Pediatric Neurology 95 (2019) 26–33

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Hemorrhagic Transformation of Arterial Ischemic and Venous Stroke in Children

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ARTICLE INFO

Article history:
Received 30 November 2018
Accepted 31 January 2019
Available online 8 February 2019

Keywords:
Hemorrhage
Stroke
Arterial
Venous

ABSTRACT

Hemorrhagic transformation can complicate both arterial ischemic stroke and cerebral sinus venous thrombosis. Risk factors for hemorrhagic transformation after adult arterial ischemic stroke include larger infarct volume, cardioembolic stroke, and anticoagulation in the acute period. Large hemorrhagic transformation in adults is associated with poor outcome. Therefore hemorrhagic transformation is used as a safety end point for most arterial ischemic stroke acute treatment and secondary prevention trials. Up to 30% of children with arterial ischemic stroke have hemorrhagic transformation, most of which are petechial. As in adults, large infarct size is the greatest predictor of hemorrhagic transformation, but in children, acute anticoagulation is not a clear predictor of hemorrhage. As use of acute endovascular interventions for arterial ischemic stroke has expanded in adults, these therapies have also been used in some teenagers and even younger children. More information, including safety data with end points like hemorrhagic transformation, is needed in the pediatric population. In adults with cerebral sinus venous thrombosis, including those with hemorrhagic transformation, acute anticoagulation is associated with better outcomes and is the standard of care. Some hemorrhagic transformation may be evident at baseline in over half of children and neonates with cerebral sinus venous thrombosis. Anticoagulation-associated hemorrhage in pediatric cerebral sinus venous thrombosis occurs in about 10% of children but is not clearly related to outcome, whereas lack of anticoagulation may be associated with clot propagation and worse outcomes. This review provides background on hemorrhagic transformation of ischemic stroke in adults and summarizes literature regarding hemorrhagic transformation of pediatric arterial ischemic stroke and cerebral sinus venous thrombosis, with a focus on implications for acute treatment and outcome.

Introduction

Ischemic stroke, which includes arterial ischemic stroke (AIS) and cerebral sinus venous thrombosis (CSVT), can be complicated by hemorrhagic transformation. Hemorrhagic transformation can occur spontaneously in infarcted tissue or as a complication of acute thrombolytic and antithrombotic therapies like antiplatelet and anticoagulation agents. Hemorrhagic transformation can be associated with worse outcomes in adults and has been a major safety end point in adult acute treatment and secondary prevention trials.[1–4]

Childhood ischemic stroke affects 1.2 to 2.4 per 100,000 children per year in developed countries,[5–9] but there are limited data about hemorrhagic transformation in the pediatric population. Here we review the pediatric literature on hemorrhagic transformation following AIS and CSVT in the context of the adult literature and with a focus on implications for treatment and impact on outcomes. AIS and CSVT are discussed separately.

Acute arterial ischemic stroke

Hemorrhage identification and classification

Hemorrhagic transformation can be identified on computed tomography (CT) or magnetic resonance imaging (MRI). On noncontrast CT, hemorrhage appears hyperdense. Distinction must be made between areas of calcification and islands of noninfarcted

Conflict of interest and source of funding statement: None.
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https://doi.org/10.1016/j.pediatrneurol.2019.01.023
0887-8994/

tissue at the margins of the stroke.[10–12] On MRI, known signal characteristics of blood on T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences can be used to identify blood products of various ages (Table 1). T2* gradient echo and susceptibility-weighted sequences are the most sensitive for detecting intraparenchymal blood. Hemorrhage appears hypointense on T2* gradient echo, echoplanar spin echo T2, and susceptibility-weighted imaging.[10–12]

Hemorrhagic transformation must sometimes be distinguished from primary intracerebral hemorrhage (ICH). Hemorrhagic transformation of AIS is usually easily distinguished from primary hemorrhagic stroke because hemorrhagic transformation typically occurs within a larger area of infarcted tissue that corresponds to a vascular distribution on diffusion-weighted imaging (DWI). However, it is possible for large hemorrhagic transformations to occur at the time of acute infarction, particularly if a patient has a coagulopathy or is pharmacologically anticoagulated. Furthermore, primary hemorrhages can be in vascular territories with a rim of restricted diffusion. Therefore it is not always possible to firmly differentiate between a primary hemorrhagic stroke and an acute hemorrhagic transformation of an AIS. In cases in which the primary process is unclear, careful history, evaluation of stroke risk factors, examination of DWI and apparent diffusion coefficient maps, and follow-up imaging may assist in determining the primary process. Finally, CSVT can have hemorrhagic transformation at presentation, and hemorrhage is often more easily recognized on CT than the CSVT itself. Careful examination of the venous sinuses with T1-weighted postcontrast MRI and magnetic resonance venogram can establish an underlying CSVT accompanied by hemorrhagic transformation in children with risk factors for CSVT.

