

Thrombolytic Therapy in an Adolescent Ischemic Stroke

ABSTRACT

We report the case of a 16-year-old Caucasian girl who developed acute onset of left hemiplegia, left hemisensory deficit, and dysarthria. After a negative computed tomographic scan of the brain, the patient was given intravenous recombinant tissue plasminogen activator according to established adult guidelines. The patient experienced a marked improvement within 24 hours. Stroke etiology was determined to be a paradoxical embolus via a patent foramen ovale associated with pelvic vein thrombosis. This case illustrates the importance of early recognition of stroke and the utility of thrombolytics in treating ischemic infarcts in the adolescent population. (*J Child Neurol* 2001;16:286–288).

Intravenous recombinant tissue plasminogen activator is US Food and Drug Administration-approved therapy for the treatment of acute ischemic stroke in the adult population. The indications, dosing, efficacy, and complications of thrombolytic therapy are well described based on prospective, randomized clinical trials.^{1,2} How-

ever, a literature review reveals a scarcity of reports describing the use of intravenous thrombolytic therapy for pediatric and adolescent ischemic stroke. We report the case of a 16-year-old girl who received intravenous recombinant tissue plasminogen activator for an acute right middle cerebral artery stroke.

Case Report

A 16-year-old right-handed Caucasian girl developed acute onset of left hemiplegia while working as a waitress. Coworkers initially did not recognize that she was having a stroke. Approximately 10 minutes after the onset of symptoms, the patient was transported by emergency medical services to a nearby community hospital. Examination revealed dysarthria, left central facial weakness, left hemiplegia, and hemisensory loss. Computed tomography (CT) without contrast of the brain showed no evidence of hemorrhage or early changes of ischemia. There was no history suggestive of viral infection, seizure, migraine, or other potential stroke mimic. The evaluating emergency department physician initially consulted our institution's pediatric neurology service and then the stroke team by telephone. On confirming no contraindications to thrombolytic therapy other than age, intravenous recombinant tissue plasminogen activator 0.9 mg/kg per standard adult protocol was initiated 2 hours, 48 minutes after symptom onset. The patient and her parents gave informed consent to the emergency department and stroke team staff for intravenous recombinant tissue plasminogen activator. Subsequent helicopter transfer³ to our facility followed.

On arrival to our emergency department, the patient had 2/5 motor strength of the left arm and leg, moderate dysarthria, and decreased sensation to all modalities on the left side. A bedside transcranial Doppler, was

