Case Report

Rare thrombotic complications as an initial presentation of nephrotic syndrome

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ABSTRACT

Thrombosis in nephrotic syndrome (NS) is rare event with approximate incidence being 2–3%. Mostly these complications follow NS with involvement of superficial and deep venous system. Cerebral venous sinus thrombosis (CVST) as an initial presentation of NS is rarely reported. Here, we described two cases; an 8-year-old boy and 9-year-old girl, who developed life threatening CVST and renal vein thrombosis, respectively, as initial presentation of NS. Both cases were diagnosed with early imaging studies and treated with appropriate anticoagulant therapy with complete resolution on repeat imaging.

Key words: Anticoagulant, Cerebral venous sinus thrombosis, Imaging, Nephrotic syndrome, Renal vein thrombosis

Nephrotic syndrome (NS) is the most frequent glomerular disease in childhood, affecting 2-7:100000 children [1]. It is characterized by proteinuria, generalized edema, hyperlipidemia, and hypoalbuminemia and associated with hypercoagulable state. Infection, anasarca, hypovolemic shock, anemia, renal failure, and hormonal alterations are the most common complications. Thrombosis is a rare event; the most frequently involved vascular territories are the pulmonary artery, renal vein, inferior vena cava, femoral vessels, and rarely cerebral venous sinuses [1]. The incidence of thrombotic complication in NS is nearly 2–3% with higher incidence in steroid resistant NS (3.8%) than steroid responsive NS (1.5%) [1-3]. Clinical suspicion plays a pivotal role for early diagnosis. Appropriate imaging assessment and prompt prescription of anticoagulant therapy aid better prognosis. Renal vein thrombosis (RVT) may present with acute symptoms or remain undiagnosed because of lack of symptoms until complications like worsening of renal function occurs. The incidence of RVT due to NS and membranous nephropathy ranges from 5 to 62% [4].

CASE REPORT

Case 1

An 8-year-old well grown boy with no significant medical history presented to pediatric outpatient department with 3 days history of throbbing headache, projectile vomiting, and photophobia. No history of fever, head trauma, and hematuria. On further enquiry, there was history of oliguria. On examination, he was conscious, irritable, afebrile, pulses rate 108/min, respiratory rate 24/min, and blood pressure (BP) 96/64 mmHg (between 50th and 90th centile). He had significant right-sided periorbital puffiness with scalp edema, no evidence of edema elsewhere, and evidence of convergent squint on the right side (Fig. 1).

Central nervous system examination revealed excessive irritability with normal higher mental function. In cranial nerve examination showed right VI nerve palsy, all other nerves normal. All superficial reflexes present and plantar were extensor and deep tendon reflexes were brisk. Other systemic examination was normal.

Laboratory results revealed, hemoglobin of 11.5 g/dl, packed cell volume of 44%, total leukocyte count of 5400/mm^3, platelet count 320,000/mm^3, serum creatinine of 0.4 mg/dl (range: 0.2–0.8 mg/dl), urea of 12mg/dl (range: 10–40 mg/dl), and serum albumin of 1.6 (range: 3.5–5g/dl). Serum electrolytes were normal. Urine analysis showed 3+ proteinuria and no hematuria. Urinary protein creatinine ratio was 2.4, with nephrotic range proteinuria. Serum triglycerides and cholesterol levels were 231 mg/dl (range: <150 mg/dl) and 295 mg/dl (range: <200 mg/dl), respectively, and both were on higher side so NS was confirmed. Coagulation profile showed prothrombin time (PT) of 13 sec with international normalized ratio (INR) of 1.2 and activated partial thromboplastin time (aPTT) of 26 s. Prothrombotic work up could not be done due to financial constraints in the family. Contrast-enhanced computed tomography (CECT) brain was suggestive of cerebral edema with cerebral venous sinus thrombosis (CVST) (Fig. 2).

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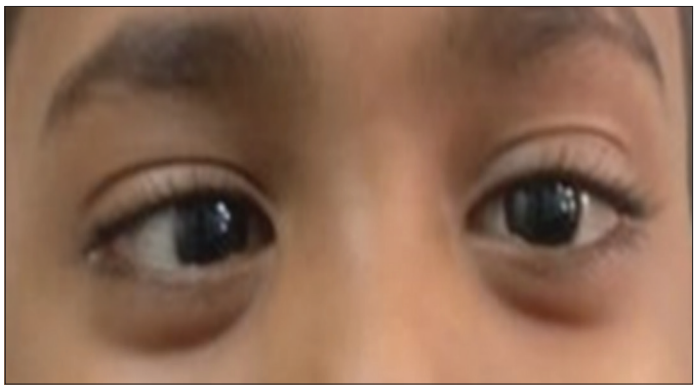

Figure 1: Right side lateral rectus palsy (false localizing sign)