To differentiate hemorrhages of different severity with possibly varied impacts on neurological outcome after AIS, adult hemorrhagic transformation has been classified as follows (Table 2): (1) hemorrhagic infarction (HI), subclassified as HI1 (Fig 1B), petechial hemorrhage without space-occupying effect, and HI2, more confluent petechial hemorrhage, and (2) parenchymal hematoma (PH), subclassified as PH1 (Fig 1D), hemorrhage in ≤30% infarcted area with mild mass effect, and PH2, large parenchymal hemorrhage affecting more than 30% of the infarcted area with significant mass effect or hemorrhage remote from the stroke location.[13] Figure 1 includes examples of HI1 and PH1 hemorrhagic transformation. PH2 has been associated with neurological deterioration and three-month mortality.[13] Childhood AIS studies have largely adopted this adult classification.[10,14]

Hemorrhagic transformation of AIS in the absence of thrombolytic or revascularization therapy

Adults

In adults, risk factors for hemorrhagic transformation of AIS include cardioembolic etiology, greater severity of neurological deficit on admission (mean National Institutes of Health Stroke Scale [NIHSS] score 9.9 [hemorrhagic transformation] versus 5.9 [no hemorrhagic transformation]; $P = 0.003$),[15] altered consciousness at presentation, infarct size, territorial infarction (88% [hemorrhagic transformation] versus 58.8% [no hemorrhagic transformation]; $P = 0.007$),[15] mass effect on initial head CT scan, and contrast enhancement of infarction on head CT scan.[15,16] The International Stroke Trial was a multicenter randomized trial that included 19,435 patients to assess the safety and efficacy of antithrombotic therapy for secondary prevention after adult AIS.[4] Patients received subcutaneous heparin within 48 hours of infarction or "avoided heparin." This trial was completed alongside a trial of acute aspirin therapy, so half of the patients in each group also received aspirin. Treatment with heparin resulted in significantly fewer recurrent ischemic strokes within 14 days of initial stroke (2.9% [heparin] versus 3.8% [no heparin], $P = 0.005$, 9 ischemic strokes prevented per 1000 treated); however, this benefit was negated by an increased rate of hemorrhagic transformation in patients receiving heparin (1.2% [heparin] versus 0.4% [no heparin], $P < 0.00001$; 8 additional hemorrhagic strokes per 1000 treated). Patients treated with aspirin also had significantly fewer recurrent ischemic strokes within 14 days (2.8% [aspirin] versus 3.9% [no aspirin], $P < 0.001$; 11 ischemic strokes prevented per 1000 treated), but did not have a significant increase in hemorrhagic transformation compared with patients not receiving aspirin (0.9% [aspirin] versus 0.8% [no aspirin]).[4] These results and data from other studies including the Chinese Acute Stroke Trial[3] support aspirin use and avoidance of heparin in the setting of acute adult AIS.

More recently, several direct oral anticoagulants (DOACs) have been developed for stroke prevention in adults, largely in the setting of atrial fibrillation. DOACs inhibit thrombin or activated factor X in a dose-dependent manner and include dabigatran, rivaroxaban, apixaban, and edoxaban. A meta-analysis of phase III trials of patients with atrial fibrillation who were randomized to receive warfarin (N = 29,272) or any of these four DOACs (N = 42,411) examined efficacy and safety, including risk of intracranial hemorrhage.[17] About 30% of patients in each of these trial groups had a prior transient ischemic attack (TIA) or stroke. Stroke or systemic embolic events were reduced by 19% in the DOAC group compared with the warfarin group (relative risk [RR], 0.81; 95% confidence interval [CI], 0.73 to 0.91; $P < 0.0001$). All-cause mortality was decreased in the DOAC groups (RR, 0.90; 95% CI, 0.85 to 0.95; $P = 0.0003$) when compared with the groups randomized to warfarin. Intracranial hemorrhage was also decreased in the DOAC groups (RR, 0.48; 95% CI, 0.39 to 0.59; $P < 0.0001$). This favorable risk-benefit profile has informed the clinical use of DOACs in practice for secondary stroke prevention.

Macha et al. then examined the early initiation of DOACs in patients with atrial fibrillation during their hospitalization for acute ischemic stroke or TIA.[18] This retrospective chart review of a prospective database included analysis of 243 patients who received DOACs during their hospital stay. Patients were divided into four groups: TIA or minor stroke (n = 41, DOAC started immediately), nonextensive supratentorial infarction (n = 170, DOAC started within three to five days), infratentorial infarction (n = 28, DOAC started within three to five days), and extensive supratentorial infarction (n = 4, DOAC started after one to two weeks). Of note, some patients did acutely receive thrombolysis, including 32% of patients with nonextensive supratentorial infarction (median NIHSS score 5), 17.9% of patients with infratentorial infarction (median NIHSS score 3), and 50% of patients with extensive supratentorial infarction (median NIHSS score 15). Intracranial hemorrhages occurred in the nonextensive supratentorial infarction group (two with asymptomatic HI,

TABLE 1.
Hemorrhage Characteristics Compared with Surrounding Parenchyma on T1- and T2-Weighted/FLAIR MRI

Time After Hemorrhage	T1-Weighted	T2-Weighted/FLAIR
<12 hr	Isointense	Hyperintense
1-3 d	Isointense	Hypointense
3-7 d	Hyperintense	Hypointense
7-14 d	Hyperintense	Hyperintense

Abbreviations:
FLAIR = Fluid-attenuated inversion recovery
MRI = Magnetic resonance imaging

TABLE 2.
Classification Scheme for Hemorrhagic Transformation of Arterial Ischemic Stroke[13]

Hemorrhagic infarction (HI): Petechial hemorrhage without space-occupying effect
HI1: Small petechiae
HI2: Confluent petechiae
Parenchymal hematoma (PH): Hemorrhage with mass effect
PH1: Hemorrhage in ≤30% infarcted area with mild mass effect
PH2: Large parenchymal hemorrhage affecting more than 30% of infarcted area with significant mass effect or hemorrhage remote from stroke location

one with symptomatic PH2). The authors concluded that increased safety concerns were not observed after the early initiation of DOACs in the in-patient setting after TIA or stroke.