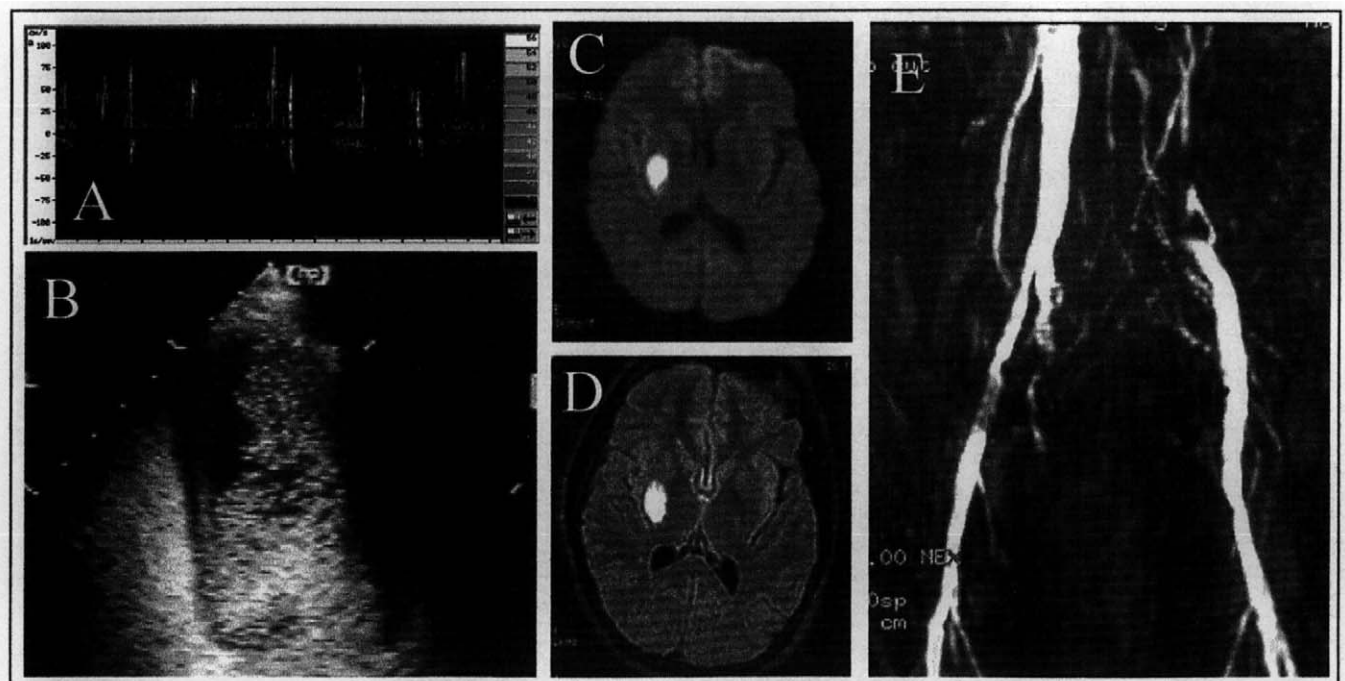


Figure 1 A, Agitated saline transcranial Doppler study. Multiple high-intensity signals are noted. These represent the ultrasound signature of the saline microbubbles that have crossed via a right to left shunt. B, Agitated saline transesophageal echocardiography of the left ventricle. A large number of "bubbles" cross via a patent foramen ovale. C, Diffusion-weighted magnetic resonance image of the brain performed 24 hours after the stroke. The infarct is hyperintense. D, Fluid-attenuated inversion-recovery magnetic resonance image of the brain performed 24 hours after the stroke. The infarct is hyperintense. E, Magnetic resonance venography of the pelvis and abdomen. The absence of flow signal represents a thrombosis of the pelvic veins.

performed in the emergency department, which showed a patent right middle cerebral artery. Multiple microembolic signals were detected on transcranial Doppler after an intravenous injection of agitated saline, indicating a functional right to left shunt (Figure 1A). Computed tomographic angiogram confirmed that the middle cerebral artery, internal carotid arteries, and posterior circulation vessels were patent. The patient was admitted to our stroke unit.

Further evaluation revealed no family history for ischemic stroke or clotting tendency. The patient did smoke half a pack per day of tobacco for 1 year, received a medroxyprogesterone acetate injection 6 weeks prior to this event, and had taken oral contraceptive pills for 3 months prior to receiving the injection. Hypercoagulable evaluation, including antithrombin III, protein C, protein S, lupus anticoagulant, anticardiolipin antibodies, and homocysteine levels, was within normal ranges. Based on the race of the patient and the lack of a family history, we did not assess for sickle cell trait by hemoglobin electrophoresis. Sedimentation rate and antinuclear antibody were negative, and there was no clinical evidence to support vasculitis. A transesophageal echocardiogram showed a large patent foramen ovale with a right to left shunt and a small atrial septal defect with a diameter of 0.5 cm (Figure 1B).

