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Case Report Open Access

# Use of tPA in a 16 Year Old with Acute MCA Stroke

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## Abstract

**Introduction:** The incidence of pediatric stroke is 1.29-13.0 per 100,000 annually. Use of fibrinolytic therapy in qualified adults with acute ischemic stroke is standard practice. However, alteplase is not recommended in pediatric patients.

**Case:** We report a case of a 16 year old Caucasian female who presented to the emergency room with aphasia and right arm numbness one hour and twenty minutes after symptom onset. National Institutes of Health Stroke Scale (NIHSS) was three. Initial computed tomography without contrast showed a hyper-dense left middle cerebral artery (MCA).

The patient was below the minimum age for alteplase administration in acute ischemic stroke. Written consent was obtained from the parents and 90 mg alteplase (0.9 mg/kg; 90 mg maximum) was administered 3 h 25 min after symptom onset. Right arm numbness resolved thirty minutes after drug administration and repeat NIHSS was one for mild expressive aphasia.

Diffusion-weighted MRI the following day demonstrated infarction of the posterior left insular cortex while sparing most of the MCA distribution. She remained stable during hospitalization and was discharged home on daily aspirin and resumed school activities with full recovery.

**Discussion:** Although stroke is among the top ten causes of mortality in this age group, there are many barriers to administration of alteplase. Use of alteplase in the pediatric population is poorly reported and there are no randomized trials conducted in this age group. Due to the challenges in conducting randomized controlled trials in children, registries provide an alternative approach to gathering and analyzing information. Clinicians are encouraged to continue reporting cases of alteplase use in pediatric stroke patients.

**Keywords** Stroke; Pediatric; Alteplase

## Introduction

The incidence of pediatric stroke in children 1 to 18 years of age is 1.29-13.0 per 100,000 annually [1]. Although rare, pediatric stroke causes significant morbidity and mortality in the youth population of the United States [2]. Guidelines remain weak regarding medical management of these patients.

Standard therapy in adult stroke patients includes supportive care and the use of fibrinolytic therapy when presenting within the defined therapeutic window and without contraindications [3-5]. Alteplase is currently the only recombinant tissue plasminogen activator (tPA) fibrinolytic product approved for use in patients with ischemic stroke [3]. Trials leading to the approval of alteplase excluded patients less than 18 years of age. The approved indications include this age restriction stating a lack of proven safety in this population [6]. Furthermore, the American Heart Association's guidelines for pediatric stroke do not recommend use of alteplase in pediatric patients outside of clinical trials [4]. Use of tPA in the pediatric population is poorly reported and there are no randomized studies investigating its use in this population.

Due to the rarity of stroke events in this population and lack of enrollment in clinical trials, retrospective data becomes increasingly important to guide clinical practice. In this report, we present a 16 year old female who received tPA and experienced an excellent recovery after presentation with acute left middle cerebral artery (MCA) ischemic stroke.

## Case Presentation

A 16 year old, right-handed, Caucasian female started experiencing aphasia and right arm numbness while at school 1 h 22 min prior to presentation in the emergency room. Her past medical history was notable for a remote history of febrile seizures. She was not on chronic medications and was allergic to cefprozil. She denied tobacco, alcohol and illicit drug use. Her family history was positive for hypertension in her father, migraines in her mother, and stroke in her maternal grandmother at an older age.

On admission, her temperature was 99°F, heart ratewas 86 beats per min, blood pressure was 139/95 mm Hg, respiratory rate was 15 breaths per min and oxygen saturation was 100% on room air. Point-of-care glucose was 105 mg/dL. The patient weighed 115 kg and measured 5 ft 7 in Pertinent laboratory results, including complete blood count, serum electrolytes, creatinine, serum lipids, c-reactive protein, erythrocyte sedimentation rate, and hemoglobin A1c were

within normal limits. A urine toxicology screen for amphetamines, barbiturates, opiates, cocaine, benzodiazepines, phencyclidine, tetrahydrocannabinol and methadone were negative. Her neurologic exam was abnormal for aphasia and right arm drift. The National Institutes of Health Stroke Scale (NIHSS) was used yielding a score of three.

