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Intravenous thrombolysis at 3.5 hours from onset of pediatric acute ischemic stroke: a case report (84 char)

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Abstract

Acute thrombolysis has a proven benefit for adults presenting with acute ischemic stroke, but data within the pediatric population is extremely limited. Herein, we report the case of a 14-year-old girl who presented with right-sided weakness and ataxia, loss of sensation and altered mental status. Magnetic resonance imaging with diffusion weighted imaging showed an acute lesion in the distribution of the left posterior cerebral artery, and magnetic resonance angiogram demonstrated occlusion of the third branch of the left posterior cerebral artery. With parental consent, clinicians decided to infuse an adult dose of weight-adjusted intravenous alteplase at 3.5 hours from onset of symptoms, with subsequent improvement in National Institutes of Health Stroke Scale from 11 to 3. Computed tomography angiogram at 24 hours showed recanalization of the occluded vessel with no evidence of intracranial hemorrhage. Stroke scale at discharge was 3, with a modified Rankin Scale (mRS) at discharge of 1 and at 90 days of 0. This case highlights the importance of magnetic resonance imaging in diagnosing pediatric acute ischemic stroke and suggests consideration of thrombolysis in select confirmed pediatric stroke cases. However, a rigorous evidence base is lacking, and clinical trials have not been successful in recruiting patients.

Keywords

pediatrics; cerebral infarction; acute ischemic stroke; thrombolysis; alteplase; emergency medicine

Introduction

Cerebrovascular disease is the 10th most common cause of death in children, with pediatric acute ischemic stroke (AIS) occurring at a rate of roughly 1 to 2 children per 100,000 per year in the United States^{1,2}. Of these estimated 1,000 annual pediatric strokes, very few receive off-label thrombolysis for emergent treatment^{3,4}. Little objective data exists in regards to the use of intravenous tissue plasminogen activator (IV tPA) for AIS outside case reports, and its use remains controversial. The evidence for endovascular therapy, whether intra-arterial thrombolysis or mechanical stent retrievers, is also limited. Though the

American Heart Association/American Stroke Association (AHA/ASA) 2015 adult guidelines endorse the use of IV tPA for adult patients who present within 4.5 hours of AIS, its latest pediatric guidelines recommended against pediatric tPA outside clinical trials^{5,6}, though there are no current prospective interventional trials to our knowledge. In 2010, the Thrombolysis in Pediatric Stroke (TIPS) consortium, funded by the National Institute for Neurologic Disorders and Stroke (NINDS), sought to rigorously study thrombolysis for pediatric stroke in a Phase II dose finding model⁷, however; the TIPS trial was closed in 2013 for lack of accrual. The International Pediatric Stroke Study (IPSS)⁸ collected data on an observational cohort of pediatric stroke patients, some of whom received thrombolysis. Herein we report a case of pediatric AIS treated with thrombolysis within 3.5 hours of symptom onset.

Case Report

A previously healthy 14-year-old female developed sudden onset weakness at home after dropping a cup of hot chocolate her mother handed her, beginning to stagger and cry. The parents were certain this was the time of onset of symptoms; however, she had been cleaning the bathroom earlier and had just awoken from a nap. Emergency medical services were immediately activated, and she presented to the emergency department 30 minutes after symptom onset. The timeline per her parents was: cleaning the bathroom at some point earlier in the day, followed by a nap of unknown duration, followed by waking up neurologically intact, followed by her mother handing her the cup and her dropping it, staggering and crying (the onset of symptoms) and activation of the EMS system. Thirty minutes later she arrived in the emergency department, the work up of MRI/MRA, labs (all normal), EKG (NSR), and multiple specialist consultations took place over the next three hours followed by the start of tPA bolus at 3 hours and 30 minutes from stroke onset.

Triage had noted chemical exposure to bathroom cleaners and altered mental status. The patient did not take birth control pills or smoke. She was afebrile with an initial blood pressure of 143/85, mild tachycardia, normal respirations, normal oxygen saturation and normal glucose. She was disoriented to time and displayed some left-right confusion. Moderate weakness of the right upper and lower extremity was noted along with severe ataxia and decreased sensation in these limbs. Estimated NIHSS at this time was 11, (1 point for LOC, 2 for month and age, 1 for blink eyes/squeeze hand, 1 for right arm motor, 2 for right leg motor, 2 for limb ataxia, 2 for sensation). Unilateral symptoms made toxic encephalopathy unlikely, but other cerebral lesions were much more common than acute ischemic stroke (AIS) in this clinical scenario.

