illnesses was common (23%), including dehydration (22%), fever (7%), gastroenteritis (9%), shock (8%), sepsis (3%), acidosis (3%), and meningitis (3%). As already defined, 40% had evidence of an acute neonatal illness.

Associated cardiac factors were identified in 43 (18%) of the infants. Complex congenital heart disease was most common (38 of 43 [88%]). Echocardiography details were insufficient for further analysis. Acquired cardiac conditions were rare (2 [<1%]). Diagnosis within 72 hours of a cardiac procedure was reported in 12 cases (28% of cardiac cases, 5% overall), including cardiac surgery[6] and catheterization (6 [5 diagnostic]). No cases of clinically asymptomatic heart disease presenting with stroke were described. Five (2%) strokes were associated with extracorporeal membrane oxygenation.

Results of prothrombotic testing were inconsistent. The presence of a possible thrombophilia (see "Methods") was reported in 47 (19%) of the cases, including an increased lipoprotein(a) level,[13] methylene tetrahydrofolate reductase (MTHFR) mutations (11 [7 hetero, 4 homozygous]), elevated β-2 glycoprotein level,[8] factor V Leiden,[6] prothrombin gene 20210A,[5] low antithrombin III level,[3] antiphospholipid antibodies,[2] plasminogen activator inhibitor 1,[2] and low protein S level.[1] Six children had multiple prothrombotic abnormalities.

Treatment

Only fifty-two (21%) of the infants received antithrombotic medication. Most of them were anticoagulated (42 [17% overall]) with low molecular weight heparin (28 [11%]), unfractionated heparin (12 [5%]), or warfarin (2 [<1%]). Antiplatelet therapy (acetylsalicylic acid) was given to 14 (6%). Multiple antithrombotic medications were given to 10 (19% treated, 4% overall). Treatment patterns for antithrombotic medications differed geographically ($P = .01$): Europe, 44%; Canada, 27%; Australia, 17%; South America, 16%; Asia, 14%; and United States, 14%.

Univariate analysis revealed an association between antithrombotic treatment and cardiac disease (OR: 2.8; $P = .005$) or presence of thrombophilia (OR: 2.7; $P = .005$). Several markers of disease severity were associated with antithrombotic treatment, including presentation with diffuse signs (OR: 2.25; $P = .02$) or altered level of consciousness (OR: 2.1; $P = .02$). Congenital or acquired heart disease was an independent predictor of receiving unfractionated heparin (OR: 13.77; $P < 0.001$ and OR: 59.67; $P = .008$, respectively).

Anticonvulsant treatment was common (169 [67%]). Early discontinuation of anticonvulsants is suggested, because they were present at discharge in only 2% of those treated. The only other common medications were antibiotics (23%).

Outcomes

Durations of hospital stay could not be accurately determined because of ethical restrictions on the use of birth dates. A majority of the infants were discharged from the hospital (95%). Neurologic deficits at discharge were documented in 49% of them. Data regarding type and severity of deficits were incomplete. Only 5 deaths were reported (2%). Long-term outcome data are not yet available. In univariate analysis, only vaginal delivery (OR: 1.87; $P = .04$) predicted discharge deficit, whereas urgent cesarean delivery seemed protective (OR: 0.41; $P = .01$). Neonatal predictors of discharge deficit in univariate analysis included focal deficits (OR: 8.67; $P < .0001$), hemiparesis (OR: 1.29; $P < .0001$), tone abnormality (OR: 4.56; $P < .0001$), feeding difficulties (OR: 2.31; $P = .01$), vasculopathy (OR: 9.45; $P = .04$), prothrombotic state (OR: 2.24; $P = .02$), and fever (OR: 3.77; $P = .02$). Newborn presentation with seizure decreased the probability of discharge deficit (OR: 0.37; $P = .001$). Infarct characteristics associated with deficits included right hemispheric lesions (OR: 2.36; $P = .008$), whereas left hemispheric lesions (OR: 0.39; $P = .001$) and hemorrhage outside the infarct (OR: 0.32; $P = .04$) were inversely associated.

