Published in final edited form as:
Stroke. 2011 April ; 42(4): 941–946. doi:10.1161/STROKEAHA.110.604199.

Hemorrhagic Transformation of Childhood Arterial Ischemic Stroke

Lauren A Beslow, MD[1], **Sabrina E Smith, MD, PhD**[1], **Arastoo Vossough, MD, PhD**[2], **Daniel J Licht, MD**[1], **Scott E Kasner, MD, MSCE**[3], **Christopher G Favilla, BA**[3], **Aviva R Halperin, BA**[1], **Danielle M Gordon, BA**[1], **Charlene I Jones, BA**[1], **Andrew J Cucchiara, PhD**[4], and **Rebecca N Ichord, MD**[1]

[1] Division of Neurology, The Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, 10th Floor Room10011, Philadelphia, PA 19104

[2] Division of Neuroradiology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Philadelphia, PA 19104

[3] Department of Neurology, The Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, PA 19104

[4] Clinical and Translational Research Center, The University of Pennsylvania, 160 Dulles Pavilion, 3400 Spruce Street, Philadelphia, PA 19104

Abstract

Background and Purpose—To describe the occurrence of hemorrhagic transformation (HT) among children with arterial ischemic stroke (AIS) within 30 days after symptom onset and to describe clinical factors associated with HT.

Methods—Sixty-three children age 1 month to 18 years with AIS between January 2005 and November 2008 were identified from a single center prospective pediatric stroke registry. All neuroimaging studies within 30 days of stroke were reviewed by a study neuroradiologist. Hemorrhage was classified according to the European Cooperative Acute Stroke Study-1 definitions. Association of HT with clinical factors, systemic anticoagulation, stroke volume, and outcome was analyzed.

Results—HT occurred in 19 of 63 children (30%; 95%CI 19–43%), only 2 (3%) of whom were symptomatic. Hemorrhage classification was HI1 in 14, HI2 in 2, PH1 in 2, and PH2 in 1. HT was less common in children with vasculopathy (RR 0.27; 95%CI 0.07–1.06; p=0.04) than in those with other stroke mechanisms. HT was not significantly associated with anticoagulation versus antiplatelet therapy (RR 0.6; 95%CI 0.2–1.5; p=0.26) but was associated with larger infarct volumes (p=0.0084). In multivariable analysis, worse PSOM scores were associated with infarct volume ≥5% of total supratentorial brain volume (OR 4.0; 95%CI 1.1–15; p=0.04), and a trend existed toward association of worse PSOM scores with HT (OR 4.0; 95%CI 0.9–18; p=0.07).

Conclusions—HT occurred in 30% of children with AIS within 30 days. Most hemorrhages were petechial and asymptomatic. Infarct volume was associated with HT and worse outcome.

*Communicating author: Lauren A Beslow, MD, Division of Neurology, The Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, 10th Floor Room10011, Philadelphia, PA 19104, Phone: 1-215-590-4142, Fax: 1-215-590-1771, beslow@email.chop.edu.

Disclosures

Dr. Ichord is on the Clinical Event Committee for the Pediatric Berlin Heart Trial (industry sponsored). None of the other authors has any conflict of interest or disclosures.

Keywords

hemorrhagic transformation; arterial ischemic stroke; anticoagulation; pediatric

Introduction

Arterial ischemic stroke (AIS) affects 1.2 to 7.9/100,000 children per year[1]. No clinical trials have characterized the risks and benefits of antiplatelet or anticoagulation therapy in childhood acute stroke. Therefore, notable differences in treatment exist among experienced centers, some starting systemic anticoagulation acutely in most patients and others starting treatment with antiplatelet agents while using anticoagulation more selectively. In adults, no net benefit has been established for systemic anticoagulation compared to aspirin, even with cardioembolic stroke, mostly because of increased risk of hemorrhagic transformation (HT)[2–4]. However, since stroke mechanisms and coagulation and fibrinolytic pathways are different in children versus adults, findings from adult clinical trials of antithrombotic therapy cannot be extrapolated to children[5].

