CASE REPORT

Sagittal sinus thrombosis - rare complication of nephrotic syndrome in a young child

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ABSTRACT

The nephrotic syndrome (NS) is caused by increased glomerular permeability. We report a case of NS in a 3-year-old girl, complicated with central nervous system venous thrombosis. Physical examination revealed anasarca (edema, pleurisy, and ascites), intensely foaming urine. The lab tests showed severe, non-selective proteinuria, marked hypoproteinemia, dyslipidemia; also associated with abnormal thyroid panel due to urinary binding protein loss. Once the diagnosis was established and pathogen-specific treatment was started, the clinical and paraclinical evolution were favorable. A prolonged right body seizure was the onset symptom of cerebral venous infarction due to sagittal sinus thrombosis. Short- and long-term outcomes of the thrombosis can be severe, so anticoagulant therapy was promptly initiated.

KEYWORDS: nephrotic syndrome; anasarca; hypercoagulability; sagittal sinus thrombosis

INTRODUCTION

Thromboembolic events are rare complications of nephrotic syndrome (NS). Venous thromboembolism (VTE) occurring in NS patients mainly include thrombus burden in renal veins, deep veins of extremities, and pulmonary arteries (incidence reported from 2% to 37% and prevalence 10% to 35%). Arterial thrombotic events are less well reported (annual incidences 4.4% to 5% and prevalence 2%) [1].

The pathophysiology of hypercoagulability and the risk of VTE in NS are not fully understood yet. It is believed to be related to an increased synthesis of prothrombotic factors, e.g., increased fibrinogen, factor VIII levels. They can act as acute phase proteins and are upregulated in inflammation. The loss of albumin and resultant hypoalbuminemia results in increased hepatic synthesis of fibrinogen and other procoagulant factors [2].

Abnormalities are also found in platelet function with reported increased aggregation and adhesiveness in NS, which may play a role in promoting thrombotic complications (increased free arachidonic acid and formation of thromboxane A2 may be responsible for platelet hyperaggregability) [3-4].

CASE PRESENTATION

A 3-year-old girl was admitted to the Department of Pediatrics in September 2024 for generalized edema, distension, and abdominal pain. She had been transferred for facial edema and abdominal distention from a county hospital, a drug allergy being suspected. The mother was unable to identify the onset of edema, nor could she provide information on recent weight growth. From the family history, both parents and sister appeared to be in good health, mother denied any obstetrical (abortions) or hematological history.

On admission vitals were: temperature 36.9°C, heart rate – 115 beats/min, blood pressure - 121/89 mmHg, respiratory rate - 25 breaths/min and SpO_2-99% on room air. On clinical examination, the patient had 16 kg and 100 cm, body mass index (BMI) on 68th percentile for age and gender, was in poor general condition, with pale skin, warm, puffy, generalized edema (palpebral, upper and lower limbs, lumbar region), spastic cough, groaning, abolished vesicular murmur in the lower third of the right hemithorax, abdominal distension with displaceable dullness on percussion, abdominal circumference 60 cm (normal value for age 50-54 cm), normal diuresis, intensely foamy urine.

The lab tests showed hypochromic anemia (hemoglobin 9.5 g/dL), low serum iron (29 µg/dL), marked hypoproteinemia (3.3 g/dL, normal value 5.7-8 g/dL) by hypoalbuminemia (1.56 g/dL, normal value 3.7-5.5 g/dL), hyperlipemia (1747 mg/dL, normal value 400-800 mg/dL), hypercholesterolemia (479 mg/dL, normal value 0-200 mg/dL) and hypertriglyceridemia (579 mg/dL, normal value 0-150 mg/dL). Renal functional tests were altered: increased uric acid (7.37 mg/dL, normal value 2.6-6 mg/dL) and urea (59 mg/dL, normal value 10.8-38.4 mg/dL). The urine samples revealed numerous proteins, non-selective proteinuria

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(5 g/day, 0.32 g/kg/day), urinary albumin/urinary creatinine ratio - 113 mg/g. Abnormal thyroid panel was also observed: high TSH (17.20 µIU/mL, normal value 0.3 - 4.5 µIU/mL) with inadequately increased free T4 (2.42 ng/dL, normal value 0.90 - 1.75 ng/dL) in the context of non-selective urinary loss of thyroid hormones binding protein.

The abdominal ultrasound showed a large amount of free intraperitoneal fluid (Figure 1) and the pleural ultrasound small bilateral pleural effusion (Figure 2).