After her parents arrived to confirm the history and time of onset, the patient was taken directly to the MRI suite for MRI/MRA, and images were reviewed by the emergency physician, neuroradiologist, stroke neurologist and pediatric neurologist. Diffusion Weighted Imaging (DWI) (Fig. 1) showed an acute infarct in the left posterior cerebral artery (PCA) distribution (thalamus, medial temporal lobe), while T1 and T2 images (Fig. 2) were normal, suggesting an early stroke. The MRA showed occlusion of the left third branch of the PCA (P3) and a distal cortical branch (Fig. 3), and there was no vertebrobasilar or carotid dissection. With parental consent, clinicians administered IV tPA at the standard adult dose

of 0.9 mg/kg divided into a bolus and one hour infusion beginning at 3.5 hours from symptom onset. Within hours, the patient showed improvement in motor and sensory function, with next-day computed tomography angiogram (CTA) (Figs. 4–6) showing recanalization of the occluded vessel and confirming no apparent dissection. Her functional status continued to improve, though her NIHSS at discharge stayed at 3 for right upper extremity symptoms of weakness, decreased sensation and ataxia (an mRS of 1). Post-stroke workup including cardiac telemetry, echocardiogram with bubble study, hypercoagulability panels, and CTA yielded no identifiable etiology, thus making this a “cryptogenic” stroke.

She was discharged on two 81 mg aspirin per day and routine physical therapy for 6 months. At 90 days she had no residual symptoms (mRS 0), was fully able to jump rope, run, ride a bicycle and write clearly with her right (dominant) hand.

Discussion

The case illustrates the benefits of increased pediatric stroke recognition, the importance of MRI and preparedness to give tPA in select cases, but the evidence base is sparse. The IPSS cohort included 687 children with AIS enrolled from 2003–2007, 15 of whom received acute thrombolysis. None of the thrombolized patients experienced death or symptomatic intracranial hemorrhage⁸. The later prospective TIPS trial had strict inclusion and exclusion criteria for thrombolysis⁷. Though it was discontinued due to insufficient patient accrual (one patient enrolled), the 30 participating facilities developed pediatric primary stroke center capacities in the formation of stroke teams, stroke alerts, stroke order sets, and tPA protocols⁹. The inclusion and exclusion criteria from TIPS were consulted in the decision to give IV tPA in this case.

Though the 2015 AHA/ASA guidelines recommend CT or CTA alone as sufficient grounds for thrombolysis in adults, the TIPS study importantly included MRI as a confirmatory measure in acute pediatric stroke^{5,9}. While a sudden onset hemiparesis in an adult with a normal non-contrast CT might reasonably be assumed to be AIS, the same is not true for a child in which other etiologies and stroke mimics, e.g. complex migraine, are much more common. Indeed, pediatric guidelines now recommend bypassing CT and going directly to MRI in suspected stroke^{10,11}.

MRI may prove a powerful tool not only in confirming acute pediatric stroke, but also in managing strokes with unknown time of onset. The MR WITNESS study, a recently completed phase IIa investigation, tested the safety of MRI as a surrogate for time in patients with unwitnessed or “wake-up” strokes for thrombolysis eligibility¹². The MRI in this case, showing a lesion on DWI but a normal T2 FLAIR provided further support that the stroke was early and thus safe for thrombolysis. The report from parents that she had awoken from a nap just before symptom onset had created some concern for the accuracy of the timing of the AIS, but the treating team decided based on the totality of the data that this was not a “wake up” stroke.

Greater preparedness might improve outcomes for pediatric AIS^{13,14}. Ideally, this would require the coordination of a pediatric stroke team, including stroke fellow and attending

physician, pharmacist, critical care physician, neuroradiologist, and anesthesiologist^{10,11}. However, this degree of preparedness for such a relatively rare event is uncommon in pediatric medical centers. In our case, the emergency physician coordinated management with a pediatric neurologist, adult stroke neurologist, pharmacist, critical care physician, and radiologist in order to administer the first dose of tPA ever given to a child for AIS at our facility.

