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Case Report

Unusual suspect in a common diagnosis: think beyond 'minimal'

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ABSTRACT

Nephrotic syndrome is a glomerular disease commonly seen in paediatric population. The disease is characterized by a hypercoagulable state and risk of thromboembolic complications. Cerebral venous thrombosis (CVT) is a rare complication in children associated with nephrotic syndrome with an incidence of 0.67/100000 with very few case reports described. 12-year-old girl with steroid dependent nephrotic syndrome- minimal change disease, with a background of recent COVID-19 infection, presented with vomiting, headache, altered sensorium and an episode of generalized tonic clonic seizure. Diagnosis established by magnetic resonance imaging (MRI) brain and MR venogram which showed superior sagittal sinus thrombosis. Child was started on anticoagulant therapy, gradually recovered with no neurological sequelae. Thrombosis should be suspected in nephrotic syndrome with the added risk of hypercoagulable state associated with COVID-19 infection. Cortical vein thrombosis, even though rare, should be considered in any patient with nephrotic syndrome who presents with neurological signs or symptoms, especially in this era of COVID-19 pandemic. This highlights the importance of suspecting and recognizing post COVID hypercoagulability as a triggering factor for neurological complications. Thromboembolic events are rare in paediatric patients with COVID-19 infection, but a high index of suspicion should be maintained in children, particularly those with comorbidities.

Keywords: Nephrotic syndrome, Venous thrombosis, Post COVID hypercoagulability

INTRODUCTION

Nephrotic syndrome, a glomerular disease that mostly affects the paediatric population. It is characterized by massive proteinuria (>40 mg/m^2/hour), hypoalbuminemia (<2.5 g/dl), generalized edema and hyperlipidemia and hypercholestrolemia. Nephrotic syndrome is a hypercoagulable state with risk for venous and arterial thrombosis. Multiple factors contribute to this hypercoagulability. A post COVID state may add to this hypercoagulability.

Reported incidence of thromboembolic complications in nephrotic syndrome ranges from 1.8% to 5.3 %. Thromboembolism as a complication of multisystem inflammatory syndrome in children (MIS-C) ranges from 1.4 to 6.5 %.[1]

Cortical vein thrombosis (CVT) is a rare complication in children with nephrotic syndrome with very few case reports described. The diagnosis of CVT is difficult, delayed or missed in many cases because of the highly variable clinical presentation. The diagnosis is made with appropriate imaging and its treatment consists mainly of anticoagulant therapy.

This case report describes a 12-year-old girl with steroid dependent nephrotic syndrome resulting from a minimal change disease, with relapse following COVID-19 infection, which developed into cortical vein thrombosis.

CASE REPORT

A 12-year-old girl, diagnosed case of nephrotic syndrome since 1 and half years of age with multiple relapses, who was a biopsy proven minimal change disease, and who is currently on Tacrolimus for the past 11 months and has been off steroids for the past 8 months. There is a h/o COVID-19 infection 1 month prior to the presentation and she was on relapse since then and was restarted on oral steroids. She was brought with headache and vomiting to outpatient department (OPD). On examination, she was lethargic, her vitals were stable, except for blood pressure (BP) at 90th centile. She had a puffy face with mild pedal edema. Abdominal examination revealed no distension or tenderness. Neurological examination showed no focal neurological deficits and had normal motor and sensory function. She was admitted for evaluation and observation in view of suspected raised intracranial pressures.

After admission, she became drowsy, with receeding GCS (11/15) and had an episode of brief lasting generalized tonic clonic seizure which aborted with IV midazolam and levetiracetam.

Management and outcome

Her initial investigations done showed hemoconcentration (Hb-16.4 g/dl, PCV-48%) with elevated total count (TC-15400/cu.mm) and elevated erythrocyte sedimentation rate (ESR). Serum electrolytes and renal function test done were within normal limits. She had hypoalbuminemia (S. alb-2.1 gm/dl). Urine analysis showed proteinuria (Alb 4+) with urine P:C ratio 61:1. Investigations are summarized in Table 1.

Table 1: Investigations.

Investigations	Value
Haemoglobin	16.4 g/dl
Total counts	15,400/cu.mm
Platelet count	2,70,000/cu.mm
PT/INR	14.5 sec/1.09
Serum albumin	2.1 g/dl
Urea/creatinine	25/0.4 mg/dl
Na/K	136/5.1 mmol/l
Urine analysis	Proteinuria (4+)
UP/UC	61:1

Magnetic resonance imaging (MRI) brain and MR venogram (MRV) was done for her which showed a filling defect within the superior sagittal sinus with absent flow related enhancement in venogram - Suggestive of thrombus (Figure 1). Renal doppler was done and ruled out renal vein thrombosis. APLA was done to rule out other prothrombotic states and turned out to be negative.