Looking at a patient with generalized edema and polyserositis (pleurisy and ascites), several pathologies were considered in the differential diagnosis. Viral hepatitis B and C, human immunodeficiency virus (HIV) serologies were negative, also, the QuantiFERON® test. A series of tests for an immune cause were also performed with normal findings: serum complement (C_3, C_4), antinuclear, anti-thyroperoxidase, and anti-thyroglobulin antibodies.

The patient received a low-sodium, low-lipid, normal protein diet and pathogenic treatment with Methylprednisolone (2 mg/kg/day) and human Albumin (1 mg/kg/day). The edematous syndrome and polyserositis resolved, normal blood pressure and diuresis were maintained throughout the hospitalization, there was significant improvement in biological tests (dyslipidemia half of the initial values, normal proteinemia, non-dosable proteinuria).

In our case, the patient responded very well to pathogenic treatment, and the edematous syndrome was almost completely resolved, but on the fourth day of hospitalization, the patient suddenly presented a prolonged right body seizure with altered state of consciousness (lateral deviation of the head and gaze, hand, and foot clonus), vocalization, without loss of sphincter control, in afebrile condition. Multiple anticonvulsants were administered successively (Diazepam, Phenytoin, Midazolam, Propofol), but only after ~45 minutes the seizure was controlled with Thiopental. Right limb clonus elicited by minimal stimuli (tactile, verbal) persisted for 24 hours.

An emergency brain computed tomography (CT) scan with contrast described: superior sagittal sinus thrombosis, normal-sized ventricular system, no midline deviations, no obvious supra- or infratentorial masses, preserved cortico-subcortical differentiation (Figure 3).

Anticoagulant treatment (subcutaneous Enoxaparin) was promptly initiated, and anticonvulsant therapy was continued (Phenytoin and Sodium Valproate).

24 hours later, the patient was conscious, answered simple questions, cranial nerves were within normal limits, right upper limb presented a slight muscle tone deficit (muscle strength 3/5) with intermittent clonus; left upper limb performed voluntary, but weak movements; right lower limb maintained a complete motor deficit, plantar clonus; left lower limb had normal tone, but reduced movements.

A brain magnetic resonance imaging (MRI) was performed a week later to assess consequences of the venous thrombosis and it revealed a small area of venous infarction in the left fronto-parietal subcortex (19/7 mm) and discrete edema in the adjacent cortical gyri, without intrinsic hemorrhagic petechiae (Figure 4).

In less than a weak the patient presented in good general condition, conscious, with normal behavior, weight 12.8 kg, had no edema, the abdominal circumference was 53.5 cm, bilateral symmetrical murmur was present, diuresis was normal with normal appearing urine and no longer presented clonus, active movements of upper and lower

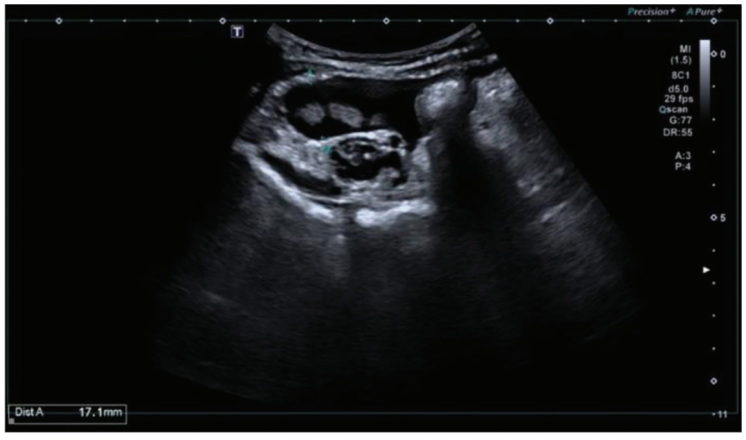

Fig. 1. Abdominal ultrasound - free intraperitoneal fluid (ascites).

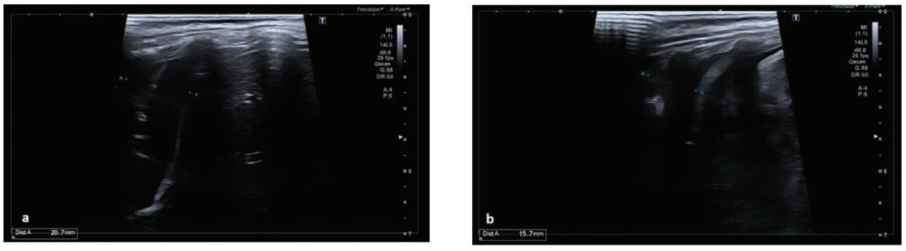

Fig. 2. Pleural ultrasound - pleural effusion, 20 mm on the right side (a) and 15 mm on the left side (b).