Because presentation with focal deficits and hemiparesis were strongly collinear, the former was not included in the multivariate model. Only the presence of hemiparesis (OR: 7.09 [95% CI: 1.54–32.47]; $P = .01$) or tone abnormality (OR: 4.43 [1.30–15.10]; $P = .02$) at presentation were indepen-

dently associated with discharge deficit.

DISCUSSION

To our knowledge, this is the first report of a large multinational cohort of newborns with symptomatic AIS. Our data include several clinically relevant findings. Our population was generally "sicker" than those in previous studies. Neonates with AIS are typically described as nonencephalopathic, otherwise well children who present at 1 to 2 days of life with seizures.[3,13–15] However, at least 25% of our neonates showed signs of acute illness, including emergent cesarean delivery, resuscitation, low Apgar scores, and/or systemic illness. Despite this, the term "birth asphyxia" or suggestion of global hypoxic-ischemic encephalopathy was rare. Although they likely share risk factors and AIS can cooccur with hypoxic-ischemic encephalopathy,[16] most cases seemed to clearly distinguish the two. Such increased accuracy in diagnosis might reflect a combination of better neuroimaging (diffusion MRI), enhanced experience of the IPSS investigators, and better awareness of disease patterns. Such distinctions are essential for choosing investigations, treatment options, outcome prediction, family counseling, and research progress.

Neonates were unlikely to present with focal deficits, which emphasizes the need for a high index of clinical suspicion and prompt neuroimaging to diagnose stroke. Modern neuroimaging has greatly improved the detection and understanding of neonatal AIS. Our findings support the use of MRI with diffusion-weighted sequences as the first-line imaging modality in most cases of neonatal encephalopathy, which facilitates the accurate diagnosis of neonatal AIS. The role of CT scanning is limited and has little advantage over MRI but poses additional risk of radiation to the neonatal brain.[17] Our results have helped better characterize hemorrhagic changes associated with neonatal AIS. Associations with markers of acute disease suggest that systemic processes such as altered hemostatic mechanisms might increase the likelihood of intracranial bleeding. Although not evaluated in detail, severe hemorrhages that required a change in management were not reported. Therefore, repeat imaging for hemorrhagic changes might not be required, particularly with CT scanning. Addition of blood-sensitive magnetic resonance sequences (gradient echo, susceptibility-weighted images) is a viable alternative, and incorporation of such sequences to neonatal neuroimaging protocols might enhance our understanding of disease mechanisms.

Noninvasive vascular imaging is now routinely available and recommended by current pediatric stroke consensus guidelines.[8] Despite this, fewer than half of the neonates with AIS had cerebral angiographic studies performed. Furthermore, dedicated angiography of the cervical vasculature was rarely reported. Arterial dissection in neonates has been described and might represent an underrecognized entity with cervical imaging so underperformed. The documentation of arterial occlusion in $<$10% of the cases with angiographic studies suggests multiple possibilities. This finding is perhaps most consistent with systemic embolic events, although obvious risks for embolism are present in a small minority of patients (eg, congenital heart disease). In addition, recanalization of cerebral arteries might occur quickly, and with most imaging performed days after birth, occlusions might often not be evident. It is interesting to note that despite a very low number of cases, "arteriopathy" was associated with deficits at discharge (8 of 9 cases). Routine vascular imaging of the head and neck is required in neonatal stroke protocols to help resolve this issue.