Current guidelines published in 2018 by the American Heart Association and the American Stroke Association[19] include initiation of aspirin in the acute setting after AIS and avoidance of empirical anticoagulation acutely. There are ongoing studies to determine the efficacy and safety of DOACs in the acute AIS setting.

Children

Few pediatric AIS studies have examined hemorrhagic transformation. Beslow et al. reviewed neuroimaging for 63 pediatric

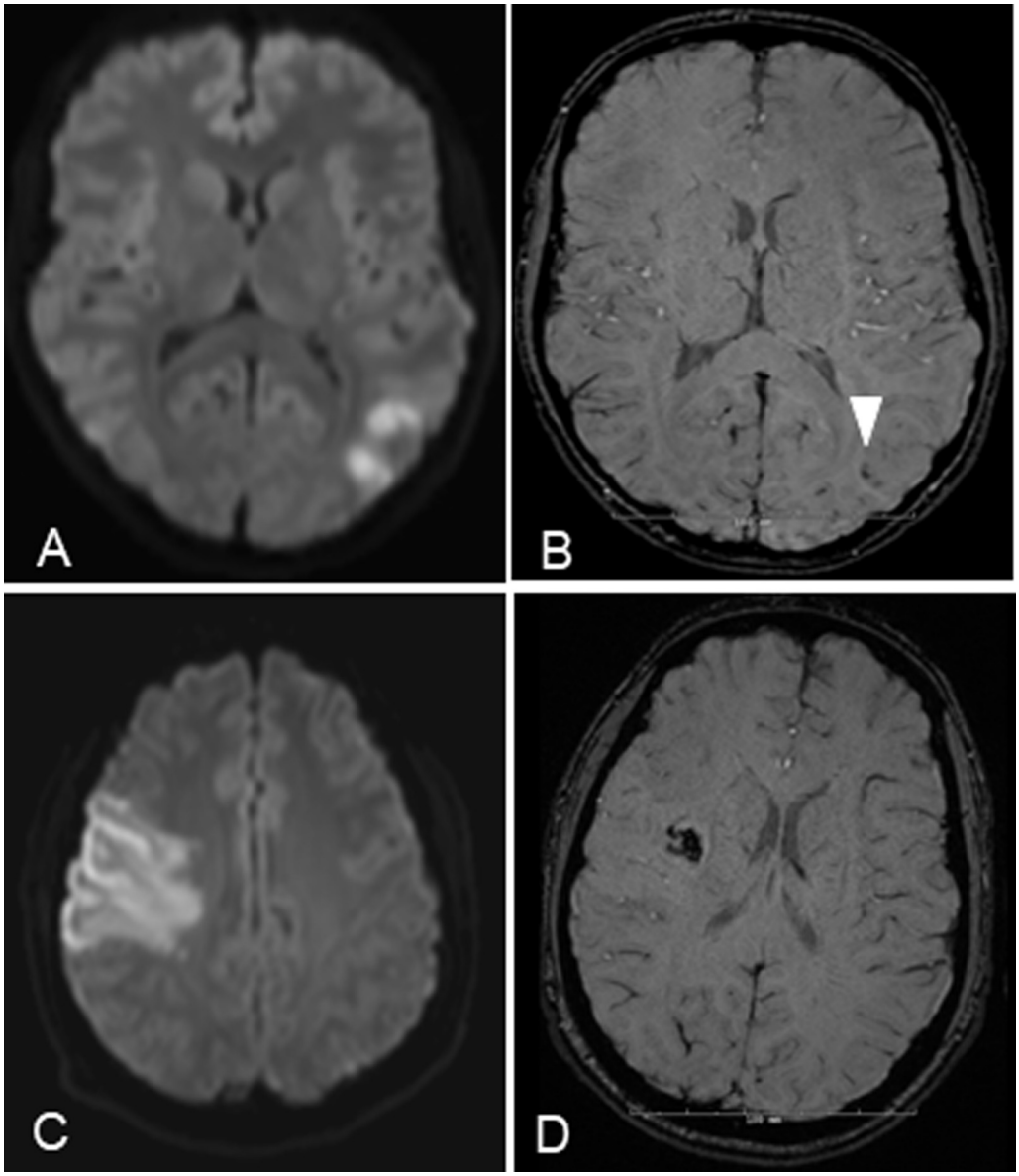

FIGURE 1. Examples of HI1 and PH1 hemorrhagic transformation. (A) Diffusion-weighted magnetic resonance imaging of a 15-year-old boy with acute infarction in the left middle cerebral artery territory who was treated with intravenous tPA. (B) Susceptibility-weighted imaging from the same patient as in (A) one day after presentation, now with small petechial HI1 hemorrhagic transformation (arrowhead). The area of petechial hemorrhage is hypointense. (C) Diffusion-weighted magnetic resonance imaging from a 16-year-old boy with an acute right middle cerebral artery infarction due to a mitral valve thrombus. (D) Susceptibility-weighted imaging from the same patient as in (C) six days after presentation. A confluent area of PH1 hemorrhagic transformation is noted as a hypointense region and occupies less than 30% of the infarcted area. HI1, petechial hemorrhage without space-occupying effect; PH1, hemorrhage in ≤30% infarcted area with mild mass effect; tPA, tissue plasminogen activator.

