Case Report

Cerebral Arterial Thrombosis in a Child with Nephrotic Syndrome

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Abstract

Nephrotic syndrome (NS) in childhood may be associated with thromboembolic complications, mainly in venous origin. However, arterial thrombosis may also be seen as a very rare and life-threatening complication. Herein, we described a case of steroid-resistant NS who did not respond to full-dose steroid treatment for 8 weeks and was complicated by neurological findings. The renal biopsy was consistent with focal segmental glomerulosclerosis. His cerebral magnetic resonance angiography showed the sudden termination of M3 branch of the left middle cerebral artery which corresponded with subacute infarction in the left frontoparietotemporal area. Thrombosis panel yielded the results of hyperhomocysteinemia (46.1 μmol/L, range: 5–15 μmol/L) and heterozygous methylene tetrahydrofolate reductase mutation (C677T, A1298C). After that, the patient was given medical therapy including anticoagulant treatment. Improvement in the neurological outcome was determined on the 1st month of follow-up examinations.

Keywords: *Arterial thrombosis, cerebral infarction, children, nephrotic syndrome, treatment*

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Introduction

The risk of thromboembolic phenomenon in children with nephrotic syndrome (NS) is estimated to be 1.8%–5%. However, higher risk has been reported in children with steroid-resistant NS than in those with steroid-sensitive NS.[1] The majority of thrombotic episodes are of venous origin. Although it is rare, cerebral venous thrombosis has been reported most commonly in the sagittal sinus.[2,3] Cerebral arterial thrombosis in children with NS is a very rare complication, and to the best to our knowledge, only eight cases have been reported to date.[4,5] Herein, we report a case of steroid-resistant NS who was complicated by neurological findings of cerebral arterial thrombosis to contribute to the literature.

Case Report

An 11-year-old boy was seen in our pediatric nephrology clinic with the complaint of swelling in eyelids for last 3 days. The patient had complaints of recurrent swelling on the face and headache during the last 2 years, especially after upper respiratory tract infections. In his medical history, he had febrile convulsion and inguinal hernia operation. Arterial blood pressure was within normal limits (110/80 mmHg, <95%), and his height and weight were at 10th percentile. Physical examination revealed edema of the eyelids and (1+) pretibial edema. Other system examinations were normal. Laboratory studies revealed a normal complete blood count with serum biochemical parameters as follows: urea 62 mg/dL (range: 10–40 mg/dL), creatinine 0.8 mg/dL (range: 0.2–0.8 mg/dL), total protein 3.7 g/dL (range: 6–8 g/dL), albumin 1.8 g/dL (range: 3.5–5 g/dL), and total cholesterol 320 mg/dL (range: <200 mg/dL). Serum C3 and C4 complement levels were within normal limits. Urine analysis revealed (2+) proteinuria and microscopic hematuria (11 erythrocytes). Spot urine protein/creatinine ratio was 4.6 (nephrotic ratio >3.5 g protein per g creatinine) and 24-h urine proteinuria was 45 mg/m²/h (NS proteinuria >40 mg/m²/h). These urine findings indicated the glomerular injury caused by NS. Ultrasonography (US) of the urinary tract was

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normal. Besides, renal Doppler US was also assessed as normal. The kidney biopsy could not be done because the family did not allow it. Furosemide (1 mg/kg/day) and methylprednisolone (2 mg/kg/day) treatments were started with the diagnosis of NS. After the amelioration of edema, the patient was discharged with oral methylprednisolone treatment.