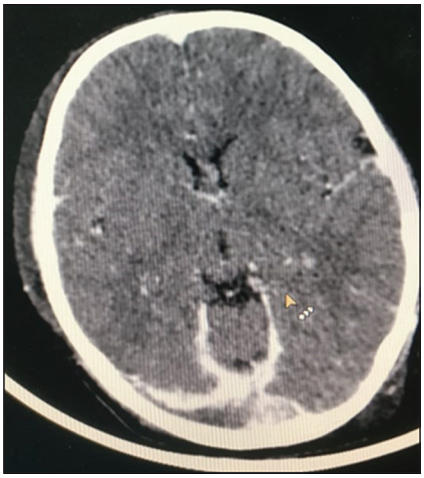

Figure 2: Contrast-enhanced computed tomography brain showing cerebral venous sinus thrombosis and cerebral edema

Child was diagnosed as NS with CVST as a presenting complaint and was started on oral prednisolone as per International Study of Kidney Disease in Children (ISKDC) regimen along with injectable anticoagulant; low molecular weight heparin, subcutaneously (1 mg/kg/day) and later shifted to oral warfarin for next 3 months with INR monitoring. After 15 days of admission, child had achieved remission and was discharged on oral prednisolone (2 mg/kg/day) for further 4 weeks, followed by a reduced dose of (1.5 mg/kg/day) on alternate day for next 6 weeks and oral warfarin. At 12 weeks of follow-up, his urine analysis showed trace proteinuria and repeat CECT brain was suggestive of partial recanalization of venous sinus.

Case 2

A 9-year-old well grown girl with no significant medical history presented to pediatric outpatient department with the right-sided severe excruciating loin pain for 7 days associated with nausea and vomiting. There was no history of fever, oliguria, and hematuria. On examination, child was conscious, afebrile, and pulse rate was 98/min, respiratory rate was 22/min, and BP was 102/68 mmHg (between 50th and 90th centile). She had pitting edema over bilateral lower limbs. On systemic examination, abdominal examination revealed tenderness over right loin, no ascites, and organomegaly. Other systemic examination was normal. Therefore, the initial

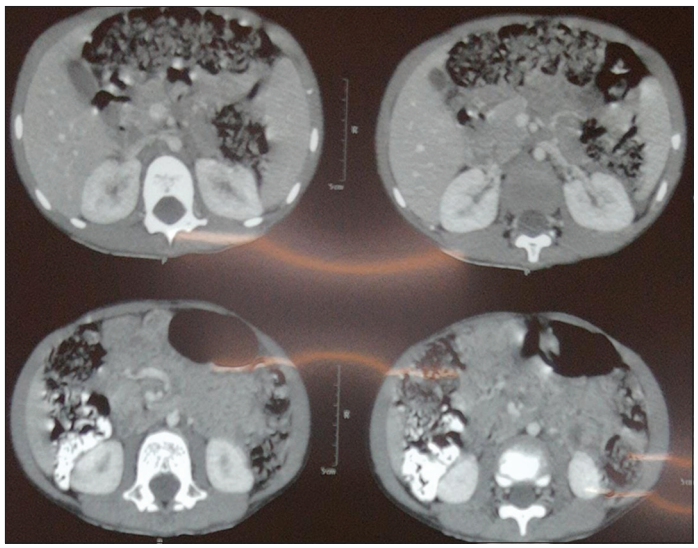

Figure 3: Contrast-enhanced computed tomography abdomen showing right renal vein thrombosis

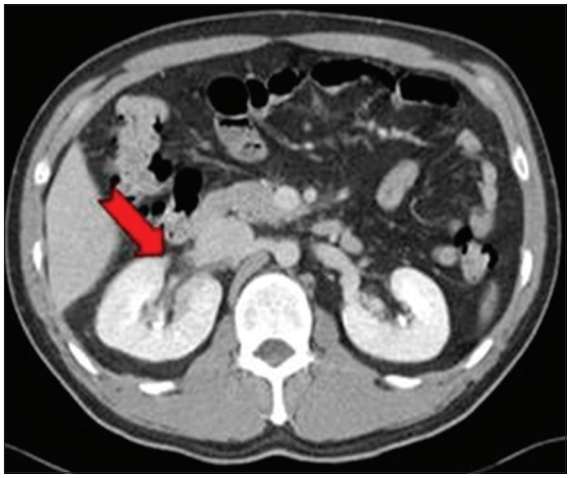

Figure 4: Contrast-enhanced computed tomography brain showing right renal vein thrombosis

clinical impression was acute abdomen with differentials being renal calculus, pyelonephritis, and ovarian torsion.

Laboratory results showed hemoglobin of 10.5 g/dl, packed cell volume of 42%, total leukocyte count of 4200/mm^3, platelet count 380,000/mm^3, serum creatinine of 0.6 mg/dl, urea of 8 mg/dl, and serum albumin of 1.3 g/dl. Serum electrolytes were normal. Urine analysis showed 4+ proteinuria with no microscopic hematuria or cast. Urinary protein:creatinine ratio was 16.7 and urine and blood cultures were normal. Serum triglycerides and cholesterol levels were on higher side 243 mg/dl and 372 mg/dl, respectively. Above clinical and laboratory findings were suggestive of NS, so with suspicion of RVT, prothrombotic work up was planned. Coagulation profile showed PT of 15 s with INR of 1.4 and aPTT of 32 s. Prothrombotic work-up showed normal protein C, protein S, anti-thrombin III, and factor V Leiden mutation.