Similarly, thrombolysis studies for AIS in children are limited, and risk of HT in this context is uncertain[6]. Reliable estimates of HT rates obtained from carefully studied cohorts are essential for planning trials of thrombolytic and antithrombotic therapies in children with AIS. The primary goal of this study was to determine the proportion of children with HT in a prospectively identified consecutive cohort of children with AIS. Secondary objectives were to determine whether specific stroke risk factors, infarct volume, or acute antithrombotic treatments were associated with greater risk of HT and to determine whether HT was associated with worse clinical outcome.

Materials and Methods

Study design

Children 1 month to 18 years with acute AIS between January 2005 and November 2008 were prospectively identified and included in the stroke registry of a large tertiary care children's hospital with informed consent from parent or guardian. With institutional review board approval, retrospective analysis of this cohort was performed.

Case identification

During acute hospitalization, patients were identified by neurology providers participating in a multidisciplinary neurovascular care program targeting children admitted to the hospital with acute AIS. Acute AIS was defined as acute-onset neurological deficit of any duration consistent with focal brain ischemia in an arterial distribution and confirmed by acute infarction on neuroimaging corresponding to the clinical deficit.

Clinical data

Acute hospital records were abstracted. Diagnostic studies were performed as part of a multidisciplinary, consensus-based pediatric stroke protocol following current American Heart Association pediatric stroke treatment guidelines[7]. This protocol typically included MRI brain imaging, craniocervical vascular imaging, an echocardiogram, and a thrombophilia profile. Cases were classified by primary stroke risk factor as vasculopathy, cardiac conditions, tumor-related, meningitis, isolated thrombophilia, sickle cell anemia, or other systemic disease. Cases with no stroke risk factor identified after comprehensive evaluation were classified as cryptogenic. Vasculopathy was classified according to methods

of Sebire et al and modified by Amlie-Lefond et al and included arterial dissection, focal cerebral arteriopathy of childhood, moyamoya disease, and autoimmune vasculitis[8, 9].

Normal ranges for blood pressure based on sex and height were used to classify the first available blood pressure (BP) for each subject as normal, mildly elevated if the systolic or diastolic BP was between the 95th and 99th percentile for 95%th percentile of height, or moderately elevated if the systolic or diastolic BP was greater than 99%th percentile for 95% percentile of height. BP at the time of the HT was not available.

Treatment was defined as follows: 1) systemic anticoagulation - received unfractionated heparin, low molecular weight heparin, or warfarin; 2) antiplatelet therapy - received aspirin but not anticoagulation; 3) both - received anticoagulation and aspirin simultaneously; and 4) neither - received neither anticoagulation nor antiplatelet therapy. The one patient treated with both aspirin and anticoagulation simultaneously was pooled with patients receiving anticoagulation alone for analysis as done by Goldenberg et al[10]. Ten children were treated sequentially with aspirin and anticoagulation. Those treated with anticoagulation for more than 1 day were considered to have been treated with anticoagulation.

Outcome was assessed at routine stroke clinic follow-up. Neurologic outcome was classified using a standardized neurologic examination scale, the Pediatric Stroke Outcome Measure (PSOM). The examining neurologist classifies findings using the PSOM to characterize deficit type and severity[11]. Subscores are assigned in 5 domains: sensorimotor left, sensorimotor right, expressive language, receptive language, and cognition/behavior. PSOM subscores are graded 0 (no deficit), 0.5 (mild deficit that does not interfere with function), 1 (moderate deficit that interferes with function), and 2 (severe deficit with loss of function). Total PSOM score ranges from 0–10. Maximal score (10) was imputed for children who died.

Hemorrhagic transformation analysis

Neuroimaging studies at admission and within 30 days of stroke onset were reviewed by a board-certified pediatric neuroradiologist (AV) blinded to clinical histories and clinical image interpretations. While head CT (HCT) was usually the first image performed, and MRI/MRA were obtained in most cases, additional follow-up imaging was individualized. Follow-up imaging within 30 days was obtained at the clinicians' discretion for a clinical change in the patient's status. Presence of hemorrhage was evaluated on all CT and MRI studies. When obtained at our study site, CT imaging was performed on 16- or 64- detector CT scanners (Siemens, Erlangen, Germany), and MRI was performed on 1.5 or 3 Tesla magnets (Siemens). MRI sequences utilized T1-weighted, T2-weighted, fluid attenuation inversion recovery (FLAIR), T2* gradient echo susceptibility, EPI-SE-T2 (B0 images of diffusion-weighted imaging), and susceptibility-weighted imaging (SWI).

