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Venous sinus thrombosis in a child with nephrotic syndrome: a case report and literature review

Trombose de seios venosos em criança com síndrome nefrótica: relato de caso e revisão da literatura

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ABSTRACT

Nephrotic syndrome is associated with a hypercoagulable state and an increased risk of thromboembolic complications. Cerebral venous sinus thrombosis is a rare complication of nephrotic syndrome, with few cases described in the literature, although the disease may be under-diagnosis. The true incidence of cerebral venous sinus thrombosis may be underestimated because many events are asymptomatic or are not diagnosed in time. Here, we describe the case of a male child, 2 years and 10 months old, with nephrotic syndrome presenting with headache, epileptic seizures and sensory inhibition who was diagnosed with superior sagittal and transverse sinuses thrombosis. An international literature review was performed with a defined search strategy in the PubMed, SciELO and Lilacs databases using the terms 'nephrotic syndrome' and 'cerebral sinovenous thrombosis'. The diagnosis of venous thrombosis should be considered in any patient with nephrotic syndrome who presents with neurological signs and symptoms, as early clinical diagnosis promotes favorable outcomes.

Keywords: Sinus thrombosis, intracranial/etiology; Venous thrombosis; Nephrotic syndrome/complications; Child; Case reports

INTRODUCTION

Nephrotic syndrome (NS) is associated with a hypercoagulable state due to the increase in the plasma levels of fibrinogen and coagulation factors V and VIII, urinary loss of antithrombin III, changes in the fibrinolytic system, thrombocytosis and increased platelet activation and aggregation. The incidence of thromboembolic complications in children with NS varies between 2 and 5% and is less than in adults. The age distribution of NS subtypes explains this difference; membranous nephropathy predominates among adults and is more associated with thromboembolic events; minimal lesion NS predominates among children and presents a lower risk of those outcomes. Thrombosis can be venous or arterial, although arterial events are less commonly associated with NS. The most frequently affected vessels include the renal vein, the pulmonary artery, the deep veins of the lower limbs, the inferior vena cava and the femoral artery.[1-7]

In conjunction with an international literature review using defined search strategy in the PubMed, SciELO and Lilacs databases with the terms 'nephrotic syndrome' and 'cerebral sinovenous thrombosis', the discussion of this case emphasizes that early diagnosis of thromboembolytic syndrome in NS is crucial to the introduction of anticoagulant therapy and good prognosis.

Conflicts of interest: None.

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CASE REPORT

Informed consent to present this case report was obtained from the responsible parties.

A 34-month-old Caucasian male child with a 1-month history of NS treated by corticotherapy with prednisolone associated with loop diuretics (furosemide) was admitted in the pediatric intensive care unit (PICU) of the *Hospital Santa Isabel* in Ubá (MG) from Emergency Services. Upon hospital admission, the patient exhibited headache, vomiting and liquid diarrhea of 48-hour duration with sensory loss. The day of admission, the child experience subintrant generalized tonic-clonic convulsive seizures. The mother reported recent use of azithromycin to treat an upper respiratory tract infection. On physical examination, the child exhibited pallor, borderline dehydration, arterial hypertension, photoreactive pupil, edema ++/4+, and no signs of meningeal irritation. Venous access was obtained, and diphenylhydantoin and continuous infusion of midazolam were administered. Laboratory exams revealed leukocytosis (global leukocytes: 28,000/mm^3), hypoalbuminemia (2.1g/dL), a normal ionogram and C-reactive protein (CRP) of 25.9mg/dL (reference value: up to 6mg/dL). We chose to collect cephalorachidian liquor, which revealed hyperproteinorachia (67mg/dL; reference values: 15 to 40mg/dL), cellularity, normal cytometry and glycorrhachia. Cerebral magnetic resonance imaging was conducted, which revealed an image compatible with superior sagittal sinus and transverse sinus thrombosis, largely restricted to the left hemisphere (Figure 1). Sagittal, axial and coronal planes at T1, T2, T2* and Flair sequences revealed the presence of a hypointense lesion on T1 and a hyperintense lesion on T2 inside the superior sagittal sinus and the left transverse sinus, suggesting thrombosis in both sinuses. There was no enhancement of pathologic area after the injection of contrast.

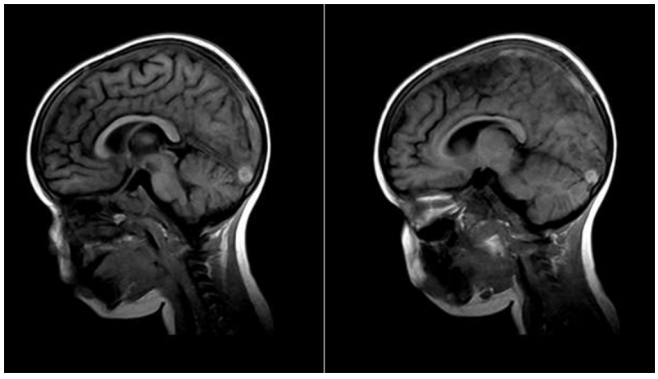

Figure 1 - Sagittal view in T1-weighted sequence.

