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CEREBRAL SINOVENOUS THROMBOSIS IN A NEPHROTIC CHILD

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ABSTRACT - Nephrotic syndrome in infancy and childhood is known to be associated with a hypercoagulable state and thromboembolic complications, but cerebral sinovenous thrombosis (CST) is a very rare and serious one, with only a few isolated reports in the literature. A case is presented of a 9-year-old boy with nephrotic syndrome that acutely developed signs and symptoms of intracranial hypertension syndrome. CST was diagnosed on cranial CT and MRI and he gradually recovered after treatment with anticoagulants. The diagnosis of CST should be considered in any patient with nephrotic syndrome who develops neurologic symptoms. The discussion of this case, coupled with a review of the literature, emphasizes that early diagnosis is essential for institution of anticoagulation therapy and a successful outcome. This report also illustrates the difficulties that may be encountered in managing such a patient.

KEY WORDS: cerebral venous thrombosis, sagittal sinus thrombosis, nephrotic syndrome, child.

Trombose venosa cerebral em uma criança com síndrome nefrótica

RESUMO - A síndrome nefrótica na criança é sabidamente associada a um estado de hipercoagulabilidade e complicações tromboembólicas, entretanto a trombose venosa cerebral (TVC) é uma complicação muito rara e grave, com poucos relatos na literatura. Relatamos o caso de um menino de 9 anos com síndrome nefrótica que agudamente desenvolveu sinais e sintomas de uma síndrome de hipertensão intracraniana. TVC foi diagnosticada através de CT e IRM de crânio e o paciente gradualmente se recuperou após o tratamento com anticoagulantes. O diagnóstico de TVC deve ser considerado em qualquer paciente com síndrome nefrótica que desenvolva sintomas neurológicos. A discussão deste caso, associada à revisão da literatura, enfatiza que o diagnóstico precoce é essencial para instituição da terapia anticoagulante e para o bom prognóstico. Este relato também ilustra a dificuldade em manejar este tipo de paciente.

PALAVRAS-CHAVE: trombose venosa cerebral, trombose do seio sagital, síndrome nefrótica, criança.

Arterial and venous thromboses are well-recognized classic complications of nephrotic syndrome, however these are far less frequent in children than in adults[1] Cerebral sinovenous thrombosis (CST) associated with nephrotic syndrome in children is extremely rare and only a few isolated reports exist in the literature[2-13].

CASE

A 9-year-old white boy with steroid-responsive nephrotic syndrome of undetermined cause, diagnosed when he was 4-years-old, acutely developed a severe generalized throbbing headache four days prior to admission to the São Paulo Hospital. He described it as continuous, with photophobia and phonophobia, without relieving factors. Eight days prior to the onset of that clinical picture he started with vomiting and upper abdominal pain not related to food intake, with worsening signs and symptoms of nephrotic syndrome. He was on tapered treatment with alternate day, single dose of prednisone. An esophagogastroduodenoscopy was performed, disclosing a severe non-erosive gastritis and ranitidine was started. Past medical history was negative for migraine headaches, head trauma, febrile illness, substance abuse, vitamin intake or thrombophlebitis. Family history was unremarkable.

On admission his vital signs were normal. He was generally uncooperative, and appeared to be experiencing significant discomfort. Neurologic examination disclosed

