Imaging diagnosis and clinical findings of cerebral venous thrombosis in full-term neonates without brain damage: a ten-year review*

**OBJECTIVE:** To describe and compare imaging methods and clinical findings of cerebral venous thrombosis in four full-term neonates without brain damage, admitted to a neonatal intensive care unit. MATERIALS AND METHODS: Ten-year review of four cases diagnosed with cerebral venous thrombosis by transfontanellar ultrasonography associated with Doppler fluxometry and confirmed by magnetic resonance imaging/magnetic resonance angiography in correlation with clinical findings and neurological progression. RESULTS: Ultrasonography presented normal results in 75% of cases and magnetic resonance imaging in 100%. Doppler fluxometry and magnetic resonance angiography were abnormal in 100% of cases. Hypoxia (100%) and early seizures (100%) were predominant among clinical findings with evoked potential changes in 50% of cases. In the assessment of the neurodevelopment all the areas remained within normality parameters up to the conclusion of the present study. CONCLUSION: Ultrasonography in association with Doppler can identify changes related to cerebral venous thrombosis and should be complemented with magnetic resonance imaging that is the gold standard for diagnosis in these cases.

**Keywords:** Cerebral venous thrombosis; Full-term neonates; Magnetic resonance imaging; Magnetic resonance angiography; Ultrasonography and Doppler.

INTRODUCTION

Cerebral venous thrombosis (CVT) in neonates is a severe and rare condition, with an incidence of less than one case for every 100 thousand newborns per year. This condition has been increasingly diagnosed mainly because the huge developments in diagnostic imaging methods. The most frequent predisposing factor for the development of CVT is hypoxic-ischemic encephalopathy (HIE), with a considerable morbitmortality rate.

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**Resumo**

**OBJETIVO:** Descrever e comparar os métodos de imagem e os aspectos clínicos em quatro recém-natos a termo diagnosticados como trombose venosa cerebral, sem dano encefálico, adscritos a uma unidade de terapia intensiva neonatal. MATERIAIS E MÉTODOS: Revisão em 10 anos com quatro casos diagnosticados como trombose venosa cerebral por meio de ultrassonografia transfontanelar com Doppler e confirmados por ressonância magnética/angiografia, correlacionados aos aspectos clínicos e evolução neurológica. RESULTADOS: A ultrassonografia foi normal em 75% dos casos e a ressonância magnética, em 100%. No caso alterado, a dilatação venosa foi identificada. O Doppler e a angiografia estavam alterados em 100% dos casos. Dos aspectos clínicos, a hipoxia (100%) e a convulsão precoce (100%) predominaram, com potencial evocado alterado em 50% dos casos. Na avaliação do neurodesenvolvimento, todas as áreas estiveram dentro da normalidade até a última avaliação. CONCLUSÃO: A ultrassonografia associada ao Doppler é capaz de identificar as alterações da trombose venosa cerebral, devendo ser complementada com a ressonância magnética, que é o padrão ouro de diagnóstico.

**Unitermos:** Trombose venosa cerebral; Recém-nascidos a termo; Imagem por ressonância magnética; Angiografia; Ultrassonografia e Doppler.

nosis\(^5\). In approximately 85% of cases, the thrombosis affects either the superior sagittal sinus or the transverse sinus\(^8\-\(^10\). Among the imaging methods, transfontanellar ultrasonography (TFUS) associated with Doppler fluxometry is the initial evaluation method, particularly because of the wide availability and bed-side capability, with low cost, and non-necessity of sedation or ionizing radiation exposure, but magnetic resonance imaging (MRI) remains as the gold standard for the diagnosis of CVT\(^5\,\(^6\,\(^9\,\(^11\,\(^12\)).

The present study was aimed at describing the imaging findings, comparing the methods used in the neonatal period, as well as describing the clinical findings and the neurological progression in four term neonates diagnosed with CVT, with no brain damage, admitted to a neonatal intensive care unit over a 10-year period.

MATERIALS AND METHODS

In the period from May 1999 to May 2009, 2,865 neonates were admitted to the Neonatal Intensive Care Unit (ICU) of Casa de Saúde São José (CSSJ) in Rio de Janeiro, RJ, Brazil. Among these neonates, 2,547 were submitted to TFUS as a routine procedure of the ICU, or for different clinical indications, with 10% of such studies due to a precise indication. In this group, nine full-term neonates were diagnosed with CVT. Two cases of CVT associated with bacterial meningitis, and three associated with the presence of a cerebral lesion were excluded. All of the four selected cases were submitted to magnetic resonance angiography (MR angiography) for diagnosis confirmation. All the neonates underwent evoked auditory potential study to evaluate their degree of auditory loss associated with CVT.

