Successful treatment of pediatric stroke with recombinant tissue plasminogen activator (rt-PA): a case report and review of the literature

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ABSTRACT
Pediatric stroke is a rare disorder with a paucity of evidence-based treatment options, and can result in significant morbidity and mortality. In contrast to adult acute ischemic stroke, where the use of recombinant tissue plasminogen activator (rt-PA) has been studied in several large, randomized clinical trials, no high-level evidence exists for the use of thrombolytics in children with stroke. We report a case of a 15-year-old girl who suffered an acute ischemic stroke and had a dramatic improvement in symptoms following the administration of intravenous rt-PA.

Keywords: pediatric stroke, ischemic stroke, thrombolysis

Introduction
Acute ischemic stroke is a rare but important cause of morbidity in children. Long-term complications of pediatric stroke include hemiparesis, seizure disorders and learning disabilities. Historically, the treatment of strokes in both adults and children was largely supportive. More recently, thrombolysis has become an accepted treatment in highly selected adults with acute ischemic stroke. However, no high-level evidence exists for the use of recombinant tissue plasminogen activator (rt-PA) in children. We report the case of a 15-year-old girl who suffered an acute ischemic stroke and was successfully treated with intravenous (IV) rt-PA.

Case
A 15-year-old, right-handed girl developed acute onset of headache, right-sided weakness and aphasia, and was quickly brought to a pediatric emergency department by her parents. Her past medical history was remarkable for dysmenorrhea, for which she was taking an oral contraceptive (drospirenone 3 mg and ethinyl estradiol 0.03 mg). She also had a history of a cholesteatoma in her left ear.
which had been resected 4 years earlier. There was no history of smoking, alcohol or illicit drug use. There was no family history of vascular or hematologic disorders or early stroke.

Physical examination revealed a pulse of 77 beats/min, a blood pressure of 130/83 mm Hg and a respiratory rate of 16 breaths/min. Her oral temperature was 36.9°C and a finger-stick glucose measured 8.9 mmol/L. Neurologic examination revealed a left gaze preference, upper motor neuron right-sided facial weakness, a dense right hemiplegia and global aphasia. A computed tomography scan was performed and showed a hyperdense middle cerebral artery consistent with a thrombus. After consultation with a neurologist and a radiologist, it was decided to recommend the administration of IV rt-PA to the patient. The decision to give rt-PA was discussed in detail with the patient and her parents, with a complete explanation of benefits and risks, including death, and a discussion of the lack of evidence for the efficacy of this treatment in children. The patient and her family consented to the treatment and rt-PA was administered approximately 2.5 hours after symptom onset. Because no procedure for the administration of rt-PA to children exists at our institution, we elected to follow the adult stroke protocol, which resulted in an IV bolus dose of 5.8 mg followed by an IV infusion of 53 mg over the following hour, for a total dose of 58.8 mg (0.9 mg/kg).

Over the next 24 to 48 hours the patient’s condition dramatically improved. Her strength recovered and she began to use her right arm and right leg; however, she remained globally aphasic. Pertinent laboratory findings included a normal complete blood count, serum electrolytes, urea, creatinine and serum lipids. A pregnancy test was negative. A toxicology screen for salicylates, acetaminophen, cyclic antidepressants, ethanol, cocaine and amphetamines were all negative. A hypercoagulable screen including antiphospholipid antibody, Factor V Leiden, antithrombin III deficiency, proteins C and S deficiency and lupus anticoagulant were all negative. Urine testing for organic acids was negative, as were the 24-hour collections for amino acids and creatinine. Multiplanar, multisequence magnetic resonance imaging of the brain, including contrast enhanced magnetic resonance imaging of the neck and circle of Willis, demonstrated an evolving left middle cerebral artery territory stroke with no underlying abnormalities. Duplex and Doppler ultrasounds of both calves did not reveal a deep venous thrombosis. A 2-dimensional echocardiogram identified a patent foramen ovale; however, both the cardiology and neurology consultants believed that this was probably an incidental finding. Upon discharge to a rehabilitation hospital 10 days after presentation, the patient had good muscle strength and her dysarthria had resolved, although she still had mild speech apraxia. The stroke was deemed to be cryptogenic (nonatherosclerotic), and the patient was advised to refrain from using oral contraceptives.

Discussion

The incidence of ischemic stroke in the pediatric population is estimated to be 7.91 per 100 000 children per year. Of these strokes, 25% occur in neonates. Neonatal stroke, defined as a cerebrovascular event occurring in patients between 28 weeks’ gestation and 28 days of age, may be hemorrhagic or ischemic, with each occurring approximately 50% of the time. The most common cause of neonatal stroke is thrombosis secondary to a congenital coagulation disorder, although cardiac or vascular abnormalities may also lead to stroke. In addition, there are a number of fetal–maternal factors that may predispose a patient to stroke, including prematurity, pre-eclampsia and fetal or maternal sepsis.

Childhood stroke, defined as a cerebrovascular event occurring in patients between the ages of 30 days and 18 years, may also be ischemic or hemorrhagic, although ischemic stroke is far more common. In contrast to neonatal stroke, embolism is the most common mechanism, and a cardiac source from a congenital abnormality is the leading cause. Sickle-cell disease is an important risk factor; 10% of children homozygous for sickle cell disease suffer a symptomatic stroke by the age of 20 years. There are a number of other vascular and autoimmune disorders that may result in childhood stroke. Some of the risk factors for pediatric stroke mirror those seen in the adult population, including hypertension and smoking, although others, such as diabetes and hyperlipidemia, do not appear to increase risk. Approximately 25% of children with stroke have no identifiable risk factors.