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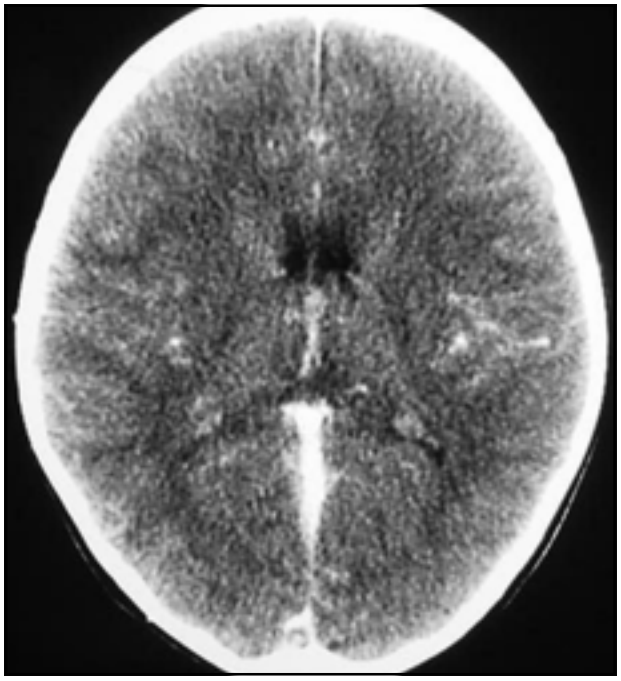

Fig 1 Axial contrast-enhanced cranial CT shows a filling defect in the region of the venous confluence (the empty delta sign) associated with a dilated straight sinus.

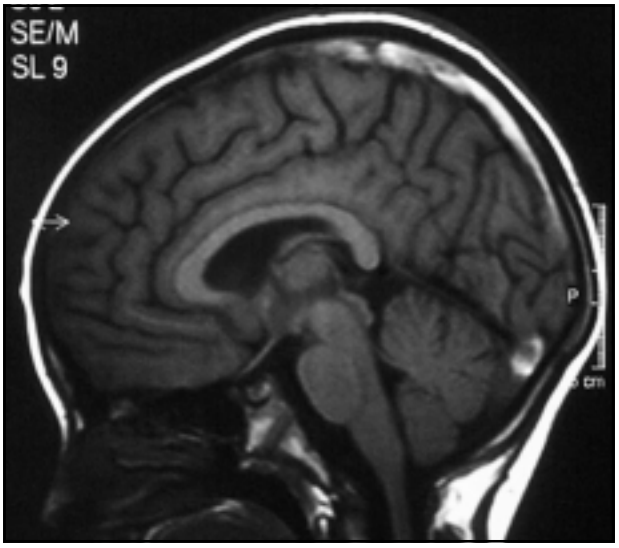

Fig 2 Sagittal T1-W image reveals increased signal intensity within the superior sagittal sinus and in the region of the venous confluence.

remarkable meningeal irritation signs (nuchal rigidity, Brudzinski sign and Kernig sign) and papilledema. The remainder of the examination was within normal limits. Normal values were obtained for the following laboratory data: complete blood count (CBC), serum electrolytes, glucose, urea and creatinine. Serum albumin was 1.7 g/dL and 24-h urine protein excretion was 18 g/day.

Noncontrast-enhanced cranial CT revealed the dense-triangle sign and the contrast enhanced phase showed a dilated straight sinus and the empty-delta sign (Fig 1). There was no mass effect, midline shift or venous stroke image. Cranial magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) demonstrated superior sagittal and left transverse sinus thrombosis. There were no cerebral parenchyma or brainstem lesions (Figs 2 and 3).

A loading dose of heparin of 50 U/kg was given IV followed by a continuous infusion of 10 U/kg per hour and morphine was given to provide analgesia. We