All the neonates were male, with gestational age ranging between 37 and 41 weeks (mean, 39 weeks), weight ranging between 3,010 and 4,085 g (mean weight, 3,548 g), and Apgar score at the first minute between 2 and 8 (mean, 5), and at the fifth minute between 7 and 9 (mean, 8).

Also, risk factors for CVT were evaluated according to the following classification: neonatal risks (perinatal hypoxia and sepsis), and maternal risks (diabetes and infection, including infections of any etiology, in any region or organ, during the prenatal period). The clinical evaluation of the neonates was based on the presence, or not, of early (up to 24 hours of life) or late onset seizures, and on the presence of respiratory disorders. All the neonates were evaluated by a single pediatric neurologist from their admission to the ICU up to discharge or follow-up abandonment.

A Sonoline Versa-Pro ultrasonography unit (Siemens Medical Systems; Erlangen, Germany), with a convex, multifrequency transducer was utilized. Transfontanellar US with Doppler fluxometry was performed through the anterior fontanelle, with acquisition of images in the coronal and sagittal planes. Resistance index (RI) was evaluated for both the right and left middle cerebral artery, anterior cerebral artery, and basilar artery, and was considered as altered in the setting of increased RI in at least two vessels. The venous flow was mapped with color Doppler. MR angiography was performed in a Harmony, 1 tesla unit (Siemens Medical Systems; Erlangen, Germany). The neonates received sedation with chloral hydrate as necessary, and in none of the cases, paramagnetic contrast agent was intravenously administered. The imaging evaluation was aimed at identifying and localizing the thrombosis, its association with parenchymal lesions, and the presence, or not, of hydrocephalus.

RESULTS

Table 1 consolidates the clinical data and imaging findings.

The neonatal risk factors observed were associated hypoxia and sepsis in three cases (75%) and hypoxia alone as a single risk

### Table 1: Clinical and imaging findings.

<table>
<thead>
<tr>
<th>Case</th>
<th>Neonatal risk</th>
<th>Maternal risk</th>
<th>RI</th>
<th>US</th>
<th>MRI</th>
<th>CVT site</th>
<th>Evoked potential</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypoxia and sepsis</td>
<td>Diabetes</td>
<td>RMCA: 0.80, LMCA: 0.83, ACA: 0.64, BA: 0.87</td>
<td>Normal</td>
<td>Normal</td>
<td>Sigmoid sinuses</td>
<td>Severe, bilateral auditory loss</td>
<td>Normal up to 10 years of age</td>
</tr>
<tr>
<td>2</td>
<td>Hypoxia and sepsis</td>
<td>Infection</td>
<td>RMCA: 0.82, LMCA: 0.84, ACA: 0.68, BA: 0.58</td>
<td>Straight sinus venous dilation</td>
<td>Normal</td>
<td>Straight sinus</td>
<td>Mild/moderate left auditory loss</td>
<td>Normal up to 2 years of age</td>
</tr>
<tr>
<td>3</td>
<td>Hypoxia and sepsis</td>
<td>Infection</td>
<td>RMCA: 0.91, LMCA: 0.88, ACA: 0.86, BA: 0.88</td>
<td>Normal</td>
<td>Normal</td>
<td>Superior sagittal sinus</td>
<td>Normal</td>
<td>Normal up to 9 years of age</td>
</tr>
<tr>
<td>4</td>
<td>Hypoxia</td>
<td>—</td>
<td>RMCA: 0.89, LMCA: 0.86, ACA: 0.70, BA: 0.88</td>
<td>Normal</td>
<td>Normal</td>
<td>Transverse sinuses</td>
<td>Normal</td>
<td>Normal up to 3 years of age</td>
</tr>
</tbody>
</table>

RI, resistance index; US, ultrasonography; MRI, magnetic resonance imaging; CVT, cerebral venous thrombosis; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; ACA, anterior cerebral artery; BA, basilar artery.
factor in one case. As regards maternal risks, the most frequent one was infection in two cases (50%) and diabetes in one (25%). In one case no maternal risk factor was identified.

The predominant clinical sign was early seizure onset observed in 100% of cases. Respiratory failure occurred in the cases 1, 2 and 4, and apnea in one case (25%).