Five days later, he was re-presented to our clinic with the complaints of right arm weakness and speech disorder. The patient had suffered from severe headaches for 2 days. On his physical examination, blood pressure was 120/95 mmHg and he was conscious but restless and had incomprehensible speech. He had right lower facial nerve paralysis and (2+) pretibial edema. While the muscle strength in the right arm and leg were 2/5, it was 5/5 in left arm and leg, and right-sided Babinski reflex was positive. Laboratory investigations demonstrated persisting hypoalbuminemia and hyperlipidemia with normal complete blood count and coagulation tests (prothrombin time-international normalized ratio, partial thromboplastin time, and bleeding time). Cerebral magnetic resonance (MR) angiography demonstrated the sudden termination of M3 branch (thrombus) of the left middle cerebral artery (MCA) which was corresponded with subacute infarction in the left frontoparietotemporal area [Figure 1]. Echocardiographic examination performed to exclude the possible accompanying thromboses was assessed as normal. The patient's steroid treatment was continued. After taking blood samples for the thrombosis panel that include testing for the protein C and S activities, antithrombin III, antiphospholipid and homocysteine levels, and mutations for methylenetetrahydrofolate reductase (*MTHFR*) gene (C677T), prothrombin (Factor II) gene G20210A, and factor V Leiden, the patient was started on treatment with low-molecular-weight heparin and acetylsalicylic acid with an antiaggregant dose (100 mg/day). The patient was subsequently switched to oral warfarin therapy and followed up by coagulation tests (prothrombin time-international normalized ratio). Antihypertensive treatment was started due to increased blood pressure. On the second day of treatment, anisocoria, somnolence, and complete loss of muscle strength (0/5) in the right upper and lower extremities (right hemiplegia) were developed. On day 25, control MR angiography demonstrated again a subacute infarct area containing hemorrhagic transformations in the left frontoparietotemporal MCA irrigation area, a shift of 8 mm to the right in midline structures, and a decrease in calibration of distal left MCA M1 branch secondary to edema. Following the mannitol therapy, he regained consciousness and anisocoria has improved. The patient who did not respond to full-dose steroid treatment for 8 weeks and developed renal failure was planned to undergo renal biopsy with the consideration that he had a steroid-resistant NS.[6] However, since the patient received warfarin and acetylsalicylic acid treatment, the biopsy was delayed, and high-dose methylprednisolone (30 mg/kg/dose) for 3 consecutive days and also cyclophosphamide treatment were started for the steroid-resistant NS.[6] Molecular analysis of the genes of glomerular capillary wall proteins, which are associated with steroid-resistant NS, revealed homozygosity for nephrin *NPHS1* gene (A1105G) and podocin *NPHS2* gene (T318C). Thrombosis panel yielded the results of a homocysteine level of 46.1 μmol/L (range: 5–15 μmol/L) and heterozygous *MTHFR* mutation (C677T, A1298C). Antinuclear antibodies and antiphospholipid antibodies were found to be negative. Hemodialysis was planned because of the rapid impaired renal function tests (urea: 454 mg/dL and creatinine: 4.17 mg/dL) and new-onset oliguria. Therefore, the family was reinformed about the importance of kidney biopsy, and then, approval was obtained. After vital signs were kept under control, the renal biopsy was performed on the 40th day of hospitalization. Light microscopy demonstrated the findings of focal segmental glomerulosclerosis, and immunofluorescence revealed IgG- and C1q-positive focal granular staining in the glomerular basement membrane. Biochemical findings of the patient are summarized in Table 1.

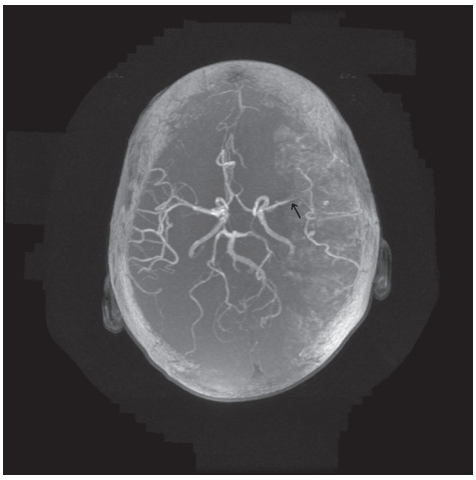

Figure 1: An image of cerebral magnetic resonance angiography showing the sudden termination of M3 branch (thrombus) of the left middle cerebral artery and subacute infarction in the left frontoparietotemporal area (black arrow)

The patient has been followed up for about 2 years. He still receives prophylactic anticoagulant therapy, renal replacement therapy, and physiotherapy. In the 1st month of follow-up, the patient's right-sided hemiplegia recovered considerably (muscle strength was 4/5 in the lower extremity and 3/5 in the upper extremity), while his facial palsy did not improve.