Many questions remain regarding the use of tPA for AIS in children. Pediatric patients may require higher relative doses of tPA as compared to adults. Like the few other cases in the literature on pediatric thrombolysis, we elected to infuse at a standard adult dose. It has been theorized, however, that higher plasminogen activator inhibitor-1 levels, lower tPA levels, an increased volume of distribution, and more rapid hepatic clearance in children combine to support a higher dose of tPA in pediatric AIS^{13–15}. The TIPS trial had been designed to collect data on this question.

This case illustrates the challenges of identifying and treating pediatric AIS, the limited evidence upon which to base clinical decisions and the importance of MRI in confirming the diagnosis. The case suggests select pediatric AIS cases may benefit from tPA, but the therapy is unproven and rigorous evidence will likely remain elusive.

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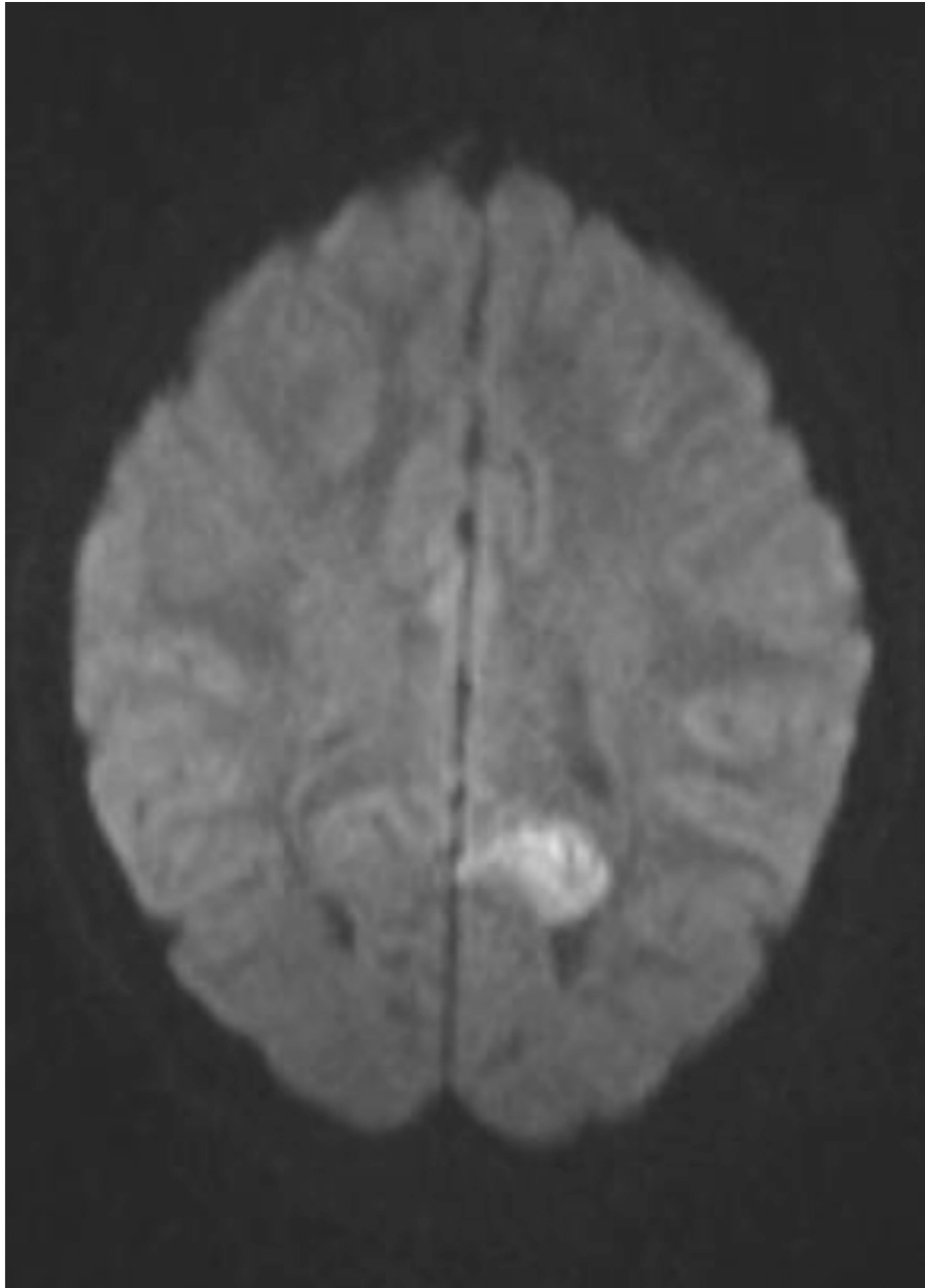


