Cerebral sinus venous thrombosis in a child with nephrotic syndrome

Ahmed R. Al-Rumayyan, *FAAP, FRCPC.*

ABSTRACT

الخثار الوريدي الدماغي نادراً ما يحدث كأحد المضاعفات لدى الأطفال الذين يعانون من المتلازمة الكلوية، على الرغم من تزايد الخصائص الإكلينيكية، إلا أنه لم يتم توثيق الخطة العلاجية والنتائج الإكلينيكية بشكل جيد، هذا التقرير يبين حالة فتاة تبلغ من العمر 10 أعوام أصيبت بجفاف صاحبه صداع وانخفاض مستوى الوعي لديها، هذا الأمر تطلب وضع أنبوب فموي عن طريق الجهاز التنفسي وبعد الكشف بالتصوير الدماغي تبين وجود الخثار الوريدي الدماغي. وقد بدأ العلاج بواسطة حال الخثرة و قد أدى ذلك إلى نتائج سريرية جيدة وكذلك كشف التصوير الدماغي وجود تحسن في مجرى الوريد، وقد استعرضت الأدبيات العلمية لطريقة علاج هذه الحالة والإستفادة منها للحالات المصابة بمضاعفات تهدد الحياة.

Cerebral venous thrombosis (CVT) as a complication in children with nephrotic syndrome is rarely reported. Although clinical characteristics are increasingly recognized, therapeutic management and clinical outcomes are not well documented. This case report presents a 10-year-old female who presented with dehydration associated with headache and decreased level of consciousness, which required intubation. Brain imaging revealed CVT. Thrombolytic therapy was started, and she showed a good clinical, as well as radiological recovery. The literature was reviewed to highlight the benefit of such therapy in cases with life threatening complications.

Neurosciences 2014; Vol. 19 (2): 127-129

From the Department of Pediatrics, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

Received 9th September 2013. Accepted 3rd December 2013.

Address correspondence and reprint request to: Dr. Ahmed R. Al-Rumayyan, Department of Pediatrics, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, PO Box 3660, Mail Code 3130, Riyadh 11481, Kingdom of Saudi Arabia. Tel. +966 (11) 4295243. Fax. +966 (11) 4295245. E-mail: rumayyana@ksau-hs.edu.sa

Cerebral venous thrombosis (CVT) as a complication in children with nephrotic syndrome is rarely reported. Although clinical characteristics are increasingly recognized, therapeutic management and clinical outcomes are not well documented.[1-3] This case report describes a 10-year-old female who presented with dehydration associated with headache and decreased level of consciousness. The effectiveness of local tissue plasminogen activator (tPA) as a thrombolytic therapy was assessed in this case report. The objective in presenting this particular case is to highlight the benefit of such therapy in cases with life threatening complications.

Case Report. A 10-year-old female, known case of nephrotic syndrome was admitted to our hospital with headache and decreased level of consciousness. She was clinically stable and in a remission state until one week before admission when she was noticed to have eye puffiness upon awakening from sleep that dissipated during the day. Two days later, she started to have frequent bowel motion, vomiting, abdominal pain, and fever. On the day of admission she had evidence of dehydration associated with headache and decreased level of consciousness, which required intubation. She was then transferred to the pediatric intensive care unit with a suspected diagnosis of cerebral sinus venous thrombosis (CSVT). A head CT scan showed an extensive CSVT with evidence of mild effacement of the sulci and basal cistern; there was no tonsillar herniation noted, and no signs of ischemia or hemorrhage (**Figures 1A & B**).

Her history was unremarkable except for cleft lip and palate status post repair. At school, she was enrolled in grade 3 and her academic performance was at average level. She was on no medication prior to her admission, and family history was unremarkable with regards to coagulopathy. Other investigations for prothrombotic disorders, including factor-V mutation in the prothrombin gene were normal. Her temperature was 36.9°C, blood pressure 111 over 36, heart rate 97

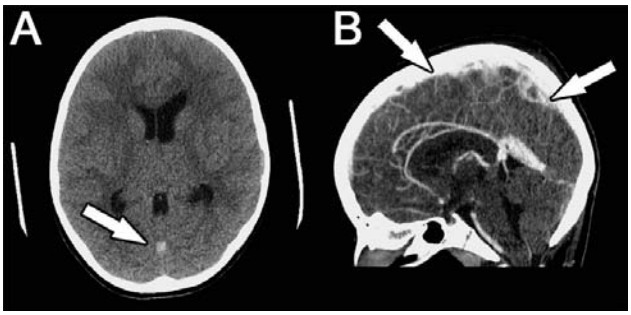

Figure 1 - Axial non-enhanced CT scan of the brain **A**) shows hyperdense focus within the midpart of the straight sinus suggestive of acute thrombus, and CT venography **B**) showing presence of filling defect at the mid and proximal part of the straight sinus with engorgement of the distal part.