Once the radiologic diagnosis was established, treatment for cerebral venous thrombosis (CVT) began with a continuous infusion of intravenous heparin. The use of corticosteroid was maintained, and loop diuretics were stopped. The patient required a gradual increase of heparin up to 35UI/kg/hour because of the mild effect on the partial thromboplastin time. When midazolam was removed, we observed hazy mydriasis without focal signs or loss of muscle strength. Ophthalmic examination revealed optic papilla with physiologic excavation and mild to moderate blurred edges, which was consistent with mild to moderate papillitis. Routine exams reveal the persistence of hypoalbuminemia and massive proteinuria, and three cycles of methylprednisolone pulse therapy were administered. Reduced proteinuria and increased serum albumin were initially observed with pulse therapy but were accompanied by rapid relapse of the nephrotic framework. With the onset of fever, chills, incoercible vomiting and cyanosis of the extremities, new exams were conducted, revealing anemia (hemoglobin: 9.7g/dL; reference values: 11.5 to 13.5g/dL), leukocytosis with left shift (19,600/mm^3) and CRP of 23.1mg/L. Antimicrobial therapy for hospital-acquired infection with ceftazidime (150mg/kg/day) and vancomycin (40mg/kg/day) began, with a gradual improvement in the infection response. Once improvements in nephrotic syndrome ceased, cyclophosphamide treatment was started, which improved the proteinuria and reduced the edema. Phenobarbital was also administered, and diphenylhydantoin was progressively reduced. The patient was discharged from intensive treatment after 45 days of hospitalization for ambulatory care in pediatric nephrology and ophthalmology because of poor visual acuity. The patient experienced no relapses of the nephrotic syndrome for 8 months after hospitalization but experienced three relapses after this period and recurrent proteinuria. Histopathology of the renal biopsy was compatible with minimal glomerular lesions. Currently, the patient exhibits good renal function without proteinuria. From the neurological point of view, he exhibits appropriate neuro-psychomotor development without focal changes. The patient experiences poor visual acuity and regularly uses glasses.

DISCUSSION

NS, a glomerular disease that mostly affects children, is classically defined by massive proteinuria (>40mg/m^2/hour), hypoalbuminemia (<2.5g/dL), generalized edema and hyperlipidemia. NS complications can occur as part of the

course of disease or as a consequence of the pharmacological treatment. Among the complications associated with the disease, CVT is an unusual condition, with few reports and case series described in the literature, especially among children. However, the recent increase in the number of cases may indicate that NS has been underdiagnosed in the past.[1-10]

Considering all possible etiologies, CVT has an incidence of 0.67 cases per 100 thousand children per year, i.e., it is likely underestimated. The exact incidence of CVT associated with NS is unknown, but CVT is believed to represent 4.7 to 6% of all CVT cases in children, excluding newborns. CVT involves the thrombosis of the intracranial venous sinus and cerebral veins, which leads to impaired venous drainage and, thus, intracranial hypertension and/or venous infarction. Because of the highly variable clinical presentation and because the disease is relatively uncommon in pediatric patients, the diagnosis of CVT is difficult, delayed or missed in some cases. The low incidence contributes to our poor understanding of the source and physiopathology of CVT in pediatric patients. Risk factors for CVT vary by age and frequently different in number and quality between children and adults. Infections are the most common factor in newborns as well as in older children, followed by hypercoagulable states and dehydration. Most of the cases arise from a combination of prothrombotic risk factors with or without subjacent clinical condition.[2,10,11-17]

NS is a known risk factor for arterial or venous thromboembolism (TE), and 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 loss of coagulation factors and acute intravascular volume depletion during this phase of the disease. The risk is also higher in corticoresistant NS compared with corticosensitive NS. Thrombosis can occur in NS due to the loss of proteins involved in systemic hemostasis inhibition, the increase in the synthesis of prothrombotic factors, or the local activation of the glomerular hemostatic system. TE-predisposing factors in NS include the following: anomalies in platelet activation and aggregation; coagulation system activation; increased synthesis of coagulation factors V, VII, VIII, and X as well as von Willebrand factor, fibrinogen, and accumulation of α2-macroglobulin; reduction of endogenous anticoagulants (antithrombin III, C protein and S protein); decreased activity of the fibrinolytic system and imbalance of the plasmin formation system; changes in the glomerular hemostatic system; intravascular volume depletion; and the use of diuretics.[1-4,6,7,9,11-15]

Considering the factors involved in the genesis of the thromboembolic framework, caution should be taken in the use of diuretics in NS because the treatment enhances hypovolemia in nephrotic patients, thereby increasing the risk for TE. The clinical manifestations of CVT are nonspecific and vary with age. Convulsive seizures (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 (hemiplegia and ataxia), headache and visual changes (diplopia and papilledema), are more commonly found in children. Among the less frequent symptoms are vertigo, somnolence, confusion and neck pain. Because CVT symptoms are nonspecific, the disease requires a high degree of clinical suspicion.[2-4,8,10-14]

In the case reported, the patient exhibited with seizure, sensory deficits, headache, vomiting and visual alterations. The child had been taking oral furosemide associated with corticotherapy. Special care must be taken when administering diuretics in NS; diuretics may be used in symptomatic treatment of edema in massive anasarca patients with difficulty breathing, cellulitis refractory to antimicrobial and corticoresistant children. Because the patient did not exhibit these conditions and because of the possible drug influence on CVT genesis, the use of furosemide was discontinued.