Hemorrhage was identified on noncontrast head CT as areas of hyperdensity. Effort was made to distinguish calcification and islands of non-infarcted tissue at the margins. On MRI, T1-weighted, T2-weighted, and FLAIR images were scrutinized for hyperacute, acute or subacute blood products based on known signal characteristics. Areas of hypointensity on T2* gradient echo, EPI-SE-T2, and SWI were also examined for hemorrhage.

HT was classified by the method used in the European Cooperative Acute Stroke Study I (ECASS I)[12], illustrated in Figure 1. ECASS HT subtypes include punctate petechial without space-occupying effect [HI1], confluent petechial [HI2], small parenchymal (≤ 30% infarcted area with mild mass effect) [PH1], or large parenchymal (>30% infarcted area with significant mass effect or hemorrhage remote from stroke location) [PH2].

Infarct Volume

Infarct volume measurements were performed on supratentorial strokes. Infarct volume and supratentorial brain volume (SBV) were measured on axial T2 MRI. Stroke volume was expressed as percent of SBV (excluding ventricular volume) to account for varying head size during development[13]. Volumes were measured by manual segmentation tracing using ITK-SNAP (www.itksnap.org)[14]. Infratentorial infarcts were not analyzed with these methods because studies have shown infarct volume for strokes involving the brainstem or cerebellum has limited association with symptoms[15].

Symptomatic HT

Children with HT were considered symptomatic if neurological symptoms were attributable to the HT including worsening neurological deficits, new neurological deficits, headache, or new-onset seizures.

Statistical analysis

STATA version 10.1 (Stata Corporation, College Station, TX) was used for all analyses. Fisher's exact test and relative risk (RR) with 95% exact confidence intervals were used to evaluate associations of HT with stroke risk factors and treatment. Multivariable logistic regression analysis was not performed due to small sample size. Wilcoxon rank-sum test was used to determine whether age and PSOM scores differed between those with and without HT. Analysis of the relationship between outcome (PSOM scores) and HT was adjusted for infarct volume for the subset of children with supratentorial stroke. Generalized ordinal logistic regression was used to evaluate the relationship between PSOM scores (categorized 0–1, 1.5–3, 3.5–6, 6.5–10) and infarct volume, HT, age, and duration of follow-up. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patient demographics

Sixty-three children [44 males (70%), 19 females (30%)] with AIS met inclusion criteria for this study. Median age at presentation was 5.7 years [interquartile range (IQR) 1.3–13.2 years]. Race and ethnicity were 43 (68%) white non-Hispanic, 15 (24%) black, 3 (5%) Hispanic, and 2 (3%) mixed race.

Stroke characteristics and risk factors

Stroke location by vascular territory is described in Figure 2. Strokes involved anterior circulation in 37 cases (59%), posterior circulation in 17 cases (27%), and both in 9 cases (14%). The most common primary risk factors for stroke in this cohort were vasculopathy (19 patients, 30%), cardiac conditions (17 patients, 27%), and thrombophilia (18 patients, 29%) (Table 1).

Imaging Timing and Modalities

Timing and modality of imaging varied widely in this cohort, dictated by variations in patient presentation and imaging availability in the facility of initial presentation. Thirty-two of 63 (51%) children presented directly to our tertiary care center. Inhospital stroke occurred in 23 (37%). Median time to the first image was 6.4 hours (IQR 3.0–22.7 hours). The first image was HCT in 49 cases (78%). MRI was performed in 61 children (97%) at a median interval from symptom onset of 26.7 hours (IQR 13.0–53.9 hours). Fifty-eight children (92%) had at least 2 images; the median number of images within 30 days of stroke was 3 (IQR 2–3).