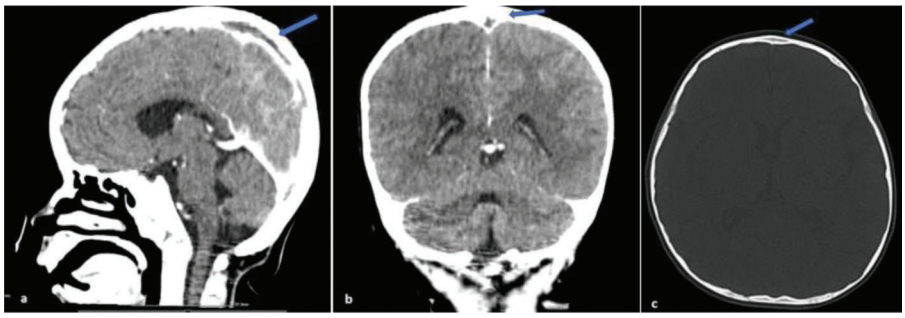

Fig. 3. Brain CT with contrast - Superior sagittal sinus thrombosis: a) Sagittal section; b) Coronal section; c) Transverse section.

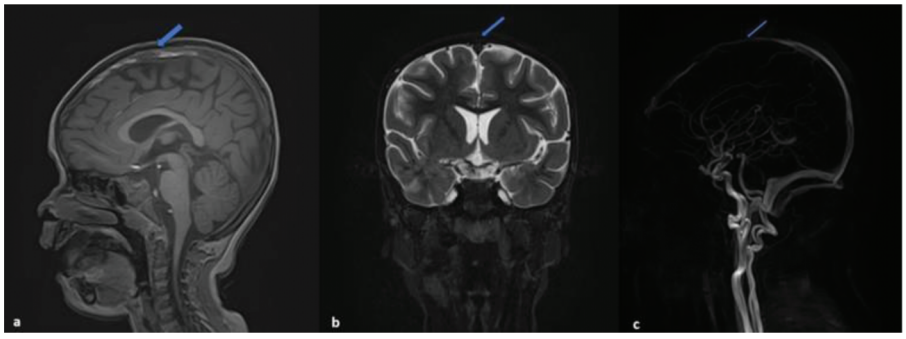

Fig. 4. Brain MRI - Venous infarction secondary to sinus thrombosis: a) Sagittal section; b) Coronal section; c) Blood vessel section.

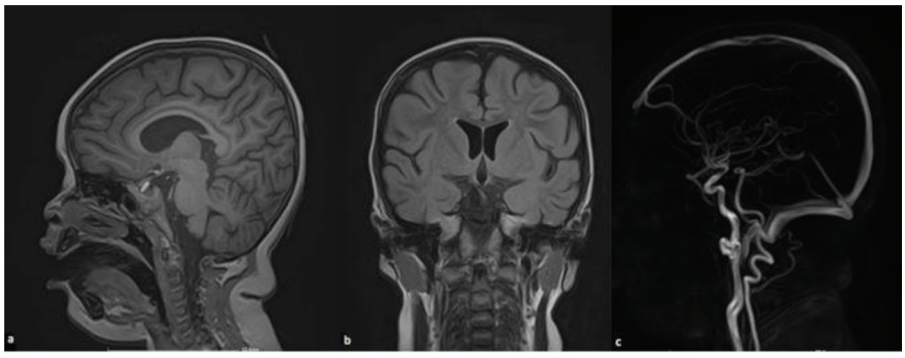

Fig. 5. Second brain MRI (2 months after venous thrombosis) - almost complete recanalization of the superior sagittal sinus and disappearance of the parenchymal lesion: a) Sagittal section; b) Coronal section; c) Blood vessel section.

limbs were symmetric. Spastic gait with the right lower limb, right upper limb with mild motor deficit persisted.

Two months after the acute cerebral venous thrombosis (CVT), the patient was neurologically evaluated (discrete motor deficit in the right upper limb, otherwise normal neurological examination), and a brain MRI compared findings to the previous investigation: homogeneous contrast uptake was observed at the sagittal sinus level; the fronto-parietal subcortical lesion on the left side was no longer described (Figure 5).

DISCUSSIONS

The pathogenesis of edema dictates the diagnostic approach. A child with progressive anasarca (especially significant periorbital edema), but minimal systemic complaints, may have NS. Corticosteroid therapy for a patient with steroid-sensitive NS will resolve edema by inducing a remission and correcting the underlying pathogenesis [5-6].