Initial computed tomography (CT) without contrast of the head showed a hyper dense left middle cerebral artery extending up to the Sylvian fissure, which was concerning for clot (Figure 1).

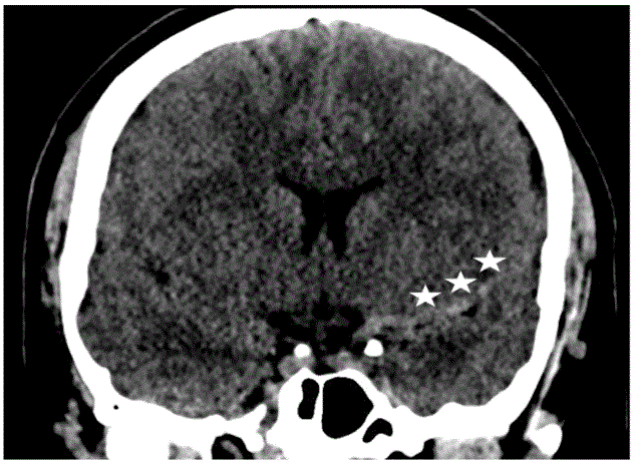

**Figure 1:** Computed tomography (CT) without contrast of the head showing an area of hyper intensity in the middle cerebral artery (stars).

The patient was younger than age 18 years, which is the minimum age per package labeling for alteplase administration in acute ischemic stroke. However, her symptoms, imaging findings, and NIHSS score were consistent with acute ischemic stroke and acute thrombus of the left MCA. After explaining the risks and benefits, as well as informing the parents about the paucity of evidence supporting use of alteplase in the pediatric population, consent was obtained from the patient's parents. The decision was made to administer tPA 3 h 15 min after symptom onset.

We used standard adult dosing for alteplase (0.9 mg/kg). We calculated the tPA dose to be 103.5 mg using 115 kg as the body weight. However, the 90 mg maximum dose was ordered per package labeling. A 9 mg IV bolus (10%) was administered, with the remaining 81 mg (90%) given over an hour as a continuous infusion. A 50 ml bag of 0.9% sodium chloride was administered at the same rate through the same intravenous line used for the alteplase to ensure complete delivery of the drug. An echocardiogram did not reveal an intra-atrial shunt. A subsequent CT angiogram of head and neck with and without contrast showed no aneurysms, flow limiting dissection, atherosclerosis or stenosis.

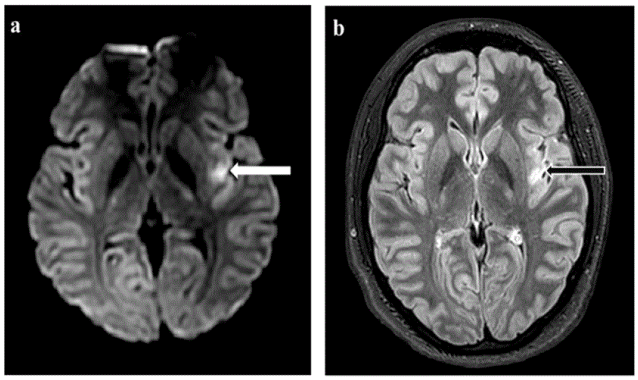


**Figure 2:** Magnetic resonance imaging (MRI) after thrombolysis. (a) A diffusion-weighted (white arrow) and (b) flair MRI that shows infarction of the posterior left insular cortex (black arrow).

Repeat NIHSS score was 1 for mild expressive aphasia 30 min after tPA administration. Right arm numbness had resolved. The patient was stabilized, continued on intravenous saline, and transferred to a local pediatric hospital. Diffusion-weighted MRI the next day demonstrated infarct of the posterior left insular cortex with sparing of most of the MCA distribution (Figures 2a and 2b). Associated flair MRI showed nonspecific flair signals within the bifrontal subcortical white mater and left posterior parietal white mater. Computed tomographic angiogram of the head and neck were within normal limits (Figures 3a and 3b). The patient was discharged home with a prescription for daily aspirin.