Among 49 children with stroke confined to the supratentorial compartment, median infarct volume, expressed as percent of SBV, was 2.0% (IQR 0.4–11.6%) with a median absolute volume of 22.4 ml (IQR 4.4–106.5 ml). Graphical analysis of infarct volumes showed frequency distribution was bimodal, with an apparent threshold between two populations defined by infarction of 5% of SBV. Infarct volume was ≤ 5% of SBV in 26 (53%) and >5% in 18 (47%).

Stroke treatment

Aspirin was used in 34 of 63 (54%) children, systemic anticoagulation in 23 (36%), both in 1 (2%), and neither in 5 (8%). Children with stroke due to cardiac conditions or arterial dissection were more likely to receive anticoagulation than those without these diagnoses [65% vs. 23%; p=0.0012; RR 2.9; 95% exact confidence interval (CI) 1.5–5.5]. No child received thrombolysis.

Hemorrhagic transformation of AIS

HT occurred in 19 children (30%; 95%CI 19–43%) within the first 30 days from symptom onset. Median time interval from stroke symptom onset to discovery of HT was 3.7 days (IQR 1–13.7 days). Of the 23 subjects imaged within 4.5 hours of symptom onset, only 1 (4%) had HT on initial scan. HT was discovered in 3/35 subjects (9%) imaged at 4.5–24 hours from symptom onset, 3/27 (11%) imaged at 24–48 hours, 1/8 (13%) imaged at 48–72 hours, 3/23 (13%) imaged at 72 hours-7 days, 8/23 (35%) imaged at greater than 7 days. Two of 19 children with HT were considered symptomatic: one had worsened focal deficits (dysarthria and hemiparesis) associated with punctuate petechial HT (HI1) in the pons; one had severe refractory headache associated with small parenchymal HT (PH1). Among 3 children with HT on initial scan, all were HI1. Among 16 children with HT on subsequent scans, 11 were classified HI1, 2 as HI2, 2 as PH1, and 1 as PH2. The single patient with PH2 had meningitis, developing petechial hemorrhage outside the stroke area. Three children had worsening HT on subsequent scans, all from HI1 to HI2. The median number of images in children without HT was 2 (IQR 2–3); the median number of images in children with HT was 4 (IQR 3–5, p=0.0002 rank-sum).

Table 2 presents analyses of factors associated with HT. HT was associated with larger infarct volumes. Median infarct volume was 10.8% of SBV (IQR 5.0–17.0%) in children with HT compared to 1.3% (IQR 0.4–6.3%) in those without HT (p=0.0084, rank-sum). In 35 subjects with isolated MCA infarction, 0/6 with pure subcortical strokes had HT, 3/18 (17%) with pure cortical stroke had HT, and 5/11 (45%) with strokes affecting the cortical and subcortical structures had HT. However, location was highly correlated with infarct size (p=0.035). Median age at presentation of children with HT was 2.8 years (IQR 1.1–16.1 years) and without HT was 6.3 years (IQR 1.8–12.6 years), but this difference was not statistically significant(p=0.82 rank-sum). The risk of HT was not associated with antithrombotic treatment group. Ten children in the AC treatment group were treated sequentially with aspirin and anticoagulation, of which 2 had HT identified while on AC for greater than 10 days. Blood pressure data were available at admission in 61/63 patients (97%). BP was normal for age and sex in 41 patients (67%), was mildly elevated in 7 (12%), and was moderately elevated in 13 (21%). The highest absolute BP in any patient was 145/97 in a 16-year-old. BP at admission was not associated with HT (Table 2).

In bivariable analysis of stroke risk factors, vasculopathy was associated with lower risk of HT (RR 0.27; 95% exact CI 0.07–1.06; p=0.04). A trend for increased risk of HT in children with cardiac conditions (RR 1.97; 95%CI 0.96–4.05; p=0.12) and meningitis (RR 2.77; 95%CI 1.37–5.59; p=0.08) existed, though not statistically significant.