Fig. 1. MRI/DWI of brain showing hyperintense-signal along the parietal and occipital lobe distributions of the third branch of the right Posterior Cerebral Artery (P3).

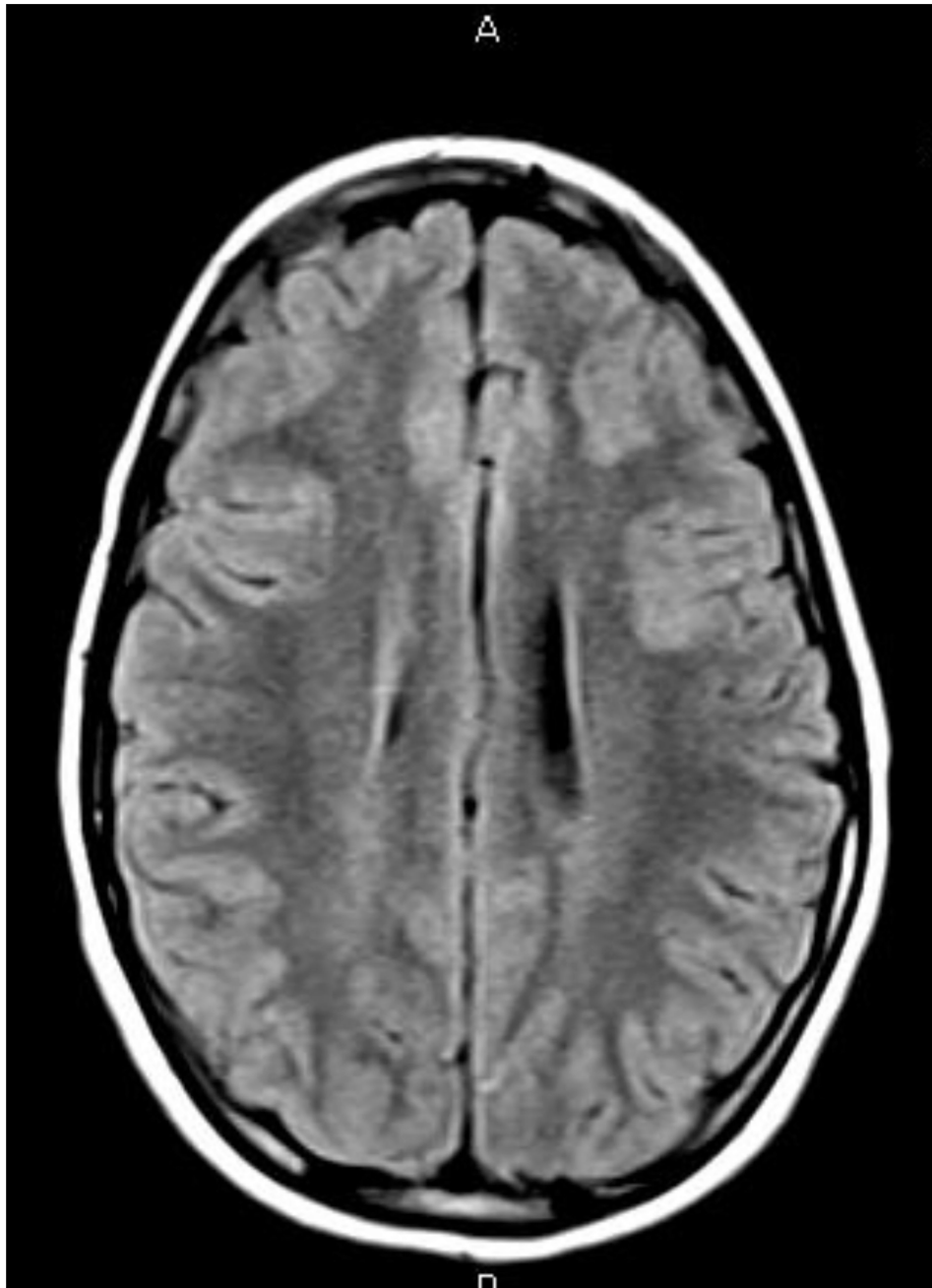


Fig. 2. MRI/T2 FLAIR showing no lesion, which along with the DWI image supports early acute ischemic stroke.