Ultrasound abdomen and kidneys, ureters, and bladder were suggestive of minimal inter bowel fluid, without evidence of renal calculus. Kidney size was normal; right measuring (8.9 × 4.5) cm and left being (8.4 × 4.2) cm, with normal corticomedullary

differentiation. Renal Doppler revealed normal flow in both renal arteries. CECT abdomen was suggestive of thrombus in the right renal vein and sub-hepatic inferior vena cava with mild renal enlargement (Figs. 3 and 4).

Child started on oral prednisolone as per ISKDC regimen and anticoagulants Inj. low molecular weight heparin, subcutaneously (1 mg/kg/day) and later shifted on oral warfarin for next 3 months with INR monitoring. Pain control was achieved with Inj. tramadol. As her symptoms started resolving and achieved remission, she was discharged on day 20 of admission, with oral prednisolone (2 mg/kg/day) for further 4 weeks and followed by a reduced dose of 1.5 mg/kg/day on alternate day for next 6 weeks and oral warfarin for next 2–1/2 months. At 12 weeks of follow-up, her urine analysis showed trace proteinuria and CECT abdomen showed the partial recanalization of vein. Repeat laboratory investigations showed serum albumin of 3.9 mg/dl and urine protein:creatinine ratio of 0.5.

DISCUSSION

NS is a glomerular disease defined by massive proteinuria (>40 mg/m^2/h), hypoalbuminemia (<2.5: g/dl), generalized edema, and hyperlipidemia [5]. Complications can occur as course of disease or as consequence of pharmacological therapy. Several mechanisms are responsible for development of hypercoagulable state, which increase the risk of clot formation. Urinary loss of anticoagulants, alteration in various coagulation factors and fibrinolytic system, altered platelet function, hemoconcentration, increased blood viscosity due to use of diuretics and steroids, dehydration and inherited thrombophilia contribute to an increased risk of thrombosis [6,7].

The incidence of CVST is believed to be 4.7–6% in children; however, the exact incidence of CVST in children with NS is unknown [5]. The overall incidence of thrombosis in NS can be up to 3% [8,9]. Various studies found that the median time to thrombotic events is about 71 days after the diagnosis of NS. Thrombotic events at presentation in NS have been rarely reported. Children older than 12 years of age, infants with congenital NS and children with high urinary protein excretion and hypoalbuminemia are at increased risk of thrombosis. Lionaki *et al*. found that those with albumin levels <2.8 g/dL have a 2.5-fold increased risk of thrombotic events [10].

CVST commonly present with headache, vomiting, altered sensorium or seizures, and cranial nerve palsy. Among all, headaches are the most common presenting symptom of CVST [11]. The classical pattern of headache in CVST is diffuse and its intensity increases gradually and subsides over a period of 2–3 weeks. About 25% of patients with CVST have isolated headache without neurological findings or papilledema [8]. Similarly, in our first case, child had vomiting, photophobia, and throbbing headache, which resolved in 3 days, 5 days, and 15 days, respectively. Causes of clinical symptoms in CVST are due to raised intracranial pressure, impaired venous flow or focal brain injury from venous ischemia/infarction [11].

RVT commonly present with flank or lower back pain, hematuria, decrease urine output and at times may be asymptomatic. Our second case also had loin pain as the only presenting complaint. Mostly, RVT goes undiagnosed and may lead to severe complications such as acute renal failure or retroperitoneal hemorrhage due to venous rupture. Therefore, an early imaging must be performed for a timely diagnosis and to prevent complications. Magnetic resonance imaging/magnetic resonance venography has a high sensitivity over computed tomography scan for diagnosis and is the imaging modality of choice in children due to low radiation risk.

In our cases, causes of hypercoagulability were severe hypercholesterolemia, hypoalbuminemia, and proteinuria. These thrombotic complications can be successfully treated with early initiation of anticoagulants along with effective immunosuppression. It is recommended to initiate anticoagulant therapy in children with NS and documented thrombosis and there is no role of prophylactic anticoagulation. Our cases were successfully treated with anticoagulation and immunosuppression with a complete resolution on follow-up. The benefits and safety of anticoagulation with unfractionated heparin, low molecular weight heparin, and warfarin in venous thrombosis have been demonstrated. Early commencement of heparin treatment can improve outcome by preventing further evolution of the existing thrombus.

CONCLUSION

Venous thrombosis has nonspecific signs and symptoms at presentation; hence, high degree of suspicion is mandatory to clinch the diagnosis early, along with the help of advanced neuroimaging modalities. Detailed evaluation for NS must be done in all the children presenting with unexplained vascular thrombosis. Early diagnosis and prompt treatment with anticoagulants is really useful to prevent sequelae of vascular thrombosis and to improve the clinical outcome.

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