HT and Outcome

Follow-up information was available in 59/63 patients (94%) and was missing in 1 child with HT and in 3 without HT. Median time to follow-up was 13.1 months (IQR 7.5–21.6 months). In the entire cohort, the median PSOM score in children with HT was 3 (IQR 1.5 to 6), significantly worse than in those without HT whose median PSOM score was 1 (IQR . 5 to 3) (p=0.0024 rank-sum) (Figure 3A).

Analyses accounting for infarct volume were performed in 41/49 children with supratentorial stroke in whom both PSOM and infarct volume were available. Median PSOM score in children with HT was 3.5 (IQR 1.5–6), significantly worse than in those without HT whose median score was 1.25 (IQR 0.5–3) (p=0.0054 rank-sum) (Figure 3B). Increasing PSOM scores correlated with increasing ECASS grades of HT (OR 2.0 per grade; 95%CI 1.0–4.0; p=0.04). Median PSOM was 1.5 (IQR 0.5–2.5) in children with infarct volume <5% SBV and 4 (IQR 1.5–6) in those with infarct volume ≥ 5% SBV (p=0.0027 rank-sum). In multivariable analysis adjusted for duration of follow-up, worse PSOM scores were associated with infarct volume ≥5% of total SBV (OR 4.0; 95%CI 1.1–15; p=0.04). Trends existed toward association of worse PSOM scores with hemorrhagic transformation of the infarction (OR 4.0; 95%CI 0.9–18; p=0.07) and with age (OR 0.90 per year; 95%CI 0.81–1.01; p=0.07).

Discussion

In this cohort, 30% (95%CI 19–43%) of children with acute AIS had evidence of HT within 30 days. In ECASS II, 39.6% of adult AIS patients in the placebo arm had HT within 7 days, but they were imaged using a standardized protocol[16]. Since our study was retrospective and observational, it is possible additional children who were not reimaged had asymptomatic HT. This limitation is highlighted by the finding that children with HT had more images than children without HT even though only 2 had symptomatic hemorrhage. However, our systematic, blinded review of all available imaging minimized bias in detection of HT. In our patients, 84% of HT was petechial, comparable to the 92% found in ECASS II placebo patients. Only PH2 hemorrhage is associated with worse outcome in adults[12], and most symptomatic adult HT is PH2. However, with only 2 symptomatic HTs in our cohort, it was not possible to determine risk factors for symptomatic HT. Even with only 3 PHs, a trend (p=0.07) existed toward worse outcome in patients with HT in multivariable analysis, suggesting that even clinically silent HTs may impact long-term recovery and function in children. Similarly, asymptomatic hemorrhage has been associated with worse outcome in adults after thrombolysis[17].

We analyzed factors predicting timing and occurrence of HT in children, since these have not been previously evaluated. Of 23 children imaged within 4.5 hours of symptom onset, only 1 had HT on initial scan, suggesting that few patients would be excluded from thrombolysis and antithrombotic treatment trials due to hemorrhage. We identified 40% of the HT at greater than 72 hours from stroke symptom onset. However, we cannot ascertain the exact timing of occurrence of HT due to the observational nature of our study. Information about prevalence of different ECASS HT grades will be important when examining potential adverse effects in any antithrombotic or thrombolysis trial. Systemic anticoagulation was not significantly associated with HT in this study, though we had limited power to detect associations or to adjust for potential confounders. For example, children with arterial dissection or a cardioembolic source were more likely to receive anticoagulation, potentially confounding any treatment association with HT. Moreover, in this selected population clinicians may have made treatment choices with antiplatelet, anticoagulant, or neither therapy because of perceived risk for HT based on clinical or radiographic data. Such confounding by indication would likely underestimate the risks of

anticoagulation. An adequately powered randomized treatment trial comparing antiplatelet therapy to anticoagulation is needed to definitively identify treatment associations with HT. Blood pressure on admission was also not associated with the risk of HT. Reduced risk for HT was seen with vasculopathy compared to other stroke risk factors, but the strength of this association is uncertain due to the small size and observational nature of our study. These preliminary findings warrant further investigation to clarify the role of stroke subtype as a risk factor in the course and pathogenesis of HT. A limitation of our study is inability to control for initial clinical stroke severity, a risk factor for HT in adults[18]. Presently, no validated method exists to estimate the Pediatric NIH Stroke Scale score retrospectively from narrative neurological examinations. Additional studies evaluating this variable are needed.