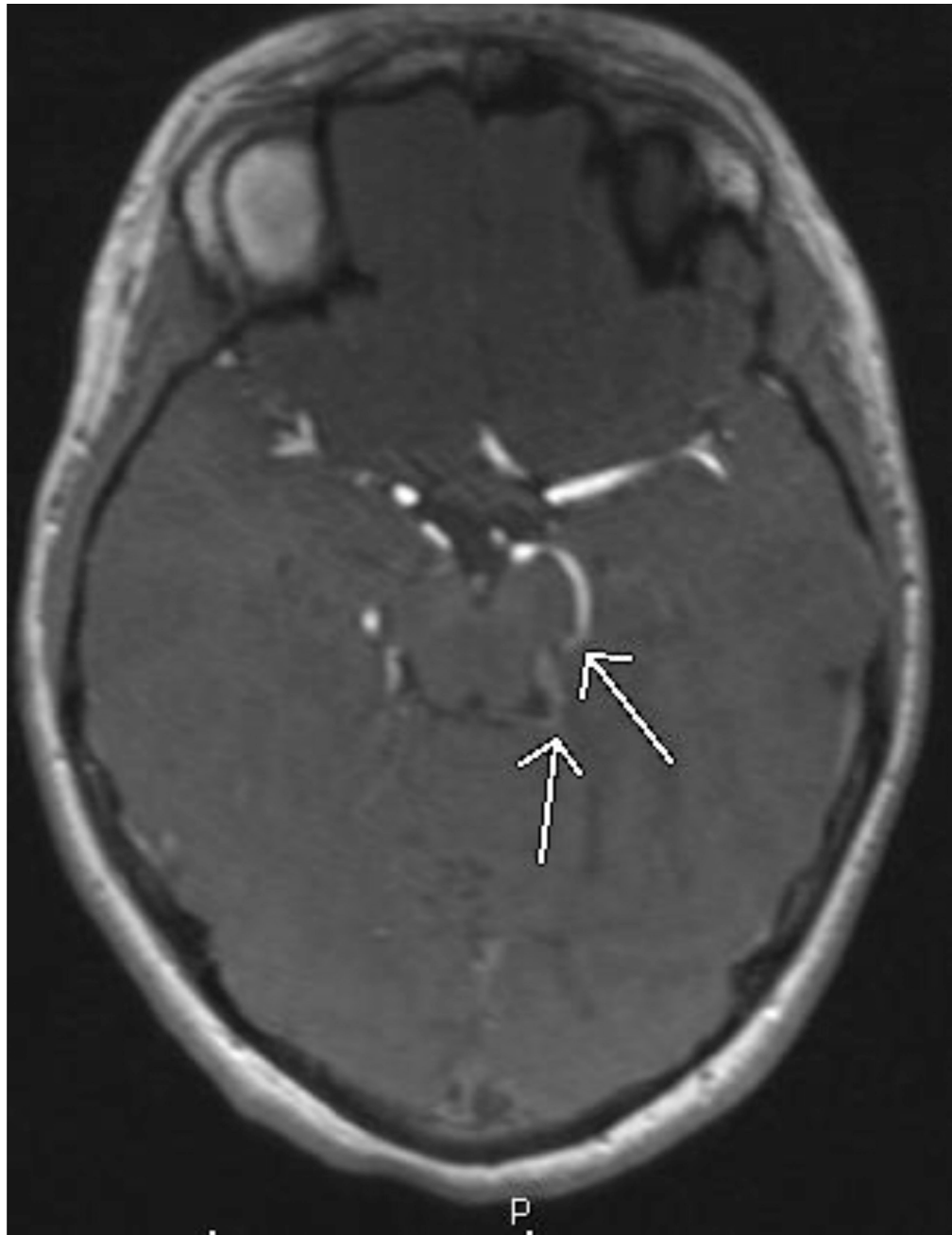


Fig. 3. MRA showing occlusion of the third branch of the Posterior Cerebral Artery (P3).