Table 1: Biochemical findings of the patient

Test	Result	Range
Serum		
Urea (mg/dL)	62-454	10-40
Creatinine (mg/dL)	0.8-4.17	0.2-0.8
Total protein (g/dL)	3.7	6-8
Albumin (g/dL)	1.8	3.5-5
Total cholesterol (mg/dL)	320	<200
Homocysteine (µmol/L)	46.1	5-15
Urine		
Protein (qualitative)	2+	
Microscopy (erythrocytes)	11	
Protein/creatinine ratio	4.6	NS>3.5
24-h proteinuria (mg/m^2/h)	45	NS>40

NS=Nephrotic syndrome

Discussion

The patient was evaluated as an NS due to the presence of edema, proteinuria, hypoalbuminemia, and hyperlipidemia, but the absence of hypertension. The patient's hematuria was at the microscopic level which could be accompanied by NS. As seen in the present case, nephrotic patients are having the risk for developed thromboembolic complications. Several thromboembolic complications have been reported in children with NS in the literature. Thrombosis in NS is associated with a hypercoagulable state arising from alteration in blood levels of various factors involved in coagulation and fibrinolytic system, alteration in platelet functions, increased blood viscosity due to hemoconcentration, elevated blood pressure, and probably administration of steroids and/or diuretics.[2,3,7]

A retrospective study conducted by Midwest Pediatric Nephrology Consortium which involved a large cohort consisting of 326 children with NS reported that 9.2% of the children had experienced at least one thromboembolic event and approximately 90% of them had deep-venous thrombosis, while arterial embolism was observed only in one child.[8] Similarly, in children with NS, 90% of thromboembolisms in the central nervous system (CNS) are of venous origin and are usually in the form of cerebral sinus thrombosis.[2,3,7,9] Fluss *et al*.[9] reported 17 nephrotic patients complicated by cerebral sinus thrombosis and emphasized that severe hypoalbuminemia might be the most frequent risk factor, followed by the decreased antithrombin levels. In patients with NS, arterial thrombosis in the CNS is very rare. In the literature, a 14-year-old nephrotic patient with right renal artery and right MCA involvements was reported in 2012.[4] Similarly, our case was complicated by left MCA thrombosis. Recently, Suri *et al*.[5] reported 34 nephrotic children with thromboembolic complications and found that cerebral venous thrombosis was the most common complication which was seen in 11 children (32.4%), while arterial thrombosis resulting from CNS infarctions was observed in 7 children (20.6%).

Because the thrombus was detected as MR finding, we distinguished it from ischemia and/or stenosis. As seen in this presented case, typical acute management of thrombosis in nephrotic children includes initial heparin infusion or low-molecular-weight heparin which is followed by switching to warfarin treatment. In such patients, prophylactic anticoagulant therapy may be useful in the prevention of future relapses.[1,7] Because of the presence of high homocysteine level due to heterozygous *MTHFR* mutation in our patient, prophylactic anticoagulant treatment was continued.

There is a tendency for thrombosis in these patients. Although both arterial and venous thrombosis can be seen as a complication, venous thrombosis is more common in such cases. However, arterial, but not venous, involvement was seen on the angiography of our patient. Therefore, our patient was deemed worthy of presentation. In addition, when evaluating whether our patient had a concomitant inherited risk factor, protein C, protein S, and antithrombin III were found not to be contributing. However, heterozygous *MTHFR* mutation was detected.

Conclusion

Cerebral arterial thrombosis is a very rare and life-threatening complication of NS in children. The accompanying hereditary thrombophilic risk factors should be investigated in these patients. It may be very judicious to start anticoagulant therapy as soon as possible, especially in patients who have hereditary thrombophilic risk factors, such as *MTHFR* mutation, to improve the outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given consent for images and other clinical information to be reported in the journal. The patient's parents understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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