Following the diagnosis of cortical vein thrombosis (CVT), child was started on unfractionated heparin IV bolus of 70 IU/kg, followed by maintenance dose. Bridging was done with oral warfarin once activated partial thromboplastin time (APTT) 2-3 times control was achieved. Nephrotic syndrome was managed as per protocol. Antiepileptics and supportive care for raised ICT with 3% normal saline were given. Her sensorium improved after initiating treatment, seizures subsided and the child improved with no neurological sequelae. Tacrolimus which was stopped during a brief period of acute kidney injury was restarted and child was discharged on oral warfarin. On long term follow up also, she had no neurological sequelae.

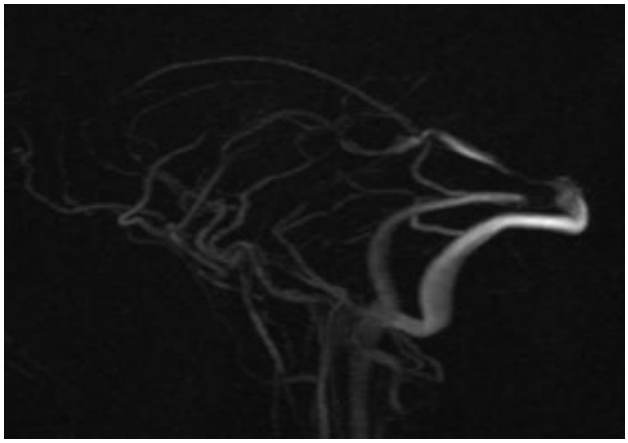

Figure 1: MR venogram showing filling defect in superior sagittal sinus.

DISCUSSION

Nephrotic syndrome is a hypercoagulable state with risk for venous and arterial thrombosis. Increase in the plasma levels of fibrinogen and coagulation factors V and VIII, urinary loss of antithrombin III, protein C, protein S, decreased activity of fibrinolytic system, thrombocytosis and platelet hyperaggregability causes this hypercoagulability. These thrombotic complications are rare in children because the usual etiology of nephrotic syndrome being minimal change lesion is not associated with thrombosis. Membranous nephropathy, the predominant lesion among adults is associated with thromboembolic events.[1]

COVID infection has been a triggering factor for neurological complications. Reported incidence of thromboembolic complications in nephrotic syndrome ranges from 1.8% to 5.3%. Thromboembolism as a complication of post COVID state ranges from 1.4 to 6.5%[1].

CVT involves the thrombosis of the intracranial venous sinus and cerebral veins, which leads to impaired venous drainage leading to intracranial hypertension and venous infarction. The diagnosis of CVT is difficult in many cases because of the highly variable clinical presentation and because the disease is relatively uncommon in pediatric patients. Infections are the most common factor in newborns as well as in older children, followed by

hypercoagulable states and dehydration. Patients with severe proteinuria exhibit a 3-4-fold increased risk of venous thrombosis. Thrombosis risk is higher at the onset of NS and during relapses because of the high loss of coagulation factors and acute intravascular volume depletion during these phases of the disease.[2] Caution should be taken in the use of diuretics in NS because the treatment worsens hypovolemia in nephrotic patients, thereby increasing the risk for thromboembolism.

The clinical manifestations of CVT are nonspecific and vary with age. However, signs of raised intracranial pressure are common. Convulsive seizures which can be generalized or focal are the most common presentation among newborns and children. Focal signs and neurological symptoms such as decreased consciousness, nausea, vomiting, motor deficits, headache and visual changes - diplopia and papilledema, are also common. Vertigo, somnolence, confusion and neck pain are also seen though less frequently. Since CVT symptoms are nonspecific, the disease requires a high degree of clinical suspicion.

In this case, the child presented with vomiting, lethargy, headache and seizures. Diagnosis requires a high index of clinical suspicion in the acute phase and imaging must be performed early in such cases.

The superficial venous system is affected more frequently than the deep venous system. The more common sites of CVT are the sagittal, superior transversal, sigmoid and straight sinuses.

The diagnosis is established by direct visualization of thrombus within the vessel in cerebral CT, the initial and transitory hyperdensity of a thrombus (called 'cord sign') is followed by hypodensity, producing a filling defect (called 'empty triangle' or 'empty delta sign'). Features of cerebral infarction on brain CT may be seen. Demonstration of an absence of a flow void and the presence of altered signal intensity in the sinus in MRI imaging. Non-visualization of the vessel i.e. no flow and the presence of collaterals at the site of occlusion in MR venogram. MRI and MR venography has a high sensitivity for diagnosis and is the imaging mode of choice because, the images obtained offer better cerebral anatomy and parenchymal lesions and its low radiation risk.

The treatment of choice is anticoagulation with unfractionated heparin or low-molecular weight heparin (LMWH) for 5 to 7 days, followed by LMWH or a vitamin K antagonist for 3 to 6 months or as long as the patient exhibits nephrotic proteinuria (albumin level <2 g/dl) or both. This reverses the thrombotic process and prevent its complications. In our case, Unfractionated heparin was administered IV at an initial dose of 70 IU/kg and then infusion was maintained at 12 IU/kg/hour which was titrated as per APTT values and was changed to oral warfarin once APTT 2- 3 times control was achieved. Unfractionated heparin was given in our child due to the background of renal dysfunction.