patients with AIS and found hemorrhagic transformation in 19 (30%) children within 30 days of stroke.[10] Most hemorrhages (16 of 19) were petechial (HI1 or HI2), and only two of 19 were symptomatic: one child had punctate petechial pontine hemorrhage and one child with PH1 had worsening headaches. The most common primary risk factors for acute ischemic stroke in this cohort differed from adult risk factors and included arteriopathy, cardiac conditions, and thrombophilia. Arteriopathy was associated with lower risk of hemorrhagic transformation (RR, 0.27; 95% CI, 0.07 to 1.06; $P = 0.04$). There were trends for increased risk of hemorrhagic transformation in children with cardiac conditions (RR, 1.97; 95% CI, 0.96 to 4.05; $P = 0.12$) and meningitis (RR, 2.77; 95% CI, 1.37 to 5.59; $P = 0.08$). As in adults, hemorrhagic transformation was associated with larger infarct volume: 56% of patients with supratentorial infarct volume ≥5% of the supratentorial brain volume experienced hemorrhagic transformation. The relative risk of hemorrhagic transformation in those with infarction ≥5% compared with less than 5% of supratentorial brain volume was 4.81; 95% CI, 1.54 to 15.08; $P = 0.0026$. The median infarct volume was 10.8% of the supratentorial brain volume in those with hemorrhagic transformation compared with 1.3% of the supratentorial brain volume in those without hemorrhagic transformation ($P = 0.0084$, rank sum). Not surprisingly, among those with middle cerebral artery infarction, those with infarct affecting cortical plus subcortical structures had the highest risk of hemorrhagic transformation. No patient with isolated subcortical middle cerebral artery infarction had hemorrhagic transformation, but these findings were correlated with infarct volume. Although this study was limited both by cohort size and possible confounding by indication in terms of which children were exposed to systemic anticoagulation versus antiplatelet agents, treatment with anticoagulation was not significantly associated with hemorrhagic transformation. In addition, blood pressure at the time of admission was not associated with increased risk of hemorrhagic transformation. With regard to outcome, multivariable analysis revealed a trend toward worse outcome in children with any hemorrhagic transformation ($P = 0.07$), regardless of whether the hemorrhage was symptomatic or petechial (HI) versus parenchymal (PH).[10] The finding that even petechial hemorrhages may affect outcome is in contrast to adult studies that report that most symptomatic adult hemorrhagic transformation is PH2 and that only PH2 hemorrhage is associated with worse outcomes.[13]

Among children with acute AIS, there is varied use of antithrombotic agents; a strong predictor of use of anticoagulation versus antiplatelet agents in the acute setting is geographic location with centers in the United States less likely to use anticoagulation acutely than those in Canada, Europe, or Australia. Given practice differences and the lack of clinical trial data regarding the safety and efficacy of anticoagulation versus antiplatelet therapy for acute childhood AIS, there is great interest in exploring whether anticoagulation poses an increased risk of hemorrhagic transformation. To assess the safety of acute anticoagulation in childhood AIS, Schechter et al. analyzed 198 children aged one month to 18 years with acute AIS, 123 of whom were treated with anticoagulant therapy.[14] In this cohort, the most frequent risk factors for AIS included cardiac disorders (34%) and arteriopathy (44%). The authors found that 14 (11%) children who received anticoagulation had intracranial hemorrhage; however, 12 (16%) children who did not receive anticoagulation had intracranial hemorrhage. Similar to the study by Beslow et al.,[10] most hemorrhagic transformations were petechial (HI1 or HI2) and hemorrhage risk was confined to the first four weeks after stroke. Hemorrhage rates were similar for each anticoagulation regimen, and there were five children (4%) who had symptomatic hemorrhages following anticoagulation. Radiographic findings were available for four of five patients with symptomatic hemorrhage following anticoagulation, and all four had HI1. There were no significant predictors of anticoagulation-associated intracranial hemorrhage; neither multiple infarcts nor cardiac disease was found to be a predictor of hemorrhage among the children who received anticoagulation. Among those with anticoagulation-associated hemorrhagic transformation, there was no difference in outcome among those with symptomatic versus asymptomatic hemorrhages (poor outcome in 80% [four of five] with symptomatic hemorrhagic transformation versus 78% [seven of nine] with asymptomatic hemorrhagic transformation, $P = 0.92$). Importantly, among the three children with anticoagulation-associated hemorrhagic transformation who died, none died because of the hemorrhage. However, among children who received anticoagulation, those with anticoagulation-associated hemorrhagic transformation tended to have abnormal neurological outcomes compared with children without hemorrhagic transformation (78.6% poor outcome [11 of 14] with hemorrhagic transformation versus 52.6% poor outcome without hemorrhagic transformation [50 of 95], $P = 0.068$),[14] a finding that supports those of Beslow et al.[10] Given the lack of difference between hemorrhagic transformation rates among those who were and who were not exposed to anticoagulation, the authors concluded that anticoagulation is a reasonable option in acute childhood AIS and that future clinical trials to assess the safety and efficacy of acute anticoagulation would be reasonable.[14]