Neonates with a stroke most commonly present with a seizure, although the clinical presentation in this group is highly variable. Childhood stroke may also present with varied symptomatology; however, hemiparesis is the most common presenting complaint. Data on the outcome and recurrence rates in pediatric patients with ischemic stroke vary widely because of differences in premorbid status, inclusion criteria, outcome measures and follow-up duration. The overall prognosis for children with ischemic stroke is similar to their adult counterparts. Although the survival rate in adults has been reported to be as high as 77%, a significant majority of adults who suffer ischemic stroke have impaired vocational capacity at long-term follow-up.
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Childhood stroke data from the Canadian Pediatric Ischemic Stroke Registry (CPISR) indicate that 27% of children with stroke are neurologically normal, 61% are abnormal, 22% have a recurring stroke and 12% are dead at the end of the outcome evaluation period. In contrast, neonatal data from the CPISR indicate a recurrence rate of 3% to 5% and, in survivors, a 33% normal outcome rate.

Physicians are appropriately apprehensive to employ adult recommendations for pediatric stroke patients, as the etiology of strokes in this population is often different from that of adults. The literature on the treatment of stroke in children, including the use of thrombolytics, consists largely of case reports and case series. Successful treatment with IV and intra-arterial thrombolytics and open thrombectomy has been reported.

Recently, 2 evidence-based treatment guidelines for pediatric stroke beyond the newborn period were released. Because no randomized clinical trials have been conducted on pediatric stroke patients without sickle-cell disease, these guidelines relied solely on observational evidence and expert opinion. Neither guideline supports the use of rt-PA, as the paucity of pediatric patients who have received this drug makes it impossible to meaningfully evaluate the treatment. Both guidelines cite the need to establish safety data on the use of rt-PA in the pediatric population.

Data from CPISR on 150 children who had a stroke indicate that 35% of the children were given antithrombotic therapy. Of these 52 children, only 1 was treated with a thrombolytic (urokinase), and the remainder were given anticoagulants or antiplatelet agents (such as warfarin or acetylsalicylic acid). None of the patients in the registry died or had complications from their treatment.

A review by Carpenter and colleagues identified a total of 44 pediatric stroke cases in which IV or intra-arterial rt-PA was used, but only 3 of the patients who received IV rt-PA experienced clinical improvement. Janjua and coworkers estimated the rate of thrombolysis administration for pediatric stroke in a review of data from the Nationwide Inpatient Sample. They found that thrombolysis was carried out in 1.6% of pediatric stroke patients. One-half of these patients received intra-arterial thrombolysis, and it is not clear from the dataset which thrombolytic agents were given.

We identified 4 case reports similar to ours describing the use of IV rt-PA for treatment of pediatric stroke. All of the cases were of adolescent girls who presented with hemiparesis and all had excellent functional outcomes with no reported bleeding complications. One patient experienced a seizure 3 hours after thrombolysis. Unlike our case, a cause for stroke was identified at the time of treatment in all 4 of these cases. Three of the cases demonstrated a patent foramen ovale on bubble study; however, unlike our case, they were associated with either left to right shunting or aortic arch hypoplasia. The remaining case was linked to nonadherence to warfarin therapy following mitral valve replacement for rheumatic heart disease. Two of these patients were also taking oral contraceptives; however, this was deemed noncontributory by the authors.

The Heart and Stroke Foundation of Canada considers the use of thrombolytics for the treatment of childhood stroke to be experimental. Although children may benefit from rt-PA therapy, the potential role of this therapy has the same overarching limitation in children as in adults; children are rarely diagnosed within the time frame required for administration of thrombolysis.

In our patient, treatment with IV rt-PA was considered because she was diagnosed quickly and we were able to begin treatment within the 3-hour window that results in a positive risk/benefit ratio for adults. Although we were unaware of the underlying mechanism of our patient’s stroke, and we considered treatment with rt-PA to be experimental, the unanimous agreement of the physicians involved allowed this treatment to take place in the absence of guidelines.

Our patient did not have any previously identified risk factors for stroke, although she was taking an oral contraceptive. A methodologically rigorous meta-analysis examining the outcome of ischemic stroke among users of low-dose oral contraceptives compared with nonusers revealed an odds ratio of 2.12 (95% confidence interval 1.56–2.86) for current users indicating a higher risk for ischemic stroke in this group.

We were unable to identify any published randomized control trials on the use of thrombolytics in pediatric stroke patients. Such studies are required to establish the dosage, safety and efficacy of thrombolytic agents in childhood stroke. The International Pediatric Stroke Study began in 2002 with the goal of developing clinical trials through the formation of a research network focused on pediatric stroke. The first stage of this research initiative involved the establishment of an international registry of pediatric stroke patients. Physicians may enroll patients in the registry by entering their data on a secure website after research ethics board approval and patient consent have been obtained. The National Institute of Neurological Disorders and Stroke established a similar database for stroke in infants and children in 2004. Physicians may contact the National Institutes of Health patient recruitment and public liaison office (prpl@mail.cc.nih.gov) for more details on enrolling patients.
Conclusion

This 15-year-old girl with a cryptogenic thrombotic stroke had a dramatic improvement in her symptoms following the administration of IV rt-PA. Although this treatment may be considered by emergency physicians in consultation with a pediatric neurologist, more research is required to define the role of thrombolysis in the pediatric population.

Competing interests: None declared.

References


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