Arteriopathy, D-Dimer, and Risk of Poor Neurologic Outcome in Childhood-Onset Arterial Ischemic Stroke

Neil A. Goldenberg, MD, PhD[1,2], Sarah Jenkins, BA[3], Jessica Jack, BA[3], Jennifer Armstrong-Wells, MD, MPH[4,13], Laura Z. Fenton, MD[5], Nicholas V. Stence, MD[5], Joyce Oleszek, MD[6], Richard Boada, PhD[5], Greta N. Wilkening, PsyD[5], Charles Wilkinson, MD[7], Jennifer B. Soep, MD[8], Shelley D. Miyamoto, MD[9], Lalit Bajaj, MD, MPH[10], Peter M. Mourani, MD[11], Marilyn J. Manco-Johnson, MD[12,13], and Timothy J. Bernard, MD[5,13]

Objective To assess whether acute findings of cerebral arteriopathy, large infarct, and acutely elevated plasma D-dimer levels are independently prognostic of poor long-term neurologic outcome as measured at ≥1 year post-event in children with arterial ischemic stroke (AIS).

Study design Sixty-one patients with childhood-onset (ie, >28 days of life) AIS were enrolled in a single-institution cohort study at Children's Hospital Colorado between February 2006 and June 2011. Data on demographic and diagnostic characteristics, antithrombotic treatments, and outcomes were systematically collected.

Results Cerebral arteriopathy and D-dimer levels >500 ng/mL (a measure of coagulation activation) were identified acutely in 41% and 31% of the cohort, respectively. Anticoagulation was administered in the acute period post-event in 40% of the children, in the subacute period in 43%, and in the chronic period in 28%. When not receiving anticoagulation, patients were routinely treated with aspirin 2-5 mg/kg once daily for a minimum of 1 year. Death, major bleeding (including intracranial hemorrhage), and recurrent AIS were infrequent. The Pediatric Stroke Outcome Measure at 1 year demonstrated poor outcome in 54% of the children. Acute cerebral arteriopathy and elevated D-dimer level were identified as putative prognostic factors for poor outcome; after adjustment for D-dimer, arteriopathy was an independent prognostic indicator (OR, 19.0; 95% CI, 1.6-229.8; $P = .02$).

Conclusion Arteriopathy and coagulation activation are highly prevalent in the acute period of childhood AIS. Although recurrent AIS and intracranial hemorrhage were infrequent in our cohort, one-half of children experienced a poor neurologic outcome at 1 year, the risk of which was increased by acute arteriopathy. Substantiation of these findings in multi-institutional cohort studies is warranted, toward risk stratification in childhood-onset AIS. *(J Pediatr 2013;162:1041-6)*.

Arterial ischemic stroke (AIS) is rare in childhood, with an incidence of approximately 1-2 per 100 000 children per year.[1-3] It is a serious disorder, with neuroromotor deficits evident in 70% of children, both acutely[4,5] and in long-term follow-up.[6-8] In addition, recurrence is common, with a 6%-15% cumulative probability of recurrent stroke at approximately 1 year.[1,9] Numerous causal and contributing factors in childhood-onset AIS have been identified, including thrombophilia (ie, hypercoagulability), acute infection, congenital cardiac disease or cardiac catheterization, cerebral/cervical arterial arteriopathy, cerebral angiitis, and other/idiopathic cerebral arteriopathies.[7,10-21] Interestingly, preliminary data indicate that plasma D-dimer concentration—a marker of coagulation activation—is often elevated acutely and varies with etiologic subtype in childhood-onset AIS.[22] Recent retrospective and mixed prospective-retrospective cohort studies have shown an important association between cerebral arteriopathy (especially its persistence/progression) and recurrent AIS in childhood.[1,23] In addition, the International Pediatric Stroke Study identified cerebral arteriopathy as a prognostic factor for death or neurologic deficit at hospital discharge.[5]

Whether acute cerebral arteriopathy and elevated D-dimer concentration are prognostic of long-term neurologic outcomes remains unknown. Accordingly, we investigated the importance of these and other characteristics in children with AIS in a single-institution mixed-cohort study. We hypothesized that acute

AIS	Arterial ischemic stroke
APS	Antiphospholipid antibody syndrome
CASCADE	Childhood AIS Standardized Classification and Diagnostic Evaluation
CT	Computed tomography
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
PSOM	Pediatric Stroke Outcomes Measure

From the [1]Division of Hematology, Departments of Pediatrics and Medicine, Johns Hopkins School of Medicine, Baltimore, MD; [2]All Children's Research Institute, All Children's Hospital, Johns Hopkins Medicine, St Petersburg, FL; [3]Graduate Medical Education Program, [4]Child Neurology Section, Department of Pediatrics, [5]Department of Radiology, [6]Department of Physical and Medical Rehabilitation, [7]Department of Neurosurgery, [8]Rheumatology Section, Department of Pediatrics, [9]Section of Cardiology, Department of Pediatrics, [10]Emergency Medicine Section, Department of Pediatrics, [11]Critical Care Medicine Section, Department of Pediatrics, [12]Hematology/Oncology/BMT Section, Department of Pediatrics, and [13]Mountain States Regional Hemophilia and Thrombosis Center, University of Colorado, Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

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findings of cerebral arteriopathy, large infarct, and acutely elevated plasma D-dimer level are independently prognostic of poor long-term neurologic outcome as measured at ≥1 year postevent in children with AIS.