Hemorrhagic transformation of AIS after thrombolysis

Adults

The efficacy and safety of acute thrombolysis with intravenous recombinant tissue plasminogen activator (tPA) in AIS was assessed in Europe and the United States. The European Cooperative Acute Stroke Study I was a large multicenter, randomized, double-blind, placebo-controlled phase III trial of patients with acute ischemic hemispheric stroke and moderate to severe neurological deficits without major early infarct signs on initial head CT scan.[1] Although, the 30-day mortality rate and overall incidence of ICHs were not different between the tPA and placebo arms, large parenchymal hemorrhages were significantly more frequent in the tPA-treated patients (6.5% of patients in the placebo arm versus 19.8% of patients in the tPA arm).[1] Fiorelli et al. utilized data from The European Cooperative Acute Stroke Study I to further investigate the outcomes of hemorrhagic transformation after intravenous tPA in AIS.[13] Among the 307 patients who received tPA, 92 (29.9%) had hemorrhagic transformation (HI1: 11, HI2: 24, PH1: 23, PH2: 34). The authors found that patients who received tPA or placebo and had PH2 class hemorrhagic transformation had increased odds of early neurological deterioration (odds ratio [OR], 32) and three-month mortality (OR, 18). In fact, about 75% patients with PH2 died by three months. Other categories of hemorrhagic transformation, including HI1, HI2, and PH1, did not increase the risk of early neurological deterioration or three-month mortality.[13] The National Institute of Neurological Disorders and Stroke tPA Stroke Study Group found that among 312 patients treated with tPA, 20 (6.4%) had symptomatic ICH within 36 hours of treatment, with 9 (2.9%) experiencing fatal hemorrhage.[2]

Hacke et al. examined the efficacy and safety of intravenous tPA administration 3 to 4.5 hours after time last known well.[20] Eight hundred twenty-one patients were randomly assigned in a double-blind fashion to receive tPA (418 patients) or placebo (403 patients). Mean time to administration of tPA was 3 hours and 59 minutes. The incidence of hemorrhagic transformation was higher in patients treated with tPA (27.0% tPA versus 17.6% placebo,

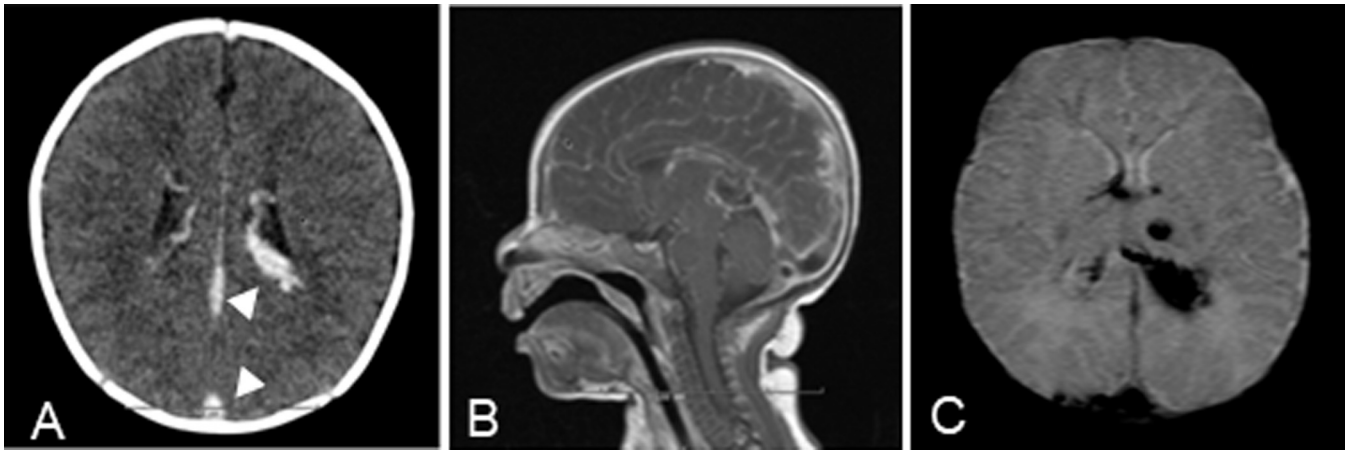

FIGURE 2. Neuroimaging in a neonate who presented with a seizure during a febrile gastroenteritis and was found to have cerebral sinus venous thrombosis with hemorrhagic transformation. (A) Head CT scan with intraventricular hemorrhage and thrombus (arrowheads) is shown. The intraventricular hemorrhage and acute clot appear as hyperdense regions in the ventricles and venous sinuses, respectively. (B) T1-weighted magnetic resonance postcontrast image shows hyperintense diffuse thrombus. (C) Gradient echo sequence shows areas of hypointense hemorrhagic transformation. CT, computed tomography.

$P = 0.001$). Symptomatic intracranial hemorrhage, defined as any hemorrhage identified as the predominant cause of neurological deterioration (NIHSS score higher by four points or more than either baseline value or the lowest value in the first seven days, or any hemorrhage leading to death), occurred more frequently in those who received tPA (2.4% tPA versus 0.2% placebo group, $P = 0.008$), whereas the incidence of death was not significantly different between the two groups (7.7% tPA versus 8.4% placebo, $P = 0.68$).[20] These findings again indicate that hemorrhagic transformation may not be a major determinant of outcome in adults.