This is the first pediatric cohort in which a relationship between supratentorial stroke volume and HT has been established, a well-known finding in adult stroke[16, 18]. While the ECASS classification for HT has not been previously used in children, in unadjusted analysis, increasing HT grade was associated with worse outcome on a validated measurement tool (PSOM) in the current study. In multivariable analysis, HT was not an independent risk factor for worse outcome. However, the study sample was small, and the p-value of 0.07 suggests further study of HT as an independent predictor of neurological outcome should be investigated in a larger cohort. Furthermore, infarct volume ≥ 5% SBV was associated with worse outcome in children with supratentorial strokes. This expands the findings of Ganesan et al who demonstrated that infarct volume >10% supratentorial intracranial volume is associated with worse outcome in children with MCA stroke[13]. This study provides hypothesis-generating information on risk factors for HT in children and on the relationship of HT to neurologic outcome that should be explored in larger cohorts.

Acknowledgments

We acknowledge The Children's Hospital of Philadelphia Research Institute. It has generously supported Dr. Ichord's development of the Pediatric Stroke Program at The Children's Hospital of Philadelphia as well as the development and maintenance of The Children's Hospital of Philadelphia Stroke Registry.

Funding Sources

Dr. Beslow is supported by grants from the NIH (T32-NS007413) and from the L. Morton Morley Funds of The Philadelphia Foundation.

Dr. Smith is supported by a grant from the National Institute of Neurological Disorders and Stroke (K12-NS049453).

Dr. Licht is supported by grants from the National Institute of Neurological Disorders and Stroke (K23-NS52380), Dana Foundation and the June and Steve Wolfson Family Fund for Neurological Research.

Dr. Cucchiara is supported by the Clinical and Translational Science Award. The project described was supported by Grant Number TL1RR024133 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Dr. Ichord is supported by grants from the NIH (R01-NS050488, K23-NS062110).

References

1. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: Ethnic and gender disparities. Neurology. 2003; 61:189–194. [PubMed: 12874397]
2. Low molecular weight heparinoid, org 10172 (danaparoid), and outcome after acute ischemic stroke: A randomized controlled trial. The publications committee for the trial of org 10172 in acute stroke treatment (toast) investigators. JAMA. 1998; 279:1265–1272. [PubMed: 9565006]

3. The international stroke trial (ist): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International stroke trial collaborative group. Lancet. 1997; 349:1569–1581. [PubMed: 9174558]
4. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: A double-blind randomised study. Haest study group. Heparin in acute embolic stroke trial. Lancet. 2000; 355:1205–1210. [PubMed: 10770301]
5. Monagle P, Chalmers E, Chan A, DeVeber G, Kirkham F, Massicotte P, et al. Antithrombotic therapy in neonates and children: American college of chest physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008; 133:887S–968S. [PubMed: 18574281]
6. Amlie-Lefond C, deVeber G, Chan AK, Benedict S, Bernard T, Carpenter J, et al. Use of alteplase in childhood arterial ischaemic stroke: A multicentre, observational, cohort study. Lancet Neurol. 2009; 8:530–536. [PubMed: 19423401]
7. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, 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; 39:2644–2691. [PubMed: 18635845]
8. Amlie-Lefond C, Bernard TJ, Sebire G, Friedman NR, Heyer GL, Lerner NB, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: Results of the international pediatric stroke study. Circulation. 2009; 119:1417–1423. [PubMed: 19255344]
9. Sebire G, Fullerton H, Riou E, deVeber G. Toward the definition of cerebral arteriopathies of childhood. Curr Opin Pediatr. 2004; 16:617–622. [PubMed: 15548922]
10. Goldenberg NA, Bernard TJ, Fullerton HJ, Gordon A, deVeber G. Antithrombotic treatments, outcomes, and prognostic factors in acute childhood-onset arterial ischaemic stroke: A multicentre, observational, cohort study. Lancet Neurol. 2009; 8:1120–1127. [PubMed: 19801204]
11. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol. 2000; 15:316–324. [PubMed: 10830198]
12. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: Relationships with early clinical deterioration and 3-month outcome in the european cooperative acute stroke study i (ecass i) cohort. Stroke. 1999; 30:2280–2284. [PubMed: 10548658]
13. Ganesan V, Ng V, Chong WK, Kirkham FJ, Connelly A. Lesion volume, lesion location, and outcome after middle cerebral artery territory stroke. Arch Dis Child. 1999; 81:295–300. [PubMed: 10490431]
14. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3d active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. Neuroimage. 2006; 31:1116–1128. [PubMed: 16545965]
15. Linfante I, Llinas RH, Schlaug G, Chaves C, Warach S, Caplan LR. Diffusion-weighted imaging and national institutes of health stroke scale in the acute phase of posterior-circulation stroke. Arch Neurol. 2001; 58:621–628. [PubMed: 11295993]
16. Larrue V, von Kummer RR, Muller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: A secondary analysis of the european-australasian acute stroke study (ecass ii). Stroke. 2001; 32:438–441. [PubMed: 11157179]
17. Dzialowski I, Pexman JH, Barber PA, Demchuk AM, Buchan AM, Hill MD. Asymptomatic hemorrhage after thrombolysis may not be benign: Prognosis by hemorrhage type in the canadian alteplase for stroke effectiveness study registry. Stroke. 2007; 38:75–79. [PubMed: 17122437]
18. Larrue V, von Kummer R, del Zoppo G, Bluhmki E. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the european cooperative acute stroke study. Stroke. 1997; 28:957–960. [PubMed: 9158632]