Disordered coagulation has long been suspected of contributing to perinatal stroke. Previous case-control data for neonatal AIS are sparse, and estimates have varied widely (20%–68%).[18–22] Evidence does support a role for thrombophilia in neonatal AIS, particularly protein C deficiency, elevated lipoprotein(a) level, and factor V Leiden.[23] A 2010 meta-analysis of thrombophilia in pediatric stroke found only 22 of 185 studies eligible, and only 6 focused on "perinatal stroke."[23] The authors concluded that studies have been "contradictory or inconclusive due to lack of statistical power."[23] Additional limiting factors of these studies and ours include inconsistent laboratory methods with a lack of controls matched for perinatal factors including age, in which developmental changes in hemostasis are paramount and normative values are not well established.[24] Our results do little to resolve the poorly understood role of thrombophilia in neonatal AIS, and fully powered, carefully controlled studies are required.

Consistent with the controversial role of antithrombotic treatment for neonatal AIS, treatment was uncommon and varied according to region. Recent neonatal cerebral sinovenous thrombosis studies within the IPSS[12] and elsewhere[25] found similar international discrepancies in treatment. Current consensus-based guidelines[8–10] vary in their recommendations regarding neonatal AIS treatment, although they consistently support anticoagulation therapy in congenital heart disease, and such an association was observed here. Our study could not examine the safety or efficacy of such interventions, although serious complications were not reported, and no association with intracranial hem-

orrhage was observed. Neonatal AIS carries an extremely low recurrence rate,[2] so withholding anticoagulation therapy would seem reasonable outside the circumstance of congenital heart disease. Antithrombotic clinical trials will not likely occur for neonatal AIS; neuroprotective interventions seem a more likely future focus.

Because most of the infants presented with seizures, the frequent use of anticonvulsants is expected. However, treatment seemed to be discontinued by discharge for most patients. This might parallel practices in other forms of neonatal encephalopathy (eg, hypoxic-ischemic encephalopathy), for which the natural history is better understood and early cessation of seizure medications might be reasonable. Stroke-induced neonatal seizures have been studied less, and the possibilities of both ongoing subclinical seizures and medication adverse effects need to be considered. Prospective studies of neonatal AIS seizure treatment including cerebral monitoring are required.

Our sample size provided a unique opportunity to perform multivariate logistic regression and generate speculative hypotheses regarding outcomes of interest. That presentation with acute focal deficits predicts the same at discharge is hardly surprising. However, could the association of neonatal resuscitation with multiple infarcts reflect underlying diseased placenta? Potential reasons for the independent association observed between hemorrhage and bilateral lesions are less evident, and a wide CI should be interpreted with caution. Currently minimal understanding of neonatal stroke pathophysiology suggests value in the consideration of such previously unreported associations.

Our analysis of a large, international sample of neonates with AIS provides important new knowledge but carries important limitations. As an international registry, our samples are not population-based, and comparative "normal" populations are not available. Unavoidable bias is present with IPSS investigators diagnosing, investigating, and enrolling patients; their expertise differs from that of general neonatologists or pediatric neurologists. Accurate and complete data collection across dozens of international centers and investigators is challenging, even with modern Web-based data-entry systems and established IPSS protocols. The detailed data and enormous sample size required to answer the most challenging questions of causation were not possible. Our neurologic outcome data were only available at discharge, whereas much longer follow-up intervals (years) are required for meaningful interpretation. Also, selection of symptomatic cases only excludes important populations, including those with ultrasound-detected subcortical "perforator" lesions[26] and later-presenting presumed perinatal ischemic stroke.[27]

CONCLUSIONS

Interpretation of our neurologic outcome data are extremely limited. Because most neonates do not manifest obvious focal deficits and admission times are generally short, it is not surprising that those who do will still have discharge deficits. However, it is now well established that children will "grow into their deficits" after perinatal brain injury. Even simple motor outcomes (cerebral palsy) are not reasonably characterized until 18 to 24 months, whereas more complex deficits (eg, learning, behavioral) are often not appreciated until school age.[4,28,29] Therefore, our results should not be used to try to predict long-term neurologic outcomes in neonates with AIS, and the potential associations described here should be considered hypothesis-generating only. Fortunately, ongoing follow-up of this IPSS cohort will facilitate future studies to more accurately characterize neurologic outcomes.