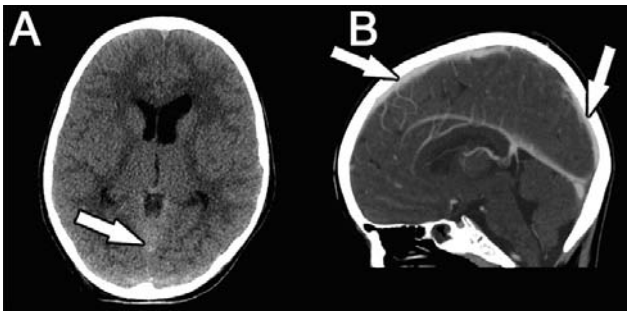

Figure 2 - Follow-up axial non-enhanced CT scan of the brain after 72 hours of mechanical thrombectomy and thrombolysis **A**) demonstrates interval resolution of the hyperdense thrombus within the straight sinus, and after 2 weeks **B**) demonstrates recanalization of the straight sinus with no residual thrombus.

beats per minute. Her weight was 42 kg. Predisposing factor for developing CSVT included dehydration and nephrotic syndrome. Treatment with low molecular weight heparin infusion was initiated. After 2 hours, the level of consciousness deteriorated and she became lethargic then comatose. Local tPA was considered. After discussing the procedure with the parents, including indications, potential complications such as allergic reaction, stroke, bleeding, blindness, renal impairment, and death, an informed consent was obtained. Using a standard neuroangiographic technique, the following vessels were selected: right internal jugular vein, right sigmoid sinus, right transverse sinus, superior sagittal, and strait sinus. Venographic runs were performed in multiple projections. Using a combination of chemical and mechanical methods, antegrade flow of the occluded straight sinus was successfully achieved. Recanalization required 14 mg of recombinant tissue plasminogen activator and a combination angioplasty and temporary intracranial stenting. At the end of the procedure, there was a small residual filling defect at the base of the superior straight sinus consistent with a small residual non-occlusive clot. Robust antegrade flow of blood through the straight sinus was confirmed with the final venogram.

A post procedural CT scan showed no evidence of intracranial hemorrhage (**Figure 2A**). Four days after the procedure, she became more awake with a Glasgow Coma Scale of 15/15, pupils bilaterally equal and reactive. At the time of the discharge from the hospital, she had a mild unsteady gait; otherwise, no focal neurological deficit. Four weeks post-discharge, she was seen in the clinic with totally improved gait, and according to the parents, she was back to her normal self and back to her regular school. A psychological evaluation revealed normal cognition. A follow up venogram 6 months later with a comparison with the previous examination showed a satisfactory opacification of the venous sinuses with no interval change in the recanalized straight sinus with a tiny linear filling defect suggestive of residual thrombosis (**Figure 2B**).

Discussion. Cerebral sinus venous thrombosis in childhood is under-recognized. The clinical manifestations are usually nonspecific, particularly in neonates where they often present with non-focal neurological symptoms and signs; this might lead to under diagnosis.[1-3] In older children, the clinical manifestations may be subtle and nonspecific mimicking other conditions such as dehydration and infection. Other neurological presentations such as decreased level of consciousness, seizures (focal or generalized), and focal neurological deficit may occur. In the present case, she presented with frequent bowel motion, vomiting, abdominal pain, and fever. On the day of admission, she had evidence of dehydration associated with headache and decreased level of consciousness. In these cases, the clinical manifestations of sinovenous thrombosis are similar to those of adults.[1-3] There should be a high index of suspicion in order to diagnose this condition early and provide appropriate management. In addition to the high index of suspicion, a diagnosis can be established by an un-enhanced CT scan, which may show a linear density in deep and cortical venous thrombosis, as in the present case. A filling defect, "empty delta" sign may be considered to indicate that the thrombus becomes less dense in the posterior part of the sagittal sinus. Venous congestion can also be detected by MRI; however, magnetic resonance venogram would be more specific in CSVT, where a lack of flow in the cerebral veins can be demonstrated.