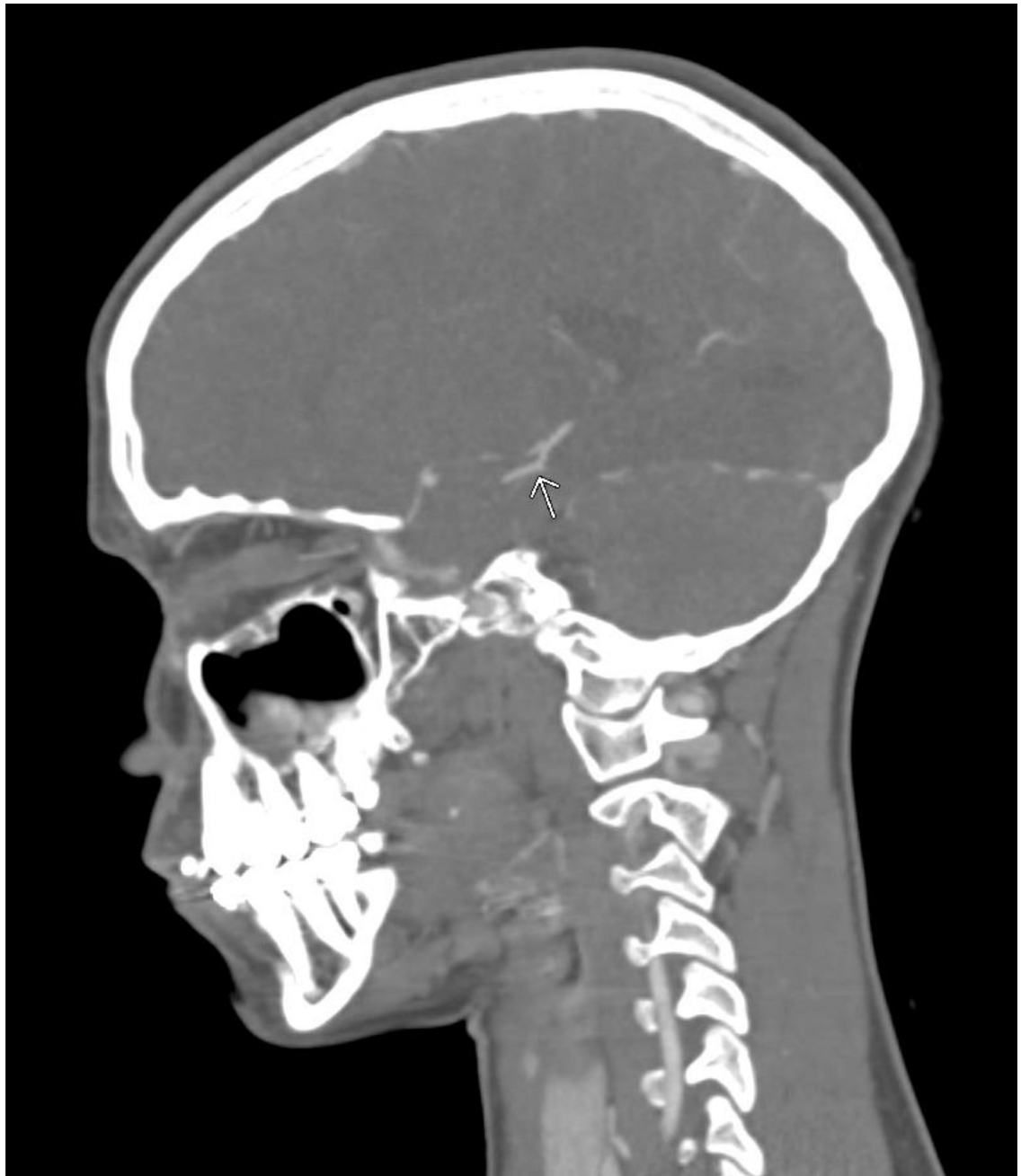


Fig. 4. CTA 24 hours after stroke sagittal image showing recanalization of the Posterior Cerebral Artery.