There was difficulty in achieving anticoagulation due to urinary loss of antithrombin III in nephrotic syndrome. Prophylactic hypocoagulation is controversial; however, prophylactic hypocoagulation should be administered in a patient with a thromboembolic event and high risk of recurrence based on an albumin concentration <2 g/dl, fibrinogen >6 g/l or an antithrombin III level <70% of the normal value (Figure 2).

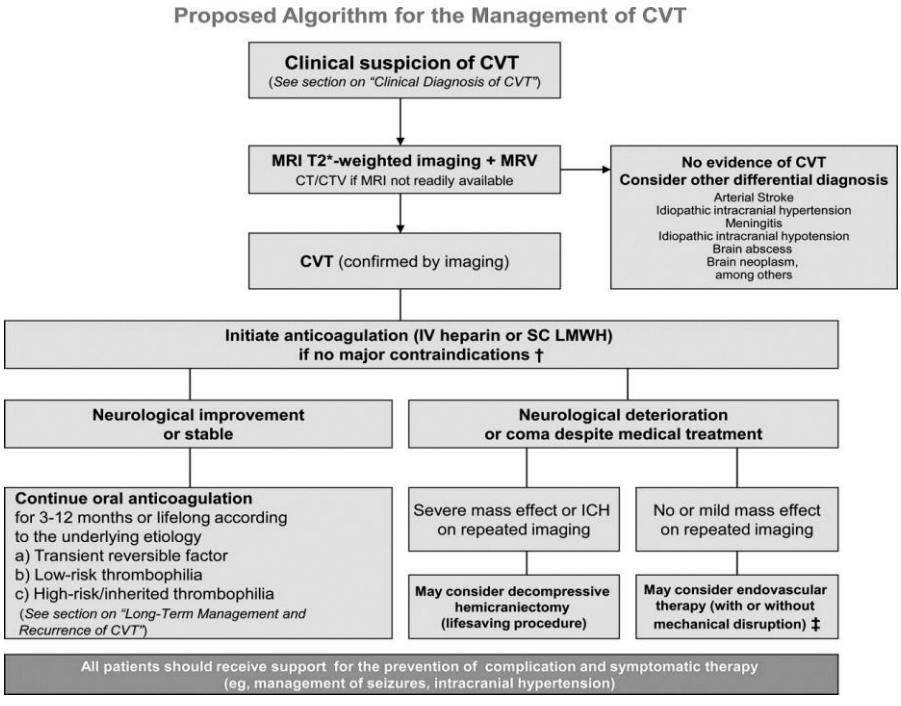

Figure 2: Algorithm for management of CVT.[3]

Duration of anticoagulation is 3 months, if associated with transient risk factors such as infection, trauma and requires longer duration of treatment (6-12 months), if associated with greater risk of recurrence, such as in pro-thrombotic states.

Long-term neurological sequelae are motor deficits (hypotonia, hemiplegia and hemiparesis), seizures, cognitive dysfunction, developmental and speech delay, and visual disturbances. The occurrence of venous infarctions, seizures, Glasgow scale <12 at admission and the presence of cerebral parenchyma lesions are associated with a worse prognosis. A European cohort study published in 2007 associated a higher risk of CVT recurrence with four factors: age over 2 years; absence of secondary anticoagulant prophylaxis; absence of recanalization; and the presence of G20210A mutation in factor II.[4] Two cohort studies described the recurrence of symptoms in 12 to 13% of 180 long-term survivors, occurring on average 12 to 18 months after initial presentation.[5]

CONCLUSION

Thrombosis should be suspected in nephrotic syndrome. Renal vein thrombosis is common among them, which is rare. Cortical vein thrombosis is rarer, should be considered in any patient with nephrotic syndrome who presents with neurological signs or symptoms. It is better to keep differential diagnosis wide enough when any child has atypical presentation. Early clinical suspicion is correlated with a more favorable outcome.

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REFERENCES

1. Meena AK, Naidu KS, Murthy JM. Cortical sinovenous thrombosis in a child with nephrotic syndrome and iron deficiency anaemia. Neurol India. 2000;48:292.
2. Torres RA, Torres BR, de Castilho AS, Honorato R. Venous sinus thrombosis in a child with nephrotic syndrome: a case report and literature review. Rev Bras Ter Intensiva. 2014;26(4):430-4.
3. Stroke. Available at: https://www.ahajournals.org/doi/10.1161/str.0b013e31820a8364. Accessed on 24 October 2022.
4. Kenet G, Kirkham F, Niederstadt T, Heinecke A, Saunders D, Stoll M, et al. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. Lancet Neurol. 2007;6(7):595-603.
5. Ichord R. Outcome in childhood cerebral venous thrombosis—new insights. Nat Clin Pract Neurol. 2008;4(1):16-7.

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