Several predisposing risk factors have been identified including dehydration, trauma, neck infections, genetic disorder, and other prothrombotic conditions such as protein S, and protein C deficiency.[1-3] In this case, the CSVT was associated with nephrotic syndrome. Association of CSVT and nephrotic syndrome is rare.[1-3] Nephrotic syndrome as a risk factor for venous thrombosis in children in one study was found to be in 3% of the cases.[3] Nephrotic syndrome might lead to the deficiency of antithrombin.[1] Some of the suggested coagulopathy associated with nephrotic syndrome is the kidney loss of antithrombin III, a decrease of plasma albumin, hyper-reactivity of the platelets, an increase in Von Willebrand factor, and other coagulation factors. Other uncommon predisposing factors, which have been identified such as high factor-VIII levels, and factor-V Leiden mutation are not clear in children.[2]

In another study, predisposing factors identified in 63 patients were infection (40%), perinatal complications (25%), hypercoagulable/hematological diseases (13%), and various other conditions (10%).[3] In our case, no specific coagulopathy was found. Management of CSVT by anticoagulant therapy (ACT) is based mainly on an adult study as the data for pediatric CSVT is scarce. One study[4] deemed ACT to be safe with a major hemorrhage documented in 6% of treated patients. Those ACT-related bleeds were all nonfatal, and the clinical result was satisfactory in 50%. Non-treatment with ACT is associated with thrombus propagation. However, currently there is no consensus based on a well-designed clinical trial in children to support treatment with antithrombotic therapy with anticoagulants or antiplatelet agents for acute CSVT.

The management of children with venous thromboembolism usually reflects emphasis on other frequent comorbid medical and surgical problems. The agents most frequently used are unfractionated heparin, low molecular weight heparin and the oral vitamin K antagonists.[5] To determine the safety and outcomes of thrombolysis with tPA of intravascular thrombus, Gupta et al[6] reported 80 children with intravascular arterial or venous thrombosis who have been treated with tPA, 65 arterial thrombi (56 after cardiac catheterization), and 15 venous thrombi (6 patients had a pulmonary embolus, and 9 patients had venous thrombus). Systemic tPA therapy was given as an intravenous infusion. Clot resolution was complete in 65% of children, partial in 20%, and there was no effect in 15%. There were major complications (hemorrhage requiring blood product transfusion, CNS hemorrhage, or CNS ischemia secondary to profound blood loss) in 40%, minor complications (bleeding from vascular puncture sites, oozing, incisional bleeding, mucosal bleeding, and any other hemorrhage not requiring blood product transfusion) in 30%, and no complications in 30%. Two patients documented with cerebral ischemia secondary to hypotension due to significant bleeding, and 2 additional patients reported with intracranial hemorrhage. The study concluded that the tPA therapy can be effective in the thrombolysis of intravascular thrombus in children, but is associated with a low margin of safety and an unknown risk-benefit ratio. In the present case, there was no major or minor complication and the patient had a full recovery.

Recently, Wasay et al[7] illustrated the safety of local urokinase thrombolysis in 3 children with CVT, 2 patients received urokinase, and one patient received urokinase followed by local tPA infusion. Recanalization was achieved in 2 patients.[7] The largest case series included 37 patients with CSVT who received intrasinus thrombolysis.[8] Complete recanalization of the superior sagittal sinus was seen in 35 patients (97%). Twenty-seven patients (73%) had good outcomes, and 7 patients (19%) had only mild deficits that were independent for activities of daily life. One patient survived with severe neurologic deficits, and 2 patients died.

In conclusion, although the subgroup of patients that is likely to benefit the most from this procedure is not clear from the literature, it is clear that intrasinus thrombolysis is safe and effective in patients with severe CSVT.

References

1. Dlamini N, Billinghurst L, Kirkham FJ. Cerebral venous sinus thrombosis in children. ***Neurosurg Clin N Am*** 2010; 21: 511-527.
2. Wright JM, Watts RG. Venous thrombosis in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. ***J Pediatr Hematol Oncol*** 2011; 33: 261-264.
3. Wasay M, Dai AI, Ansari M, Shaikh Z, Roach ES. Cerebral venous sinus thrombosis in children: a multicenter cohort from the United States. ***J Child Neurol*** 2008; 23: 26-31.
4. Moharir MD, Shroff M, Stephens D, Pontigon AM, Chan A, MacGregor D, et al. Anticoagulants in pediatric cerebral sinovenous thrombosis: a safety and outcome study. ***Ann Neurol*** 2010; 67: 590-599.
5. Chalmers E, Ganesen V, Liesner R, Maroo S, Nokes T, Saunders D. Guideline on the investigation, management and prevention of venous thrombosis in children. ***Br J Haematol*** 2011; 154: 196-207.
6. Gupta AA, Leaker M, Andrew M, Massicote P, Liu L, Benson LN, et al. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. ***J Pediatr*** 2001; 139: 682-688.
7. Wasay M, Baksh R, Dai A, Roach S. Local thrombolytic treatment of cerebral venous thrombosis in three paediatric patients. ***J Pak Med Assoc*** 2006; 56: 555-556.
8. Guo XB, Guan S, Fan Y, Song LJ. Local thrombolysis for severe cerebral venous sinus thrombosis. ***Am J Neuroradiol*** 2012; 33: 1187-1190.