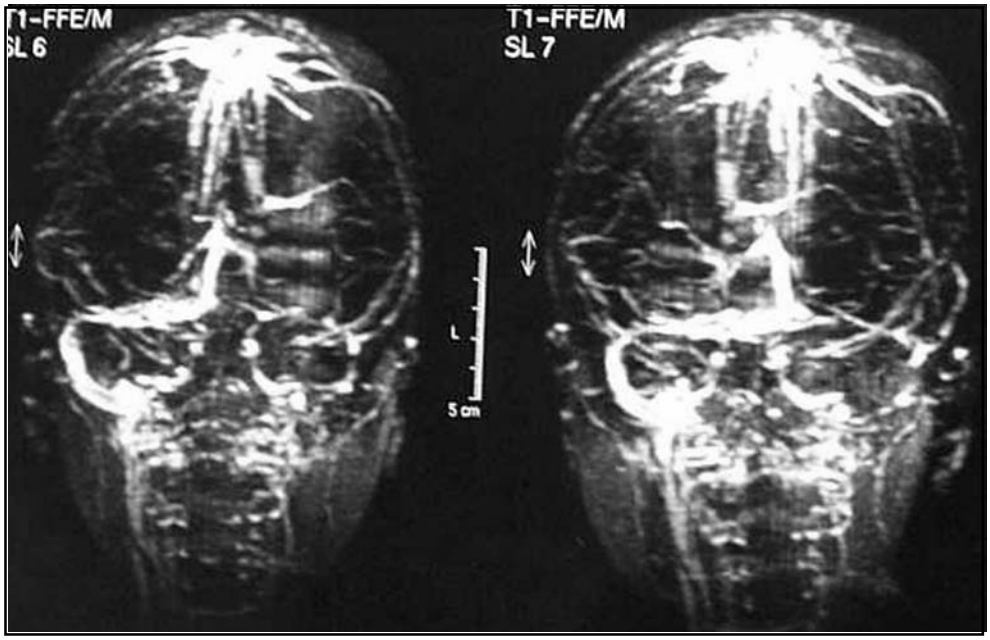

Fig 3. MRV shows dilated cortical veins associated with a filling defect of sagittal superior sinus and absence of flow in left transverse and sigmoid sinus.

Table 1. Conditions associated with aseptic CST in children.

1. Procoagulant drugs	10. Connective-tissue disease
Oral contraceptives	Systemic lupus erythematosus
Asparaginase	Behçet disease
2. Head injury and strangulation	Antiphospholipid antibody syndrome
3. Pregnancy and puerperium	11. Nephrotic syndrome
4. Postoperative states	12. Hypernatremic dehydration
5. Hematologic disorder	13. Diabetic ketoacidosis
Iron deficiency	14. Osteopetrosis
Sickle cell disease	15. Abnormal local hemodynamics
Beta-thalassaemia major	Arteriovenous malformations
Primary or secondary polycythemia	Dural arteriovenous fistula
Primary or secondary thrombocythemia	Moyamoya disease
Paroxysmal nocturnal hemoblobinuria	Sturge-Weber syndrome
6. Inflammatory bowel disease	16. Cancer
Crohn disease	17. Inherited coagulation disorders
Ulcerative colitis	Factor V (Leiden) mutation
7. Perinatal complications (neonatal group)	G20210A prothrombin-gene mutation
Hypoxia at birth	Protein S deficiency
Premature rupture of membranes	Protein C deficiency
Maternal infection	Antithrombin III deficiency
Placental abruption	18. Allogeneic bone marrow transplantation
Gestational diabetes	19. Extracorporeal membrane oxygenation
8. Homocystinuria	20. Idiopathic
9. Malnutrition	

attempted to maintain the partial thromboplastin time (PTT) between 64 to 80 s, with a control of 32 s. However, despite doses as high as 30 U/kg per hour, the increase in PTT could not be sustained. The nephrotic state was treated with prednisone (2 mg/kg/day) and remission of the nephrotic syndrome occurred 5 days after the institution of that treatment. At this time the desired levels of anticoagulation were achieved and two days later Warfarin at 0,1 mg/kg/day was added with successful control of prothrombin time. The child gradually made a complete clinical recovery over 2 weeks.

DISCUSSION

Cerebral sinovenous thrombosis in children is a rare disorder but one that is increasingly diagnosed because of greater clinical awareness, sensitive neuroimaging techniques, and the survival of children with previously lethal diseases that confer a predisposition to sinovenous thrombosis[14] It has been recognized since the 19th century, usually associated with trauma or pyogenic infections, like mastoiditis, sinusitis and facial cellulitis. However, the development and use of antibiotics greatly reduced the incidence of septic thrombosis[15] Aseptic CST is now more common and have been reported in association with acute and chronic systemic diseases (Table). Idiopathic CST represents only 3 percent of cases in children[14].