Children

Although the risks and benefits of tPA in adult AIS have been well established through randomized, double-blind, placebo-controlled trials, there are no completed clinical trials evaluating tPA in children. Application of adult hemorrhagic transformation data to children may not be appropriate given different stroke mechanisms in children compared with adults as well as differences in coagulation and fibrinolytic pathways of children, thus altering the pharmacokinetics of the drug.[21] Amlie-Lefond and colleagues analyzed data from the International Pediatric Stroke Study, a multicenter observational cohort study of patients with AIS, and of 687 children presenting with AIS, only 15 (2%) received tPA for acute stroke treatment (nine intravenous tPA and six intra-arterial tPA).[21] Median time to administration of intravenous tPA from acute stroke symptoms was 3.3 hours (mean 10.5 hours, range 2.0 to 52.0 hours). Median time to administration of intra-arterial tPA from acute stroke symptoms was 4.5 hours (mean 8.1 hours, range 3.8 to 24.0 hours). Four patients experienced intracranial hemorrhage following tPA (two after intravenous tPA, two after intra-arterial tPA), but none was symptomatic.[21]

Overall, tPA is rarely used in children, thus leading to a paucity of data to inform clinical treatment guidelines. Therefore when considered in the pediatric population, care should be taken to follow the entrance criteria for Thrombolysis in Pediatric Stroke (TIPS), a safety and dose-finding trial of intravenous tPA for children aged two to 17 years who presented within 4.5 hours of onset of acute symptoms.[22] Due to the high frequency of stroke mimics in children and the lower pretest probability of stroke in this age group, the TIPS trial required imaging confirmation of stroke and vascular imaging with occlusion or partial occlusion in the vascular territory corresponding to symptoms. Unfortunately, of the 93 children screened, only one child was enrolled, so TIPS was closed. Therefore the risk of hemorrhagic transformation after intravenous tPA in children remains unknown.

There are currently two efforts to collect information about the safety of tPA in children, including risk of hemorrhagic transformation. The TIPS Extended Results study will collect data on all children who receive tPA or endovascular therapy at former TIPS institutions, and a primary outcome is development of symptomatic hemorrhagic transformation. The Kid Clot study in France will evaluate children who received tPA or endovascular therapy from 2014 to 2017, including information about the development of hemorrhagic transformation.

Hemorrhagic transformation of AIS after endovascular therapy

Adults

In 2015, five groundbreaking studies published in the *New England Journal of Medicine* demonstrated a benefit for endovascular thrombectomy in adults with large vessel anterior circulation occlusion within six to 12 hours of stroke onset.[23–27] The Diffusion-weighted Imaging Evaluation For Understanding Stroke Evaluation 3 (DEFUSE 3)[28] and DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN)[29] trials then provided evidence that endovascular thrombectomy can be offered up to 16 and 24 hours after symptom onset, respectively. In these seven studies, rate of symptomatic hemorrhagic transformation was an important safety outcome. In the five studies that examined endovascular therapy up to 12 hours, symptomatic hemorrhagic transformation in the treatment group ranged from 0% to 7.7%.[23–27] In the two more recent trials that examined thrombectomy up to 24 hours after symptom onset, symptomatic hemorrhages occurred in 6% to 7%.[28,29] In the DEFUSE 3 trial, which examined the safety and efficacy of thrombectomy for stroke at 6 to 16 hours, the rate of symptomatic intracranial hemorrhage was not different between the thrombectomy and control groups (7% thrombectomy versus 4% control, $P = 0.75$).[28] In the DAWN trial, which examined the safety and efficacy of thrombectomy for stroke up to 24 hours after onset, the rate of symptomatic intracranial hemorrhage was not different between the thrombectomy and control groups (6% thrombectomy versus 3% control, $P = 0.50$).[29] It