The key to a neuroradiology diagnosis is a high clinical suspicion index in the acute phase; imaging must be performed early because the venous sinuses may recanalize. The superficial venous system (SVS) is affected more frequently than the deep venous system (DVS), and the more common sites of CVT are the sagittal, superior transversal, sigmoid and straight sinuses. The less frequent involvement of the SVP may reflect the current difficulty in diagnosing CVT in this system, which may demand conventional angiograms. The diagnosis is established by demonstrating the lack of blood flow in the cerebral veins with or without typical images of cerebral infarction on brain CT, which is generally the first exam performed in the emergency department. Cerebral vein thrombi can be directly visualized 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'). The images obtained from magnetic resonance imaging offer better cerebral anatomy and parenchymal lesions and represent the method of choice to establish the diagnosis of CVT. The cerebral venous flow and the drainage of the cephalorachidian liquor are intimately related; every CVT case exhibits varying levels of increased intracranial pressure, and

headache and papilledema are typical manifestations in older children.[2-4,7-14,18,19]

Treatment of CVT is based on symptomatic and supportive measures. As in any emergency, airway, breathing and circulation management are imperative. Benzodiazepine therapy is the first line of treatment of seizures in CVT. The treatment of choice is the use of heparin followed by oral anticoagulants. Difficulty in achieving anticoagulation is describe in NS-associated cases due to antithrombin III urinary loss.[11,14,20]

In the present case report, there was a need to gradually increase the heparin dose due to insufficient effects on the partial thromboplastin time, which was maintained during the acute phase, followed by oral anticoagulant throughout the remainder of the treatment and during relapses. Oral anticoagulants have similar results but exhibit less frequent adverse effects. The treatment of choice is hypocoagulation with non-fractional 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 <2g/dL) or both.

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 <2g/dL, fibrinogen >6g/L or an antithrombin III level <70% of the normal value.[6,11]

Long-term neurological sequelae, in descending order of frequency, are as follows: motor deficits (hypotonia, hemiplegia and hemiparesis), seizures, cognitive dysfunction, developmental and/or speech delay, and visual disturbances. Children who develop CVT in the neonatal period exhibit normal intellectual abilities. However, a considerable number exhibit a heterogeneous cognitive profile, with partial cognitive disorders. This finding may indicate that although intellectual functioning is generally normal, children with CVT may suffer from attention and perception disorders that are only evident during alphabetization. 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. 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.[10,11,13,16,21,22]

The patient of this report had low visual acuity as the only sequelae. He did not experience other CVT events and was administered an oral anticoagulant during NS relapses. A multidisciplinary approach to CVT in NS is imperative and must include pediatric neurology monitoring, ophthalmology and, when indicated, rehabilitative therapy.

CONCLUSION

Cerebral venous thrombosis should be considered in any patient with nephrotic syndrome who presents with neurological signs or symptoms. When suspected, imaging exams should be promptly conducted. Upon confirmation of cerebral venous thrombosis, anticoagulant therapy should be started immediately. Importantly, early clinical suspicion is correlated with a more favorable outcomes.

RESUMO

A síndrome nefrótica associa-se a um estado de hipercoagulabilidade, apresentando risco aumentado de complicações tromboembólicas. A trombose dos seios venosos cerebrais é uma complicação rara da síndrome nefrótica, com poucos casos descritos na literatura, mas com diagnósticos cada vez mais frequentes. A verdadeira incidência pode estar subestimada, uma vez que muitos eventos são assintomáticos ou não são diagnosticados a tempo. Descrevemos aqui o caso de uma criança do sexo masculino, de 2 anos e 10 meses, com síndrome nefrótica, que apresentou, na evolução, cefaleia, crises epilépticas e rebaixamento sensorial, com o diagnóstico de trombose do seio sagital superior e transverso. Foi realizada revisão da literatura internacional por meio de estratégia de busca definida, nas bases de dados PubMed, SciELO e Lilacs, utilizando os termos "*nephrotic syndrome*" e "*cerebral sinovenous thrombosis*". O diagnóstico de trombose venosa deve ser considerado em qualquer paciente com síndrome nefrótica que manifeste sinais e sintomas neurológicos, destacando que a suspeita clínica precoce tem relação com um desfecho favorável.

Descritores: Trombose dos seios intracranianos/etiologia; Trombose venosa; Síndrome nefrótica/complicações; Criança; Relatos de casos

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