ACKNOWLEDGMENTS

Original start-up funding for the IPSS was provided by the Child Neurology Foundation. The funding source played no role in the design, collection, analysis, or interpretation of data, writing of the report, or the decision to submit the article.

The original IPSS investigators were Steve Ashwal, MD (Loma Linda University School of Medicine, Loma Linda, CA), Gabrielle deVeber, MD, MHSc (Hospital for Sick Children, Toronto, Ontario, Canada), Donna Ferriero, MD (University of California, San Francisco, CA), Heather Fullerton, MD, MAS (University of California, San Francisco), Rebecca Ichord, MD (Children's Hospital of Philadelphia, Philadelphia, PA), Fenella Kirkham, MB, BChir (University College London Institute of Child Health, London, United Kingdom), John K. Lynch, DO, MPH (National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD), Finbar O'Callaghan, MBChB (Bristol Royal Hospital for Children, Bristol, United Kingdom), Steve Pavlakis, MD (Maimonides Medical Center, Brooklyn, NY), Guillaume Sebire, MD, PhD (Université de Sherbrooke Fleurimont, Sherbrooke, Québec, Canada), and Andrew Willan, BA, MSc, PhD (Hospital for Sick Children); the IPSS institutions that enrolled at least 20 patients were (numbers in parentheses indicate the number of patients enrolled) Hospital for Sick Children (147) (Gabrielle deVeber, MD, MHSc, Andrew Willan, BA, MSc, PhD, Adam Kirton, MD, Mahendra Moharir, MD, Rand Askalan, MD, PhD, and Marianne Sofronas, MA), Münster University Pediatric Hospital, Münster, Ger-