The response to evoked auditory potential ranged from normal in two cases (50%), mild/moderate, unilateral auditory loss in one case (25%) and severe, bilateral loss in another case (25%).

TFUS was normal in three cases (75%). In the case 2, TFUS identified hypoechoic tubular dilatation diagnosed as venous dilation and absent flow at color Doppler mapping of the straight sinus (Figure 1). Also, the venous Doppler mapping identified flow absence in the superior sagittal sinus, confirmed by MR angiography in the case 3 (Figure 2). In case 1, ectatic ventricular system was observed (Figure 3).

Altered RI in at least two vessels was observed in all the cases, with values ranging between 0.80 and 0.91 (mean, 0.85) for

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**Figure 1.** Case 2. US-Doppler, sagittal image (A,B) demonstrating venous dilation and failure in vessels filling in the straight sinus (arrows). On C, sagittal MRI T1-weighted image demonstrating hypersignal in the superior sagittal sinus and straight sinus (arrows).

**Figure 2.** Case 3. US Doppler, sagittal image (A) demonstrating failure in vessels filling in the superior sagittal sinus (arrow), and MR angiography, TOF sequence (B) also demonstrating failure in vessels filling in the same site (arrow).

**Figure 3.** Case 1. US coronal image (A) demonstrating ectatic ventricular system (white arrows), also demonstrated at axial MRI T1-weighted sequence (B), besides hypersignal at the sigmoid sinuses topography (black arrows). On C, MR angiography TOF sequence demonstrating failure in vessels filling in the right sigmoid sinus (arrow).
the right middle cerebral artery; between 0.83 and 0.88 (mean, 0.85) for the left middle cerebral artery; between 0.64 and 0.86 (mean, 0.75) for the anterior cerebral artery; and between 0.58 and 0.88 (mean, 0.73) for the basilar artery. The cases with low values for RI were attributed to a mechanism of cerebral self-regulation as a function of arterial redistribution resulting from venous congestion secondary to the thrombosis.

Morphological brain MRI was normal in four cases (100%). Cerebral venous thrombosis was diagnosed at T1-weighted sequences complemented by MR angiography.

All the sinuses were isolatedly involved.

As regards their neurodevelopment, all the neonates progressed within the normality parameters until their discharge or follow-up abandonment.

**DISCUSSION**

The global CVT incidence in children is of 0.67/100,000 children per year, and neonates constitute the most affected group. A retrospective study developed from 1999 to 2006 by Tekasem et al. with 71 children divided into three groups (neonates, 0–28 days; infants, 29 days–1 year; children/teenagers, 1–18 years) and diagnosed by computed tomography (CT), CT angiography MRI and MR angiography, reported 48% incidence of CVT in neonates, confirming that this group is more prone to CVT than any other pediatric age range, in spite of the fact that the true incidence rate is still unknown because of the scarcity of reliable epidemiological data. It is believed that neonates propensity to CVT is a result from a failure of protective mechanisms caused by cerebral immaturity, besides the presence of physiological prothrombotic factors and perinatal/postnatal diseases.

According to the literature, CVT is most frequent in male neonates, in a studied population of 32 neonates, similarly to the results of the present study. Risk factors for CVT can be classified into neonatal and maternal, deVeber et al., in a study with 160 children (60 neonates and 91 non-neonates) with ages ranging from NN (gestational age > 36 weeks) to 18 years, have reported the presence of any acute systemic disease in 84% of neonates with CVT and, among them, about 51% and 30% present, respectively, perinatal complications and dehydration as a risk factor for CVT. The most frequent complication was hypoxia in 30 cases, besides premature membrane rupture, maternal infection and gestational diabetes. The results of the present study are in agreement with the literature, both in terms of neonatal and maternal risks. In 25% of cases, no maternal risk factor for CVT was observed. It is interesting to note that all the patients were diagnosed with perinatal asphyxia and precociously admitted to the neonatal ICU where, probably, the associated risk factor has been hypoxia and not infection. Therefore, perinatal complications inexorably constitute the most frequent and relevant risk factor for CVT in neonates, probably resulting from the lack of protective mechanisms as a function of immaturity.