NS patients are at increased risk for venous thrombosis, particularly deep vein thrombosis and renal vein thrombosis. Limited pulmonary clots (mostly asymptomatic) are relatively common, as for thrombosis of the cerebral veins only rare case reports are found in the published literature [7-8]. Hemoconcentration determined by a moderate degree of dehydration the patient exhibited at presentation and corticotherapy might have participated together with the coagulation particularities associated with NS in the pathogeny of the thrombotic event, but we consider this highly unlikely as the patient's initial volume depletion was swiftly

corrected with intravenous rehydration in the first few hours after admission.

Although uncommon, CVT is a challenging condition. The clinical picture may include headache, segmental loss of visual filed up to blindness, seizures (focal/generalized), focal neurologic deficits, confusion, altered consciousness up to coma. Pathogenic treatment started as soon as the diagnosis is confirmed, addresses the underlying cause when known, intracranial hypertension, seizure control, anticoagulant therapy. While the overall aim is to improve outcome and future quality of life and prevent significant disability, the immediate treatment goals for CVT are: recanalization of the occluded vessel, prevention of further clotting, namely extending to the bridging cerebral veins [9]. For most patients with CVT, anticoagulation with subcutaneous low molecular weight heparin (LMWH) or intravenous heparin for children with symptomatic CVT is recommended [10]. Multiple studies identify serum albumin level as an independent risk factor for thrombotic events in NS. The recently updated KDIGO guidelines suggest that anticoagulation should be considered if serum albumin is <20-25 g/L with additional risk factors for thrombosis which include proteinuria >10 g/day, body mass index of >35 kg/m^2, family history of thromboembolism with documented genetic predisposition or other traditional risk factors [11]. We did not consider prophylactic anticoagulation necessary because the patient did not present any other additional risk factors (according to KDIGO), except hypoalbuminemia that resolved after 72 hours (15.6 g/L to 34.9 g/L).

Guidelines published in 2012 by American Academy of Chest Physicians recommend initial anticoagulation with unfractionated heparin or LMWH, followed by LMWH or vitamin K antagonists for a minimum of three months for children with CVT, but without significant intracerebral hemorrhage. Anticoagulation for an additional three months is suggested if there is still cerebral sinus/venous occlusion or ongoing symptoms [12].

After the acute phase, continuing anticoagulation for three up to 12 months is suggested. However, we found no consensus in the published papers regarding the optimal duration of anticoagulants for reducing the recurrence risk [13]. Patients who experience seizures with hemispheric CVT are started on anticonvulsants. Continuing medication is indicated until seizure-free for one year in patients with CVT associated brain lesions [14]. Considering the evolution of the case, our patient will undergo long-term outpatient treatment with anticoagulants and anticonvulsants (for a minimum of 6 months).

According to KDIGO 2021 protocol, initial treatment of NS is daily oral prednisone/prednisolone 60 mg/m^2/day or 2 mg/kg/day (maximum 60 mg/day) for 4 weeks followed by alternate day prednisone/ prednisolone, 40 mg/m^2, or 1.5 mg/kg (maximum of 50 mg) for other 4 weeks, or prednisone/prednisolone 60 mg/m^2/day (maximum 60 mg/day) for 6 weeks followed by alternate day prednisone/prednisolone, 40 mg/m^2, or 1.5 mg/kg (maximum of 50 mg), for other 6 weeks. [11]. Although the etiology of NS has not been established, our case management falls within the 2021 KDIGO recommendations for the management of the first episode of NS in patients with no syndromic features or family history. Our patient received methylprednisolone 2 mg/kg/day intravenously for the first 3 days, then orally for up to 4 weeks, then 1 mg/kg/day for the next 4 weeks and alternate days 1 mg/kg/day for the subsequent 4 weeks with good tolerance.

Corticosteroids might add to the risk in the NS procoagulant status as they shorten activated partial thromboplastin time, raise both intrinsic and extrinsic path coagulation factors, and therefore have both favorable and unfavorable effects on the coagulation system [15].

CVT has good outcome in up to 80% of patients, as did the girl presented. Around 5% die in the acute phase, the most often immediate cause of death being brain herniation; long-term mortality is nearly 10% [16].

CONCLUSIONS

Hypercoagulability in NS predisposes children to thrombosis. This event rarely occurs, possibly involving a variety of different locations, but raises significant challenges in pediatric clinical practice.

Authors reported the case of a 3-year-old with no history of renal, neurological, or hematological pathologies, diagnosed with NS, that responded swiftly to specific pathogenic treatment, but complicated with CVT (superior sagittal sinus) with venous infarction and focal status epilepticus as the initial manifestation. Clinicians should keep in mind that these rare complications generate important difficulties in terms of treatment and evolution, especially in children.

Conflict of interests

The authors declare that they have no competing interests, nor any other conflict of interests.

Source of Funding

Nothing to declare.

Informed consent

Written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images.

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