many (122) (Ulrike Nowak- Göttl, MD, Christine Düring, MD, and Anne Krümpel, MD), University of Texas Southwestern Medical Center, Dallas, Texas (94) (Michael M. Dowling, MD, PhD, Patricia Plumb, RN, MSN, Janna Journeycake, MD, and Katrina van de Bruinhorst, MA), Ohio Stroke Registry (94) Akron Children's Hospital, Akron, Ohio (Abdalla Abdalla, MD), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Tonya Phillips, MD), Cleveland Clinic, Cleveland, Ohio (Neil Friedman, MD), MetroHealth Medical Center, Cleveland (Elie Rizkallah, MD), Nationwide Children's Hospital, Columbus, Ohio (Warren Lo, MD, and Khaled Zamel, MD), Rainbow Babies and Children's Hospital, Cleveland (Max Wiznitzer, MD, and Karen Lidsky, MD), Pontificia Universidad Catolica de Chile, Santiago, Chile (78) (Marta Isabel Hernandez Chavez, MD), Royal Children's Hospital, Melbourne, Victoria, Australia (75) (Professor Paul Monagle, Mark MacKay, MD, Chris Barnes, MD, Janine Furmedge, RN, BSc, and Anne Gordon, MSc, BAppSc), University of Utah and Primary Children's Medical Center, Salt Lake City, Utah (70) (Susan L. Benedict, MD, and James F. Bale Jr, MD), Children's Hospital of Philadelphia (63) (Rebecca Ichord, MD, Daniel Licht, MD, and Sabrina Smith, MD), Loma Linda University School of Medicine (54) (Steve Ashwal, MD, and Chalmer McClure, MD, PhD), Schneider Children's Hospital, New Hyde Park, New York (46) (Li Kan, MD, MS, Robin Smith, MD, Joseph Maytal, MD, and Rosemarie Sy-Kho, MD), Children's National Medical Center, Washington, DC (39) (Jessica Carpenter, MD, Taeun Chang, MD, and Steven Weinstein, MD), University of California, San Francisco (37) (Donna Ferriero, MD, and Heather Fullerton, MD, MAS), Maimonides Medical Center (26) (Steve Pavlakis, MD, Sharon Goodman, PNP, and Kim Levinson, PNP), Riley Hospital, Indianapolis, Indiana (26) (Meredith Golomb, MD, MSc), Winnipeg Children's Hospital, Winnipeg, Manitoba, Canada (24) (Mubeen Rafay, MBBS, MSc, Frances Booth, MD, Michael Salman, MD, Charuta Joshi, MD, Namrata Shah, MD, and Monica Nash, RN), Children's Hospital of New York, New York, New York (22) (Geoffrey Heyer, MD), Great Ormond Street Hospital, London, United Kingdom (21) (Vijeya Ganesan, MBChB, MD), Stollery Children's Hospital, Edmonton, Alberta, Canada (21) (Jerome Y. Yager, MD), and Pediatric Institute Hospital, Kuala Lumpur, Malaysia (20) (Hussain Imam, MBBS, FRCP, DCH); and the IPSS institutions that enrolled <20 patients were Bangkok Hospital Medical Center, Bangkok, Thailand (Montri Saengpattrachai, MD), British Columbia Children's Hospital, Vancouver, British Columbia, Canada (Bruce Bjornson, MD), Children's Central Hospital, Tbilisi, Georgia (Nana Tatishvili, MD), Children's Hospital of Buffalo, Buffalo, New York (E. Ann Yeh, MD), Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada (Peter Humpherys, MD), Children's Hospital of Wisconsin, Milwaukee, Wisconsin (Catherine Amlie-Lefond, MD, and Harry T. Whelan, MD), Denver Children's Hospital, Denver, Colorado (Timothy Bernard, MD, and Neil A. Goldenberg, MD, PhD), Hospital Dr Sotero del Rio, Puente Alto, Chile (Manuel Arriaza Ortiz, MD), McMaster University Medical Centre, Hamilton, Ontario, Canada (Anthony Chan, MBBS), Miami Children's Hospital, Miami, Florida (Marcel Deray, MD, and Zaid Khatib, MD), Queen Mary Hospital, Hong Kong, China (Virginia Wong, MD), Université de Sherbrooke Fleurimont (Guillaume Sebire, MD, PhD), University of Rochester Medical Center, Rochester, New York (Jill M. Cholette, MD, Shalu Narang, MD, and Norma B. Lerner, MD, MPH), and University of Texas, San Antonio, Texas (Shannon Carpenter, MD, and Kurt Bischoff, MSc).

REFERENCES

1. Raju TN, Nelson KB, Ferriero D, Lynch JK; NICHD-NINDS Perinatal Stroke Workshop Participants. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics*. 2007;120(3):609–616
2. Nelson KB. Perinatal ischemic stroke. *Stroke*. 2007;38(2 suppl):742–745
3. Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr*. 2000;137(3):351–355
4. Ricci D, Mercuri E, Barnett A, et al. Cognitive outcome at early school age in term-born children with perinatally acquired middle cerebral artery territory infarction. *Stroke*. 2008;39(2):403–410
5. 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
6. Kirton A, deVeber G. Advances in perinatal ischemic stroke. *Pediatr Neurol*. 2009;40(3):205–214
7. Fullerton H, deVeber G; IPSS Investigators. Practice variability in the treatment of childhood acute ischemic stroke: results of the International Pediatric Stroke Study [abstr]. *Stroke*. 2007;38(2):485
8. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a special writing group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke*. 2008;39(9):2644–2691
9. Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008 ;133(6 suppl):887S–968S
10. Paediatric Stroke Working Group. *Stroke in Childhood: Clinical Guidelines for Diagnosis, Management and Rehabilitation*. London, United Kingdom: Royal College of Physicians: 2004
11. Golomb MR, Fullerton HJ, Nowak-Gottl U, deVeber G. Male predominance in childhood

ischemic stroke: findings from the international pediatric stroke study. *Stroke*. 2009; 40(1):52–57