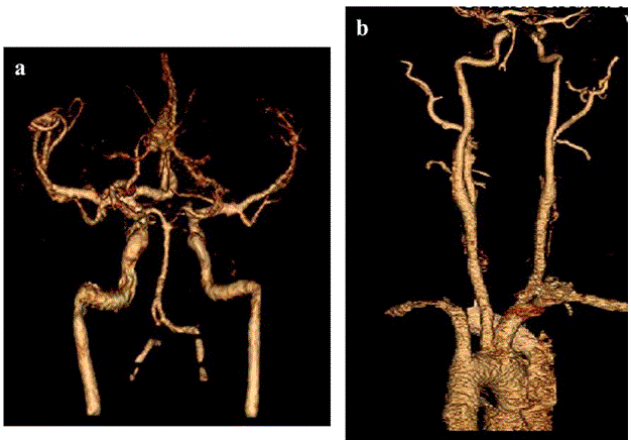


**Figure 3:** Initial computed tomography angiography (CTA) of head (a) and neck (b) did not reveal aneurysms, obstruction, stenosis and emboli.

Follow-up to determine possible cause of the stroke was unrevealing. Protein C, protein S, anti-nuclear antibodies, antiphospholipid and anticardiolipin antibody, prothrombin, homocysteine (screening for methyl-tetrahydrofolate reductase deficiency), beta-2 glycoprotein, and lupus anticoagulant were negative. Imaging after one month showed a small infarct in the posterior left insular cortex and stable signal abnormalities of the

bifrontal and left parietal subcortical flair signal (Figure 4). Her speech had returned to normal and she resumed normal school activities.

## Discussion

The incidence of ischemic stroke in the pediatric population is estimated to be 2.4 per 100,000 person years, with an even higher incidence up to 4.7 per 100,000 person years when both hemorrhagic stroke and transient ischemic attacks are included [6]. Although stroke is among the top ten causes of mortality in this age group, there are still many barriers to administration of the only treatment, alteplase, which is known to reduce poor sequela in adults [2]. Better guidelines are thus needed to curtail poor outcomes in pediatric stroke patients.

Adults presenting with ischemic stroke are deemed appropriate candidates for tPA agent in the absence of established contraindications. Patients must receive tPA intravenously within 3 to 4.5 h of symptom onset or up to 6 h for intra-arterial use per guidelines to reduce the risk of complications. Unfortunately, there is limited data and no published guidelines for the use of tPA in stroke patients younger than 18 years [3]. Clearly, this limits the use of alteplase for the very young, but controversy exists for patients approaching this age limit. Our patient presented at the age of 16 with an overweight body habitus and an otherwise uncomplicated medical history. In one retrospective study conducted by Nasr and colleagues between 2001 and 2010, more than 7,000 cases were reviewed [7]. The overall use of tPA was low (1.4%), but the data showed utility of the drug with limited side effects. The mean age of the tPA group was higher than the group not using the drug, 12.4 versus 8.5 years, illustrating a higher degree of comfort in using tPA in older children.

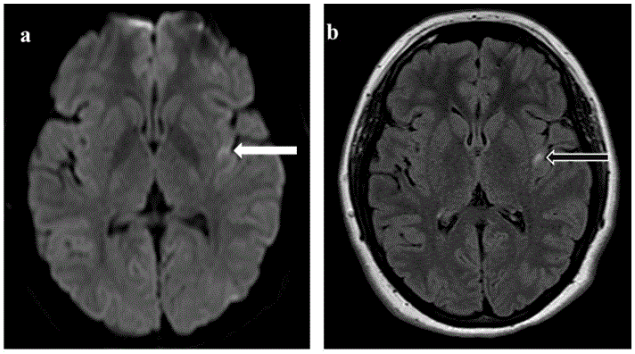


**Figure 4:** Magnetic resonance imaging (MRI) during 1 month clinic follow up. (a) A diffusion weighted (white arrow) and (b) flair MRI shows stable small infarction of the posterior left insular cortex (black arrow).