Methods

Risk factors, treatments, and long-term outcomes were systematically assessed in children diagnosed with AIS (age >28 days at symptom onset) between February 28, 2006, and June 20, 2011, and followed in the multidisciplinary Stroke Clinic at Children's Hospital Colorado. All patients were invited to participate in a local prospective cohort study designed to capture and analyze these clinically derived data (COMIRB 05-0339). For patients diagnosed with acute AIS before February 28, 2006 (n = 15), data were collected retrospectively before this date and ascertained prospectively from this date forward. Signed informed consent was required for study participation.

Diagnostic criteria for acute pediatric AIS included sudden onset of focal neurologic deficit with objective confirmation of arterial-distribution ischemia/infarct by computed tomography (CT) or magnetic resonance imaging (MRI). In the Stroke Clinic, a detailed clinical history and physical examination, as well as follow-up neurovascular imaging, were obtained at 2-6 months and 1 year after the event. Imaging studies were reviewed independently by a pediatric radiologist (L.F. or N.S.) and a pediatric neurologist (T.B.). In cases of disagreement in radiographic classification between the 2 primary reviewers, a final decision was achieved via consensus at a multidisciplinary Pediatric Neuroradiology Stroke Conference. Patients were classified according to the Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) criteria.[24] The presence of acute arteriopathy was defined by angiographic findings within 1 week of AIS symptom onset. Infarct size was measured within the clinical software for CT and MRI imaging using axial views and reported as less than one-third versus one-third or more of the middle cerebral artery (MCA) territory. Additional diagnostic evaluation included transthoracic echocardiography with peripheral intravenous saline microbubble injection and comprehensive thrombophilia testing, as described previously.[25] These were performed during acute hospitalization or the first stroke clinic visit.

Acute D-dimer concentration was defined as the results of first tests within 24 hours of AIS symptom onset. Abnormal thrombophilia results (other than DNA-based analyses) were followed via serial testing, typically at 6 weeks, 3-6 months, 1 year, and annually thereafter. Genetic thrombophilias consisted of 1 or more of the following: factor V Leiden polymorphism, prothrombin G20210A polymorphism, elevated plasma lipoprotein (a) concentration confirmed at least 6 weeks after the acute event and in the absence of recent infection, plasma protein C activity consistently <40% after 6 months of age, plasmas free protein S antigen levels consistently <40%, and plasma antithrombin activity consistently <60% after age 6 months. Transient deficiencies of protein C activity, free protein S antigen, or antithrombin activity and transient elevation of lipoprotein (a) were considered acquired. Other acquired thrombophilias included antiphospholipid antibodies and elevated plasma factor VIII activity (>191 U/dL). Acquired thrombophilias were further classified as acute if the abnormal results were obtained up to 48 hours before or 1 week after the stroke date but resolved within 12 weeks on subsequent testing. Acquired abnormalities persisting at 12 weeks were categorized as chronic.

Antithrombotic therapies were defined as therapeutic anticoagulation or antiplatelet therapy with or without preceding thrombolytic modalities. Decisions regarding antithrombotic strategies and durations were made by the treating clinicians. Periods of antithrombotic therapy were categorized as acute (first week postevent), subacute (1 week to 3 months postevent), or chronic (more than 3 months postevent). Acute therapeutic anticoagulation, when used, consisted of either unfractionated heparin by continuous intravenous infusion (adjusted to achieve a target anti-factor Xa activity of 0.3-0.7 U/mL) or low molecular weight heparin given subcutaneously twice daily (adjusted to achieve a target anti-factor Xa activity of 0.5-1.0 U/mL at 4 hours postdose). In cases of continuation of anticoagulation into the subacute and/or chronic periods, either low molecular weight heparin was administered as above or warfarin was given by mouth once daily and adjusted to maintain an International Normalized Ratio of 2.0-3.0. Clopidogrel was used in conjunction with low molecular weight heparin in the rare setting of severe carotid dissection requiring stents, or as an alternative to anticoagulation for recurrent AIS despite aspirin therapy.

Major bleeding complications of antithrombotic therapy were defined by one or more of the following criteria: (1) symptomatic central nervous system hemorrhage, confirmed by objective neuroimaging; (2) documented decline in hemoglobin by 2 g/dL in a 24-hour period in the absence of a defined nonhemorrhagic etiology; and (3) hemorrhage requiring surgical intervention to restore hemostasis. Symptomatic central nervous system hemorrhage was ascertained by CT findings of hemorrhage in the setting of new neurologic signs or symptoms; this evaluation was clinically driven and its findings were captured in the study. Neurologic outcome was based on the presence of any neuromotor deficit at 1 year, as determined by a treating neurologist (T.B. or J.W.), and by the Pediatric Stroke Outcomes Measure (PSOM), October 2003 version, format revised in November 2005. The last PSOM examination performed at ≥1 year postevent served as the PSOM finding of long-term neurologic outcome.

Originally developed by deVeber et al[8] in a Canadian prospective cohort study of AIS and cerebral sinovenous thrombosis, the PSOM contains 115 items that measure neuromuscular and neurocognitive functioning in 4 domains: Sensorimotor Deficit, Language Deficit (Production), Language Deficit (Comprehension), and Cognitive or Behavioral Deficit. Administered at least 1 year after stroke, the PSOM yielded scores categorized as either "good" or "poor" outcome, according to criteria used by deVeber et al.[8] Specifically, a score of 0.5 (mild deficit with no impact