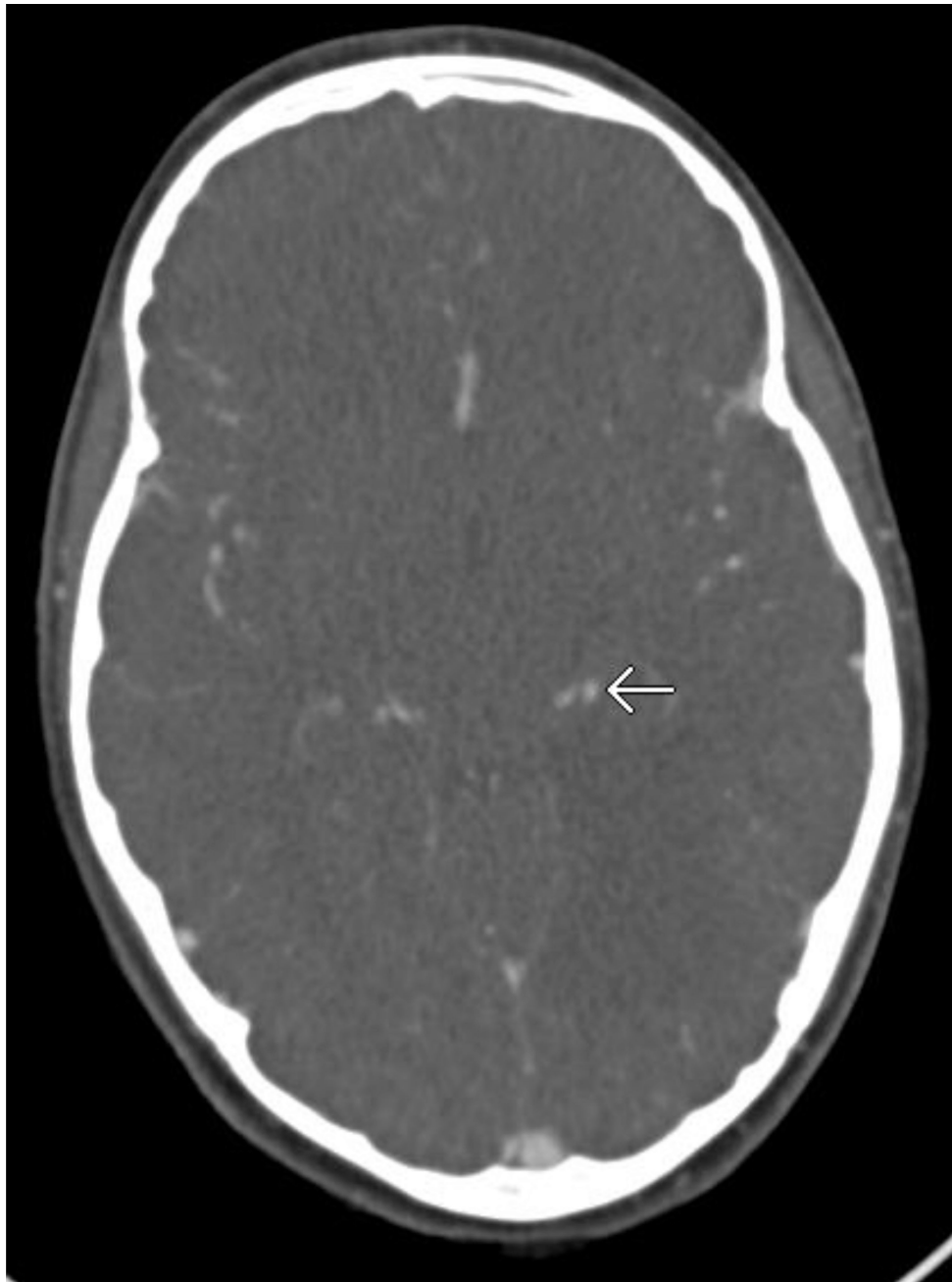


Fig. 5. CTA 24 hours after stroke axial image showing recanalization of the Posterior Cerebral Artery.



Fig. 6. CTA 24 hours after stroke axial image showing recanalization of the Posterior Cerebral Artery.