Anticoagulation with intravenous heparin and subsequently warfarin was initiated 24 hours after the intravenous recombinant tissue plasminogen activator infusion. Clinically, the patient made a remarkable recovery. Within 24 hours of her admission, she had improved to 4+/5 motor strength. Magnetic resonance imaging of the brain displayed an acute right basal ganglia-corona radiata infarct (Figure 1C, 1D), no cortical involvement, and patent intracranial vessels 48 hours after symptom onset. Lower extremity ultrasound was negative for deep venous thrombosis. Magnetic resonance imaging of the pelvis showed bilateral common iliac vein thromboses (Figure 1E). The patient underwent successful surgical patent foramen ovale¹ closure 2 months after the initial event and returned to near baseline functioning.

Discussion

The frequency of stroke in children is not as rare as once believed. Due to increased awareness, more efficient triaging, and advances in neuroimaging, more pediatric and adolescent stroke cases are being diagnosed. Current literature estimates the frequency to be approximately 2.7 pediatric cases/100,000 children per year.⁵ The greatest difference between adult and pediatric strokes lies in the diversity of etiology. A wide variety of conditions can cause or mimic stroke in the young.⁶ Although much is known about etiology, frequency, and diagnosis of stroke, a paucity of information exists on treatment of acute pediatric strokes. The lack of clinical trials may be due to the belief that children with strokes have a better prognosis in comparison to their adult counterparts, a belief that stroke mimics are more common and harder to diagnose in the pediatric population, and fear of hemorrhagic complications. Furthermore, the emergency department infrastructure required for rapid diagnosis, neuroimaging, and therapy of acute stroke does not exist at most pediatric emergency departments.

There have been no published reports examining the use of thrombolytics in pediatric or adolescent stroke. Leaker et al⁷ reviewed thrombolytic therapy in pediatric patients from 1966 to 1995 in noncerebral thrombotic complications. In 203 children treated with thrombolytic agents (including 39 patients who received intravenous recombinant tissue plasminogen activator), the complete resolution or re-establishment of flow was achieved in 81% of the patients. Partial resolution was seen in 14% and no resolution in 5%. Minor bleeding (not requiring blood transfusion) occurred in 54% of patients, and one newborn patient had an intracranial hemorrhage. Michelson et al⁸ reviewed antithrom-

botic therapy in 255 pediatric patients, citing that the incidence of bleeding requiring treatment with packed red blood cells occurred in approximately 20% of patients, the most frequent area being sites of invasive procedures, with central nervous system bleeding reported in less than 3% of the patients.

In our case, systemic intravenous recombinant tissue plasminogen activator was administered via standard adult protocol successfully and with no complications. Due to the lack of clinical trials in the pediatric and adolescent population, intravenous recombinant tissue plasminogen activator dosing and inclusion/exclusion criteria must be extrapolated from adult clinical trials. Our patient was adult size with a weight of 72 kg, a height of 6 feet, and in late adolescence. Although our results indicate the value of an aggressive approach to evaluating and treating adolescent stroke, the lack of clinical trials demonstrating improved outcome with tissue plasminogen activator versus natural history in this patient population underscores that this approach is not yet proven effective in pediatric care, especially younger children.

We have described rapid identification of arterial obstruction in the emergency department through the use of transcranial Doppler.⁹ Transcranial Doppler is also useful for real-time monitoring of clot dissolution and re-establishment of flow patency.¹⁰ Better patient outcome is associated with earlier thrombolytic restoration of flow as detected by transcranial Doppler.¹¹ This case also illustrates the use of injected agitated saline to diagnose a right to left shunt at bedside.¹² This simple test has many clinical implications, from diagnosis of stroke etiology to assistance with treatment decisions.⁷ The patent foramen ovale most likely present at birth became symptomatic when a source of thrombus developed. Patients with right to left shunts and normal lower extremity ultrasound may have pelvic vein thrombosis on magnetic resonance imaging.¹³ The importance, etiology, prognosis, and therapy of pelvic vein thrombosis remains unestablished. We hypothesize that the pelvic thrombus formed due to tobacco use in combination with oral contraceptives.^{14,15}

Thrombolytic therapy in adolescent stroke patients can be safe and effective. Clinical applications should be modeled after adult counterparts until further clinical trials define more appropriate guidelines. Furthermore, future stroke trials should allow enrollment of pediatric and adolescent patients to further define potential therapies. Pediatric neurologists and emergency medicine personnel should be familiar with intravenous recombinant tissue plasminogen activator therapy for this potentially devastating disease.