The clinical presentation is highly variable and nonspecific in this age range, and the diversity of associated predisposing factors make the diagnosis difficult and frequently delayed. Additionally, the clinical condition is influenced by the child age, extent and site of the thrombosis. Also, according to deVeber et al., 72% of neonates in their study presented some kind of seizure resulting from (HIE) and/or CVT. Besides seizures, most neonates also present some diffuse neurological sign such as agitation or lethargy. This same study shows that 67% of neonates have not presented any focal neurological deficit; on the other hand, hemiparesis, as a clinical sign, has occurred in only 6% of cases, and cranial nerve palsy in 7%. The absence or scarcity of focal signs is explained by the cerebral immaturity. In agreement with the literature, the present study observed the presence of convulsive seizures in all the patients.

In the setting of thrombosis, the intraluminal venous pressure increases, reducing the blood flow and the cerebral perfusion pressure, which induces the hemoconcentration barrier disruption and frequently results in vasogenic edema and hydrocephalus. In the multicentric study developed by Wasay et al., from 1992 to 2001, with 25 neonates with at least two imaging methods for diagnosis of CVT, hydrocephalus was present in 10% of cases. In the present study, the inclusion criterion was exactly the absence of associated encephalitic lesion.

In approximately 85% of cases, thrombosis affects the superior sagittal sinus or the transverse sinuses and in the other 15%, the other sinuses of the dura mater and deep veins of the Galen’s system. The involvement of multiple venous sinuses may be present in more than 70% of cases. The results of the present study presented isolated involvement of venous sinuses.

The brainstem auditory evoked response test allows the evaluation of the functional integrity of the auditory tract with several clinical applications, particularly as a method for auditory screening in high-risk neonates, because of its objectivity, rapidity, noninvasiveness, bed-side capabilities and applicability to any age range. It is estimated that, in Brazil, three to four in every 1,000 children have congenital deafness. This ratio increases to two–four in every 100 neonates when these children come from an ICU. Deafness associated with the occurrence of thrombosis was described by Perlman et al., one of the first authors to demonstrate the cochlear sensitivity to a vascular event. Currently, many studies suggest the existence of a cochlear vessels spasm or increase in blood viscosity associated to vascular events, like in thrombosis, to explain the temporary deafness. In the present study, in 50% of cases there was an auditory loss ranging from mild to severe.

TFUS with Doppler fluxometry presents great advantages, principally the noninvasiveness to measure blood flow velocity in intracranial vessels and to evaluate physiopathological changes in the cerebro hemodynamics, besides the bed-side capability, low cost and non-necessity of sedation and of ionizing radiation exposure. Several studies on TFUS Doppler fluxometry have demonstrated changes of RI in pathological conditions as, for example, hypoxia with presence of reversed diastolic flow, inclusive, reflecting the increased vascular resistance as a result from edema. The results of the present study are in agreement with the literature.
considering that the increased RI values were observed in all the studied vessels.

MR angiography is the most sensitive and specific method for the diagnosis of CVT and, as combined with MRI is considered as gold standard\textsuperscript{12,28,29}. In agreement with the literature, MR angiography was diagnostic for CVT in 100% of cases in the present study.

According to Teksam et al.\textsuperscript{13}, in a study with 34 neonates with CVT diagnosed by CT, CT angiography, MRI and MR angiography, 62% of neonates with CVT presented an association with parenchymal lesion, with variable location and a predominantly hemorrhagic pattern (76% of cases), but with smaller extent as compared with lesions in older children, and with higher frequency in the frontal and parietal lobes. Additionally, the parenchymal lesion is, in general, correlated with the involved territory of venous drainage (76% of cases). In the present study, association with parenchymal lesion was not observed.

The literature reports a survival rate of more than 90% among NN with associated cerebral lesion\textsuperscript{14}. A Canadian longitudinal study covering an eight-year period reports 8% survival with presence of neurological deficit in 61%, seizures in 21%, and recurrent cerebral thrombosis in 9%\textsuperscript{14}. Yet, some authors report that the best estimate was observed after 2.1 years, as 77% of neonates diagnosed with CVT were neurologically normal, although the absence of association with parenchymal lesion has not been highlighted\textsuperscript{22}.

As regards the evaluation of the neurological development, all the areas remained within the normality parameters up to the abandonment of the follow-up or contact with the clinician.

CONCLUSION

In the neonatal period, combined TFUS and Doppler fluxometry allows the early diagnosis of CVT, which can be confirmed by MRI/ MR angiography, that is the gold standard for the diagnosis of this severe disease. The absence of associated parenchymal lesion may, prospectively, represent the absence of a progressive cerebral damage.

REFERENCES