Nephrotic syndrome is defined by a urinary protein level exceeding 3.5 g per 1.73 m^2 of body-surface area per day. It is associated with a hypercoagulable state arising due to various factors like - low zymogen factors (factor IX and factor XI), increased procoagulatory cofactors (factor V and factor VIII), increased fibrinogen levels, decreased coagulation inhibitors: antithrombin III (but protein C and protein S increased), altered fibrinolytic system (α2-antiplasmin increased and plasminogen decreased), increased platelet reactivity and altered endothelial-cell function[16]. Dehydration secondary to gastritis with vomiting and steroid therapy were additional risk factors in our patient.

Thrombosis of various vessels has been reported, but CST associated with nephrotic syndrome appears to be very rare and only a few isolated reports exist in the literature[2-13]. Divekar et al. reported only 1 case

of CST out of 700 children with nephrotic syndrome followed over a period of 17 years[6].

The diagnosis of CST should be considered in any patient with nephrotic syndrome who develops neurologic symptoms. Those are different between the neonate and nonneonate groups. In the latter, the clinical findings are similar to those reported in adults: a decreased level of consciousness, headache and focal neurological signs such as hemiparesis and cranial-nerve palsies. In contrast, the primary neurologic manifestations in neonates are seizures and diffuse neurologic signs[14]. We have found, however, only one case of CST associated with congenital nephrotic syndrome[9].

Physical examination may reveal findings of increased intracranial pressure or focal deficits as previously described. Our patient presented papilledema and meningeal irritation signs, both secondary to intracranial hypertension. Lumbar puncture should be done if infection is suspected but is non diagnostic for CST. The CSF may show increased pressure and mildly increased red blood cells due to microhemorrhages. Other nonspecific findings described are increased erythrocyte sedimentation rate and mild leukocytosis. EEG findings are nonspecific[15].

In the presence of the appropriate clinical history, cranial CT provides an excellent screening procedure. In most cases, as the one presented here, a diagnosis of sinus thrombosis can be made on the basis of the CT findings. The noncontrast-enhanced scan may show the presence of small ventricles, cerebral swelling, hemorrhagic and ischemic infarcts, intracerebral hematomas, the dense-triangle sign and the cord sign. The contrast enhanced scan can disclose the so-called empty delta sign, gyral or tentorial enhancement and dilated transcerebral or medullary veins[17].

MRI with magnetic resonance venography, because of its noninvasiveness and high sensitivity, is the preferred modality for diagnosis and follow-up of cerebral venous thrombosis. The normal flow void seen in veins and sinuses on noncontrast-enhanced MRI is replaced by signals that are hyperintense or isointense to brain, depending on the sequence utilized and the age of the thrombus[18].

The treatment of choice is heparin, followed by oral anticoagulation, administered as long as the patient has nephrotic proteinuria, an albumin level below 2 g/dL, or both[16]. Difficulty in anticoagulation was encountered in our case as in all cases reported in the literature. Loss of ATIII in the nephrotic urine may be an important cause of the failure of anticoagulation with heparin. Large amounts of administered heparin may also be lost in the nephrotic urine[16]. Fresh frozen plasma was given to correct antithrombin-3 levels in some reported cases with a good response (reduction of time to achieve the desire anticoagulation level)[2,4,6,12]. The long-term neurologic outcome of sinovenous thrombosis in children is unclear and the best available estimate is that after a mean of 2.1 years, 77 percent of neonates and 52 percent of nonneonates are neurologically normal[19]. Early recognition, immediate institution of anticoagulation therapy and control of nephrotic syndrome are essential measures to ensure a good prognosis.

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