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Cognition, Attention, and Behavior in Prader-Willi Syndrome

ABSTRACT

We studied the academic, cognitive, and behavior profile of 18 patients with Prader-Willi syndrome. All had severe learning disabilities in arithmetic and writing, and the majority were also dyslexic. Their average Full-Scale IQ was 73.7 ± 8.9 , which was 1 SD below normal range, whereas their performance on executive, memory, and visuospatial tasks ranged from 2.1 to 7.0 SD below the expected means. Behavioral problems were measured using the

Child Behavior Checklist, on which the majority scored in the pathologic range for social and attention problems, delinquent and aggressive behavior, somatic complaints, and thought problems. Genotypes of the children did not predict cognitive or behavioral profile, nor could behavior be associated with parameters of weight or IQ. In summary, we found that patients with Prader-Willi syndrome have profound learning disabilities and cognitive deficits, greater than expected for their IQ. Behavioral problems, including attention-deficit hyperactivity disorder (ADHD), are also prevalent and impede the overall management of this group of patients. The genotypes were not helpful in predicting cognitive or behavioral patterns. (*J Child Neurol* 2001;16:288-290).

Prader-Willi syndrome is characterized by mental retardation, gross obesity, insatiable appetite, infantile hypotonia, hypogonadism, and dysmorphic features. It is a genetic disorder resulting from abnormalities of the active paternal genes in the proximal region of chromosome 15q, among which are deletion in the 15q11-q13, unipaternal disomy, and imprinting mutation.¹ Mild to moderate mental retardation is a major characteristic of the syndrome, but within the confines of their intellectual abilities, the pattern of cognitive strengths and weaknesses is not uniform.² These children can demonstrate impairments in memory, sequential and simultaneous processing, and/or auditory information processing.³⁻⁷ Although behavioral and emotional problems have been studied in depth, the presence of attention-deficit hyperactivity disorder (ADHD) has not been addressed.⁸⁻¹¹

Our goal was to assess the academic, cognitive, and behavioral profile of a cohort of patients with Prader-Willi syndrome. A second goal was to correlate their molecular genotypes with the cognitive and behavioral phenotype.

Methods

Subjects

The Israel Prader-Willi Syndrome Association is in contact with all individuals known to have Prader-Willi syndrome in Israel. At the time of the study, the association had registered 21 individuals, 8 years and older, 19 of whom participated. One subject was untestable and was subsequently excluded from analysis. The diagnosis of Prader-Willi syndrome was based on their physical examination and genetic findings. Among the 14 who also had had molecular methylation tests, 10 had a deletion, 3 maternal uniparental disomy, and 1 an imprinting mutation. The mean age of the 18 subjects was 14.3 ± 4.8 (Table 1). Fifteen resided at home and 3 in residential programs. All attended special education frameworks. Information on psychologic treatment was available for 14 cases; 8 were receiving psychologic treatment, and 9 of 13 children who had been previously diagnosed with ADHD were

*The Child Behavior Checklist is a measure of maladaptive behavior in children and adolescents. For this instrument, a 0-2 response format is used (0 = not true, 1 = sometimes true, 2 = true). A total behavior problem score is the sum of all responses for all of the items. The behavior disorders are classified as wide-band syndromes (internalizing and externalizing) and further classified into narrow-band syndromes. Internalizing narrow-band syndromes are anxiety/depression, somatic problems, and withdrawal. The externalizing narrow-band syndromes are aggression and delinquent behavior. Problems in the attentional, social, and thought domains are not classified as either externalizing or internalizing syndromes.