There is a limited amount of literature evaluating the safety and efficacy of tPA in the pediatric population. The Nasr study also showed that the most common adverse outcome reported with tPA use was intracranial hemorrhage (4.9 vs. 1.5%). However, this should be viewed with caution, given that none of these patients were symptomatic or suffered a fatality. In addition, the adverse outcomes in children receiving tPA are potentially biased by tPA use in more critically ill patients with high NIHSS scores at presentation and risk of poor outcomes irrespective of tPA use. It is also possible that the high rate of conversion to intracranial hemorrhage may be due to the use of tPA outside the recommended window as a last effort to save the patient. A higher percentage of patients (50.8 vs. 12.5%) were discharged to long-term care facility in the tPA group [7]. The larger portion of patients requiring long-term care in comparison to the small portion of patients with hemorrhagic complications indicates the possibility that pretreatment conditions likely predict outcomes more accurately than concerns of side effects of the drug. In properly screened candidates, there was lower mortality in the group using tPA (0 vs. 4.8%). Use of tPA in adult patients showed that 6.4% of tPA-treated patients resulted in conversion of an ischemic to a hemorrhagic event and associated systemic bleeding and death [8]. Rates of utilization of tPA for adult ischemic stroke patients have been reported as 5 to 10% [9]. Overall, use of tPA in pediatric stokes is at an extremely low rate, making it difficult to generalize the effect of using the drug. However, prognosis is generally superior in pediatric patients compared to adult stroke victims. Our patient recovered without neurological deficits and reported complete symptom resolution and function three months after her stroke. However, it should be noted that up to 41% of pediatric patients will suffer chronic neurologic deficits with about 55% not gaining full recovery from ischemic stroke [10].

Due to the dearth of well-established clinical guidelines for tPA use in pediatric stroke, aggressive management of modifiable risk factors may be beneficial to reducing the incidence of stroke. Risk factors in children ages 30 days to 16 years may not be easily modified. These include congenital heart diseases, thrombophilias, cardiac abnormalities, hypercoagulable states, vasculitis and non-atherosclerotic arteriopathies, sickle cell disease, and race [7,11]. Obesity and its associated comorbidities, hypertension, hyperlipidemia, and insulin resistance, are becoming common in younger adults [12]. Stroke incidence or mortality was much lower by 27% in a meta-analysis of combined cohort and case-control studies in physically active individuals [13]. Our patient had a remote history of febrile seizures, which was not believed to have contributed to her acute presentation. However, she was obese, with a BMI of 30, which may have contributed to her stroke.

The Thrombolysis in Pediatric Stroke (TIPS) study was halted prematurely due to a failure to enroll patients (NIH No. R01 NS065818). The studied doses were 0.75, 0.9 and 1 mg/kg body weight up to 90 kg. Although the study was abruptly stopped, there was a great deal of advancement in the preparation for the study. The establishment of 17 primary pediatric stroke centers with protocols for use of thrombolytic therapy was a major positive outcome. These centers are now better equipped to diagnose, respond appropriately and treat pediatric stroke events through the use of established protocols and reliance on subject matter experts [14]. Although this trial was not successful in determining a suitable dose of tPA, the advancements set the stage for more high-quality studies and standardization. Also, retrospective data can be gathered from these participating centers. Due to the limitations and challenges in conducting randomized controlled trials in children, registries are an alternative approach to gathering and analyzing information. For example, the Canadian registry relies on physician reported cases to build their database [15]. Also from the International Pediatric Stroke Study, plans are underway for randomized controlled studies to investigate antiplatelet verses anticoagulant use in stroke prevention [15].

## Conclusion

In the case presented, the administration of tPA in this patient was safe with excellent recovery of neurological deficit. Pediatric stroke

represents a medical conundrum. Barriers to providing the only established treatment for the condition are high. Case reports remain the only evidence for safe and beneficial use of tPA in selected pediatric stroke patients. In the absence of quality evidence for the use of tPA in this population, guidelines will remain weak. The establishment of registries, pediatric stroke centers, and training programs will provide robust data to be analyzed in the near future and increase the number of subject matter experts in the field. In addition, clinicians should be encouraged to continue reporting cases of pediatric stroke and the use of alteplase in this population. Finally, a lack of clinical guidelines should not hamper clinical judgement or reliance on current data for tPA use in pediatric ischemic stroke.

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