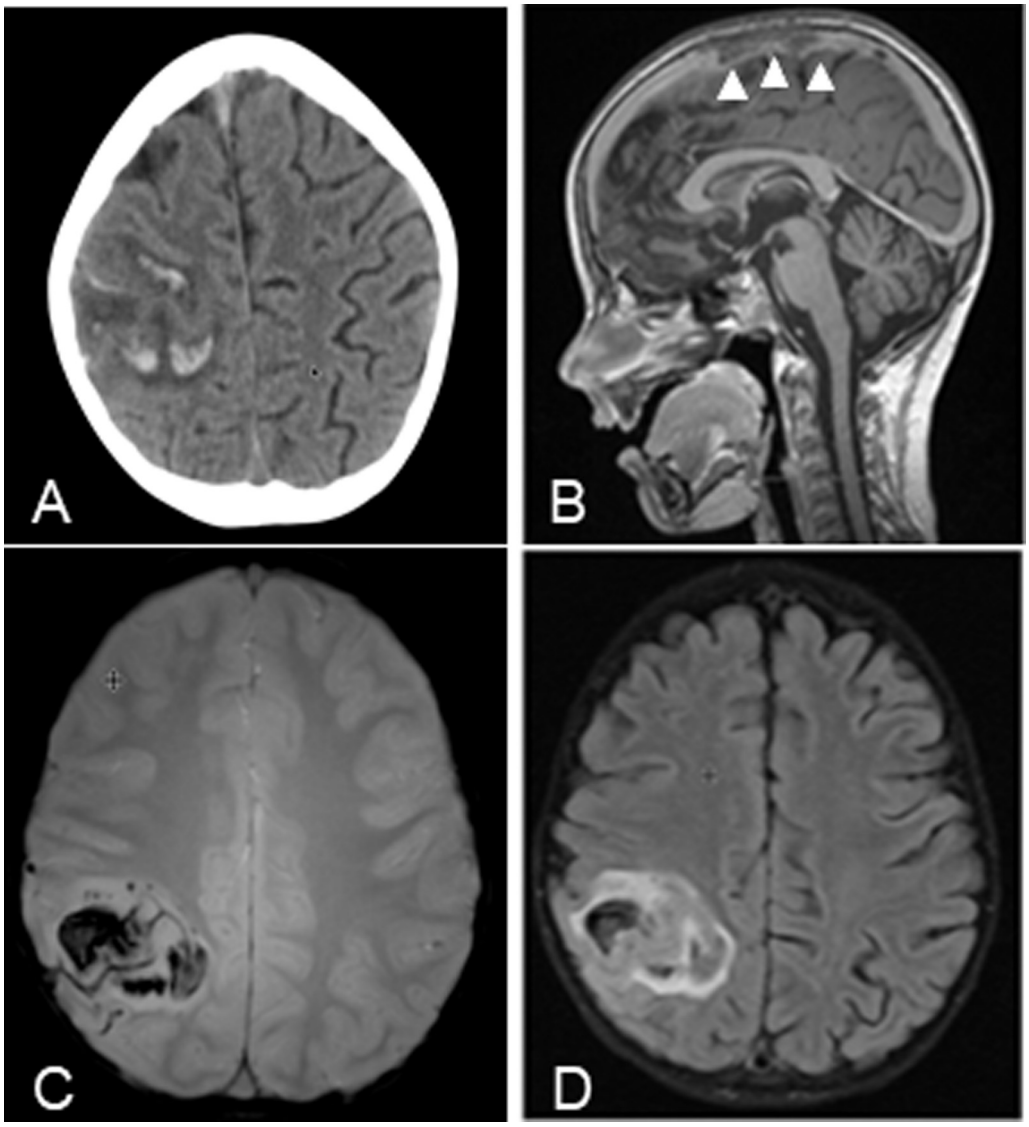

FIGURE 3. Neuroimaging in a six-year-old girl with acute lymphoblastic leukemia who presented with headache and focal seizures three weeks after treatment with pegaspargase. (A) Head CT scan shows a hyperdense area of hemorrhage in the right frontal lobe. (B) T1-weighted magnetic resonance postcontrast image demonstrates thrombus in the superior sagittal sinus (arrowheads). (C) Gradient echo sequence demonstrates the hypointense area of hemorrhage. (D) Fluid-attenuated inversion recovery sequence again demonstrates the hemorrhage as a hypointense area with a surrounding hyperintense rim of edema. CT, computed tomography.

is important to note that most patients in both the treatment and control groups of these studies received tPA.

Children

Because endovascular treatment has shown benefit in adult AIS, there is great interest in its use in children. However, given that the trials that showed benefit in adults were published in 2015 and 2018, data about endovascular therapy in children are extremely limited. In a study by Bigi et al. of 150 Swiss children who presented with AIS between 2000 and 2015 with Pediatric NIHSS $\geq$4, 16 underwent recanalization treatment. Of these 16 children, six were treated with endovascular therapy, five of whom also received intravenous or intra-arterial thrombolysis.[30] No child in the total cohort had a symptomatic ICH, and only one child (6.2%) among those who received recanalization treatment had an asymptomatic ICH. The child with hemorrhagic transformation received intravenous tPA and not mechanical thrombectomy therapy. At this time, it is unknown whether the risk of hemorrhagic transformation in children who undergo endovascular therapy for acute AIS is increased, decreased, or similar to the risk of hemorrhagic transformation in adults. As pediatric patients are considered for endovascular treatment, it is critical that information about hemorrhagic transformation be collected in a consistent manner. There are at least two studies, TIPS Extended Results and Kid Clot, which plan to collect information on the use of endovascular therapy in the pediatric population, including information about hemorrhagic transformation.

Hemorrhagic transformation of cerebral sinus venous thrombosis

Adults

Einhaupl and colleagues' landmark randomized, patient- and observer-blinded, placebo-controlled trial compared heparin with placebo for the treatment of CSVT in adults.[31] The primary end point of this study was clinical outcome. An observer who was not

aware of the treatment assignment evaluated patients daily to determine the presence of headache, focal signs, seizures, and alterations in level of consciousness. The study was expected to enroll 60 patients; however, an interim analysis after 10 patients in each group were enrolled revealed striking differences in clinical outcome between the two groups that were statistically significant ($P < 0.01$, modified Fisher's exact test). The trial was therefore stopped early. Of the patients treated with heparin, eight had complete recovery and two had slight neurological deficits after three months of treatment. In the control group, one patient recovered completely, six patients had neurological deficits, and three patients died. Furthermore, the investigators found that heparin treatment for CSVT, regardless of the presence of ICH, was beneficial. Three patients in the heparin group had ICH at presentation, and two of these patients recovered fully. The other patient with pretreatment ICH had only minimal neurological deficits. Two patients in the control group had ICH upon CSVT presentation, and an additional two patients in the control group developed ICH during the treatment phase of the study. Both patients who had ICH at presentation in the control group died. These data supported heparin treatment for CSVT, even in the setting of hemorrhagic transformation of venous infarction.[31]