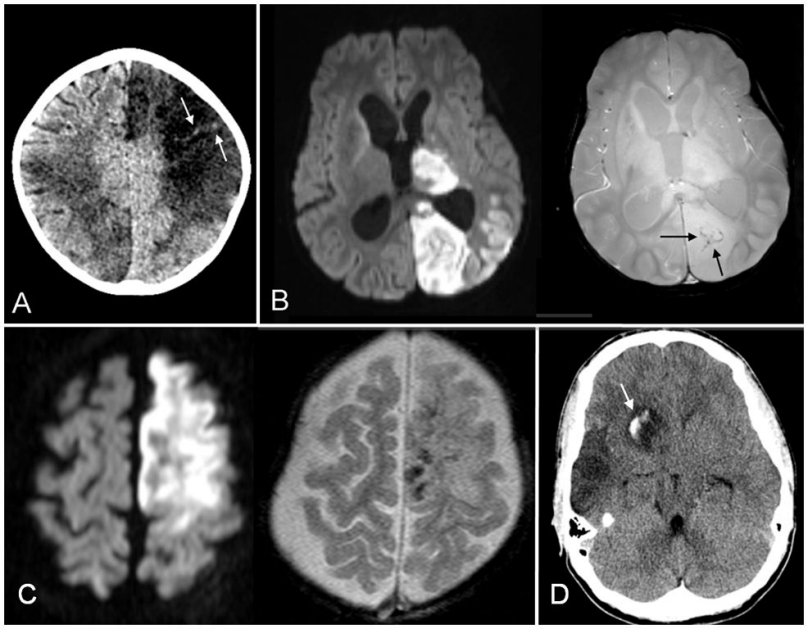

Figure 1. Examples of ECASS Classification of Hemorrhagic Transformation

A. HI1 on head CT with punctate foci of petechial hemorrhage within left frontal infarct (white arrows).

B. Diffusion-weighted MRI showing left sided infarcts (left panel). HI1 on gradient recalled echo (GRE) T2* susceptibility MRI from same patient, showing punctate foci of petechial hemorrhage within the left occipital infarct (dark arrows) (right panel).

C. Diffusion-weighted MRI showing left frontal infarct (left panel). HI2 on GRE T2* susceptibility MRI from same patient as in D, showing more confluent small foci of hemorrhage without mass effect (white arrows) (right panel).