12. Jordan LC, Rafay MF, Smith SE, et al. Antithrombotic treatment in neonatal cerebral sinovenous thrombosis: results of the International Pediatric Stroke Study. *J Pediatr*. 2010;156(5):704–710
13. Rafay MF, Cortez MA, de Veber GA, et al. Predictive value of clinical and EEG features in the diagnosis of stroke and hypoxic ischemic encephalopathy in neonates with seizures. *Stroke*. 2009;40(7):2402–2407
14. Fujimoto S, Yokochi K, Togari H, et al. Neonatal cerebral infarction: symptoms, CT findings and prognosis. *Brain Dev*. 1992;14(1): 48–52
15. Govaert P, Ramenghi L, Taal R, de Vries L, Deveber G. Diagnosis of perinatal stroke I: definitions, differential diagnosis and registration. *Acta Paediatr*. 2009;98(10): 1556–1567
16. Ramaswamy V, Miller SP, Barkovich AJ, Partridge JC, Ferriero DM. Perinatal stroke in term infants with neonatal encephalopathy. *Neurology*. 2004;62(11):2088–2091
17. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med*. 2007;357(22):2277–2284
18. Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol*. 2001;50(2):163–168
19. deVeber G, Monagle P, Chan A, et al. Prothrombotic disorders in infants and children with cerebral thromboembolism. *Arch Neurol*. 1998;55(12):1539–1543
20. Günther G, Junker R, Strater R, et al. Symptomatic ischemic stroke in full-term neonates: role of acquired and genetic prothrombotic risk factors. *Stroke*. 2000; 31(10):2437–2441
21. Lynch JK, Nelson KB, Curry CJ, Grether JK. Cerebrovascular disorders in children with the factor V Leiden mutation. *J Child Neurol*. 2001;16(10):735–744
22. Curry CJ, Bhullar S, Holmes J, Delozier CD, Roeder ER, Hutchison HT. Risk factors for perinatal arterial stroke: a study of 60 mother-child pairs. *Pediatr Neurol*. 2007; 37(2):99–107
23. Kenet G, Lutkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation*. 2010; 121(16):1838–1847
24. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. *Blood*. 1992; 80(8):1998–2005
25. Berfelo FJ, Kersbergen KJ, van Ommen CH, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. *Stroke*. 2010;41(7):1382–1388
26. Abels L, Lequin M, Govaert P. Sonographic templates of newborn perforator stroke. *Pediatr Radiol*. 2006;36(7):663–669
27. Kirton A, deVeber G, Pontigon AM, MacGregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann Neurol*. 2008;63(4):436–443
28. Westmacott R, Barry V, MacGregor D, deVeber G. Intellectual function in preschool and school-aged children with a history of acute neonatal stroke [abstr]. *Stroke*. 2007;38(2): 581
29. Westmacott R, MacGregor D, Askalan R, deVeber G. Late emergence of cognitive deficits after unilateral neonatal stroke. *Stroke*. 2009;40(6):2012–2019

Symptomatic Neonatal Arterial Ischemic Stroke: The International Pediatric Stroke Study

Adam Kirton, Jennifer Armstrong-Wells, Taeun Chang, Gabrielle deVeber, Michael J. Rivkin, Marta Hernandez, Jessica Carpenter, Jerome Y. Yager, John K. Lynch, Donna M. Ferriero and for the International Pediatric Stroke Study Investigators

Pediatrics 2011;128;e1402
DOI: 10.1542/peds.2011-1148 originally published online November 28, 2011;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Symptomatic Neonatal Arterial Ischemic Stroke: The International Pediatric Stroke Study

Adam Kirton, Jennifer Armstrong-Wells, Taeun Chang, Gabrielle deVeber, Michael J. Rivkin, Marta Hernandez, Jessica Carpenter, Jerome Y. Yager, John K. Lynch, Donna M. Ferriero and for the International Pediatric Stroke Study Investigators

Pediatrics 2011;128;e1402
DOI: 10.1542/peds.2011-1148 originally published online November 28, 2011;