To assess the effectiveness and safety of anticoagulation in the setting of CSVT further, and to examine the development of hemorrhagic transformation or extension of pre-existing hemorrhagic transformation, Coutinho and colleagues conducted a meta-analysis of randomized controlled trials that compared anticoagulant therapy with placebo or open control in patients with CSVT.[32] Only two trials qualified for inclusion: one with 20 patients[31] and the other with 59 patients.[33] Patients with hemorrhagic transformation at the time of CSVT diagnosis were included in both trials. The meta-analysis demonstrated that the absolute reduction in risk of death or dependency was 13% among those treated with anticoagulation and that no new symptomatic hemorrhages occurred in those who received anticoagulation. Although not statistically significant, improvement in clinical outcomes in patients treated with heparin for CSVT further supported international guidelines that recommend heparin for treatment of CSVT in adults, regardless of the presence of hemorrhagic transformation at presentation.[32]

Children

Extrapolation of adult data to children regarding treatment of CSVT is again problematic given the physiologic differences in systemic coagulation systems and the pathophysiology of CSVT. Moharir and colleagues reported a single-center prospective study of 162 pediatric patients with CSVT enrolled from 1992 to 2005, 99 of whom received anticoagulation (low-molecular-weight heparin or warfarin).[34] This study assessed treatment safety and outcomes. Patients with significant intracranial hemorrhage at diagnosis were excluded. Among the 83 neonates and 79 older children studied, 84 (52%) had some intracranial hemorrhage (parenchymal, intraventricular, extraparenchymal) at baseline. Of 56 with venous infarction on baseline imaging, 34 (61%) had hemorrhagic venous infarction. Among the 99 who received anticoagulation, major intracranial hemorrhage (defined as decreased hemoglobin, new symptoms, large size, or mass effect) occurred in six (6%) patients and minor ICH occurred in four (4%) patients. Of note, five of the six patients with major intracranial hemorrhage after anticoagulation had pretreatment hemorrhage. In addition, patients with major intracranial hemorrhage after anticoagulation had risk factors for hemorrhage including pretreatment ICH (five patients), supratherapeutic activated clotting time (four patients), hypertension, thrombocytopenia, ventriculoperitoneal shunt surgery with increased subdural space secondary to effusion, and cerebral atrophy predisposing to subdural hemorrhage. Overall, major intracranial hemorrhage in those who received anticoagulation was associated with the presence of intracranial hemorrhage at diagnosis ($P = 0.02$; RR, 8.8; 95% CI, 1.1 to 72.8), but not with age, number of risk factors for hemorrhage, or neurocomorbidity.[34] Of 131 patients with follow-up, outcome was unfavorable (death or deficit) in 62 (47%) patients. Notably, the outcomes of the six patients with major intracranial hemorrhage in the setting of anticoagulation treatment were similar to outcomes of other patients: three had a favorable outcome and three had an unfavorable outcome. Furthermore, Moharir et al. found a strong association between no anticoagulation use and propagation of CSVT in all patients ($P = 0.001$; RR, 5.2; CI, 1.9 to 14.2), with CSVT propagation in 17 untreated patients (31%) and only 4 treated patients (6%) among those with follow-up data available.[34]

Ichord et al. evaluated treatment and outcomes of a multicenter cohort of pediatric patients with CSVT enrolled in the International Pediatric Stroke Study from 2003 to 2007.[35] One hundred seventy patients aged one month to 19 years had a diagnosis of CSVT. Most patients, 141 of 170 (83%), received treatment (unfractionated heparin, low-molecular-weight heparin, warfarin, or aspirin). Of these 141 treated patients, 33 (23%) had ICH at the time of treatment. The authors found an association between death and nontreatment with anticoagulation with an OR of 5.2, 95% CI 1.0 to 28.[35]

These studies demonstrate that anticoagulation-related hemorrhagic transformation occurs infrequently and results in similar outcomes as in patients who do not have hemorrhagic transformation. In addition, there is risk of propagation of CSVT in untreated patients. Treatment of pediatric CSVT with anticoagulation may reduce mortality and long-term morbidity even in patients with hemorrhage. However, it is important to note that more research is needed to strengthen available evidence and to address controversies such as whether neonates with CSVT or children with significant hemorrhages should be treated with anticoagulation and whether those with thrombophilia-related CSVT require prolonged anticoagulation.[36]

Figures 2 and 3 present examples of hemorrhagic transformation of perinatal and childhood CSVT, respectively.

Conclusions

Although limited data regarding hemorrhagic transformation of arterial or venous stroke exist in children, many management decisions and concerns are informed by the knowledge of hemorrhagic transformation rates and risks in adult ischemic stroke. However, differences in risk factors and pathophysiology between adults and children may mean that certain treatments, like anticoagulation for AIS, may not have the same risk for hemorrhagic transformation in the pediatric population. Importantly, data suggest that in pediatric AIS, smaller hemorrhages may still have impact on neurological outcome. Therefore additional study is needed to elucidate any contribution of hemorrhagic transformation to neurological outcomes. If hemorrhagic transformation is related to pediatric outcomes, prevention of hemorrhagic transformation may be an additional therapeutic target. For childhood CSVT, risk of hemorrhagic transformation may be increased with clot propagation. Future large prospective cohort studies for both types of ischemic stroke in children are needed. Also, data including presence of hemorrhagic transformation, grade, and whether hemorrhagic transformation is symptomatic or not should be carefully collected for all children in

whom intravenous tPA or endovascular therapy are utilized as well as in children and neonates who do and do not receive anticoagulation for CSVT.

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