D. PH1 on head CT showing a small hematoma with mild surrounding edema within right basal ganglia infarct (white arrow).

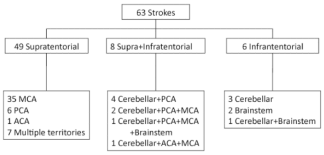

Figure 2.
Distribution of Strokes. ACA, Anterior cerebral artery; MCA, Middle cerebral artery; PCA, Posterior cerebral artery

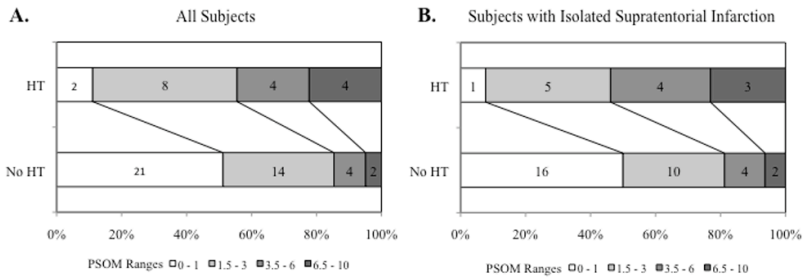

Figure 3. Distribution of Total Pediatric Stroke Outcome Measure Scores at Follow-up according to the Presence or Absence of Hemorrhagic Transformation (HT)

A. Total cohort

B. Children with isolated supratentorial infarction

Table 1

Summary of Stroke Risk Factors

Primary Stroke Risk Factor	Number of patients (%)
Vasculopathy: all	19 (30)
Focal cerebral arteriopathy	6
Moyamoya	6
Dissection	6
Vasculitis	1
Cardiac conditions	17 (27)
Intracranial tumor	8 (13)
Meningitis	4 (6)
Thrombophilia: all	18 (29)
Isolated thrombophilia, no other risk factor*	3
Thrombophilia combined with other primary risk factor**	15
Sickle cell anemia	2 (3)
Other systemic illness	2 (3)
Cryptogenic	8 (13)

* Elevated lipoprotein (a) in 3/3.

** Elevated lipoprotein (a) in 9/15; prolonged diluted Russell venom viper time and/or elevated anticardiolipin antibodies in 6/15; low protein S levels in 3/15.

Table 2

Analysis of Factors Associated with Hemorrhagic Transformation (HT)

Variable (number of cases)	Occurrence of HT	RR[§]	95% exact CI	p-value
Infarct volume (supratentorial stroke):				
<5% of SBV (26)	3 (12%)	(reference)	(reference)	(reference)
≥5% of SBV (18)	10 (56%)	4.81	1.54–15.08	0.0026
Acute antithrombotic treatment:				
Antiplatelet agent alone (34)	12 (35%)	(reference)	(reference)	(reference)
Systemic anticoagulation (24)	5 (21%)	0.6	0.2–1.5	0.26
None (5)	2 (40%)	1.1	0.4–3.6	1.00
Blood Pressure at Presentation:				
Normal (41)	12 (29%)	(reference)	(reference)	(reference)
Mildly elevated (7)	2 (29%)	0.98	0.28–3.46	0.97
Moderately elevated (13)	5 (38%)	1.31	0.57–3.03	0.73
Primary stroke risk factor:				
Vasculopathy (19)	2 (11%)	0.27	0.07–1.06	0.04*
Cardiac conditions (17)	8 (47%)	1.97	0.96–4.05	0.12
Cryptogenic (8)	1 (13%)	0.38	0.06–2.48	0.42
Tumor-related (8)	4 (50%)	1.83	0.81–4.15	0.23
Meningitis (4)	3 (75%)	2.77	1.37–5.59	0.08
Isolated thrombophilia (3)	1 (33%)	1.11	0.21–5.76	1.00
Sickle cell anemia (2)	0 (0%)	…	…	1.00
Other Systemic Disease (2)	0 (0%)	…	…	1.00

RR relative risk; CI confidence interval; TBV total brain volume

[§]Analysis of RR for primary stroke risk factors reflects comparison of each individual factor to all others in bivariable analysis.

*Although the p-value for this association is significant, the 95% CI includes 1 since the CI for the RR is extremely sensitive to small numbers