Cerebral sinovenous thrombosis in a newborn with mutation of MTHFR C677T treated with enoxaparin

Trombosis senovenosa cerebral en un recién nacido con mutación MTHFR C677T tratado con enoxaparina

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What do we know about the subject matter of this study?

Neonatal cerebral sinovenous thrombosis (CSVT) is a rare and usually serious condition thus it should be diagnosed early. There is little knowledge about its pathogenesis and its management is controversial.

What does this study contribute to what is already known?

In our patient, the treatment with low-molecular-weight heparin was successful. The second MRI at two months of age showed adequate repermeabilization and most importantly there was no extension of thrombosis.

Abstract

Introduction: Neonatal cerebral sinovenous thrombosis (CSNT) is a rare and generally serious condition about which there is little knowledge of the responsible pathophysiological mechanisms and, although controversial, it has been suggested that genetic thrombophilia may play a role in its pathogenesis. Out of concern for intracranial bleeding, the anticoagulant treatment with low-molecular-weight heparin is controversial. Objective: To present a case of a newborn with neonatal CSNT, to analyze the thrombophilic risk factors, and the management of cerebral venous thrombosis with low-molecular-weight heparin. Clinical Case: Full-term newborn who presented at eight days of life breastfeeding rejection, clonic seizures, and locomotor hypoactivity. The MRI neuroimaging showed a CSNT involving multiple venous sinuses, a right thalamic hemorrhagic infarction, and venous con-

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gestion in frontal white matter. Thrombophilia study highlighted a homozygous MTHFR C677T mutation. Treatment with low-molecular-weight heparin was associated with repermeabilization of the superior sagittal sinus after 23 days of starting therapy. **Conclusions:** The clinical presentation of CSNT in the neonate is nonspecific, probably related to the extent and severity of the injury and the development of associated complications, such as venous hemorrhagic infarctions and intraparenchymal or intraventricular hemorrhage. These complications are detected through ultrasound or MRI, and they should make us suspect a CSNT. In this experience, the anticoagulant treatment proved to be safe and prevents thrombus propagation.

**Introduction**

Neonatal cerebral sinovenous thrombosis (CSVT) is a rare condition, with an incidence of around 1-12 per 100,000 live births per year which is higher than that of the pediatric age (0.35-0.67 per 100,000 children/year)\(^1\)-\(^3\). Even so, the problem in neonates is probably underestimated since the clinical presentation is nonspecific. In fact, the diagnosis of this entity is increasing due to a higher rate of suspicion and the greater availability and diagnostic capacity of brain neuroimaging techniques\(^1\).

Although several risk factors have been associated with neonatal CSVT, there is little knowledge about the pathophysiological mechanisms responsible for most cases and it has been suggested that inherited thrombophilia (predisposition to thrombosis) may play a role in its pathogenesis, especially mutations of factor V Leiden (FVL G1691A), prothrombin G20210A (FII G20210A), and the MTHFR (C677T) since these factors have been associated with CSVT in adults. However, the evidence in the pediatric and neonatal ages is still controversial\(^4\).

Due to the high prevalence of intracranial bleeding in the infant with CSVT, anticoagulant treatment with low-molecular-weight heparin is controversial. However, because of the risk of thrombus extension and the fact that almost 50% of infants with CSVT have a further neurological disability, anticoagulant therapy has been introduced despite limited experience.

The objective is to present a case of a newborn with neonatal cerebral sinovenous thrombosis, discuss the risk factors of thrombophilia and the management of cerebral venous thrombosis with low-molecular-weight heparin.

**Clinical case**

8-day-old female newborn admitted due to locomotor hypoactivity, breastfeeding rejection, and clonic seizures in the upper limbs associated with gaze deviation. Mother with more than one delivery, with no morbid history. The patient born through vaginal delivery at 40 weeks of gestation, weighing 3,660 g. Apgar scores 9-9 at one minute and five minutes, respectively.

After admission to the neonatal intensive care unit, the aEEG (amplitude-integrated electroencephalography) showed electroclinical seizures (Figure 1), starting treatment with phenobarbital. Due to lack of response, phenytoin was added and, facing the risk of respiratory depression, the patient was intubated and started mechanical ventilation plus treatment with ampicillin and cefotaxime, which was suspended after 48 hours once blood cultures results were available, and Acyclovir which was suspended 4 days after admission. PCR test for herpesviridae (types 1, 2, and 6) was negative, normal serum procalcitonin concentration, and the CSF presented xanthochromia but did not present pleocytosis or glycorrachia.

A head CT scan at admission showed venous thrombosis in the superior sagittal sinus (SSS) and frontal white matter hypointensity. Brain ultrasound of the same day showed an increased echogenicity on the medial segment of the right thalamus but did not show any image suggestive of intraventricular hemorrhage but it showed congestion of the choroid plexuses (Figure 1). The MRI study (T1W, T2W, DWC, ADC, SWI, and TOF sequences) confirmed CSVT affecting the SSS, the straight sinus, and the vein of Galen. In addition, it showed a hemorrhagic infarction in the right thalamic area with an ischemic border in the medial aspect of it, and the patient presented medullary veins congestion in the frontal periventricular white matter (Figure 2).

At 10 days of age, after 48 hours without new seizures, ventilatory support, and aEEG monitoring were withdrawn.

The thrombophilia study (FVL G1691A, prothrombin G20210A, MTHFR C677T, Antithrombin III, Protein C, S, and homocysteine) showed no alterations, except that the patient presented a homozygous C677T mutation in the MTHFR gene. At 12 days of age, we started treatment with low-molecular-weight heparin (enoxaparin) at 1.5 mg/kg/dose every 12 hours.
through subcutaneous route. On day 35, after 23 days of anticoagulant treatment, a transcranial Doppler ultrasound showed blood flow in the SSS (Figure 3). The patient was discharged at 36 days of age without seizures, with strong suction when breastfeeding, and treatment with levetiracetam.

After 2 months of anticoagulant treatment, a control MR angiography (MRA) showed sinus repermeabilization, thinning of the corpus callosum, decreased volume of the white matter, and increased extra-axial space (Figure 3).

Discussion

The CSVT in the newborn has a non-specific and highly variable clinical presentation and severity, probably related to the extent and magnitude of the venous drainage obstruction and the development of associated complications such as intraparenchymal hemorrhage or intraventricular hemorrhage. Clinical manifestation is divided into three categories: a) focal clonic seizures due to local venous infarction or hemorrhage; b) diffuse brain injury characterized by a
variable combination of multifocal seizures, poor oral intake, irritability, hypotonia, apnea (usually epileptic), and/or impaired consciousness (lethargy, stupor, or coma) which are possibly secondary to increased intracranial pressure due to obstruction of venous drainage; and c) as an occasional finding when performing a brain imaging study in a newborn hospitalized due to another reason.\(^1,2,4\)

While in some series seizures are the predominant sign of onset, this is not consistent in all studies.\(^1,4-6\) However, the presence of neonatal seizures, whether focal or multifocal as in our patient, should be considered as a possible CSVT. Unlike ischemic arterial infarction, it is common that part of the clinical syndrome includes deterioration of consciousness in these patients.

CSVT can be observed through Doppler ultrasound or imaging studies including MRI, MRA, and especially MR venography (MRV). CT scan also allows us to establish the diagnosis and, despite using it in our patient, it should not be used in the newborn if other tests are available since its high dose of ionizing radiation. Although transcranial color Doppler ultrasound is a very specific study to rule out CSVT, MRI is the study of choice when there is no blood flow suggesting the diagnosis, and the MRV is now the gold standard to establish the diagnosis accurately.\(^4\)

Our patient presented a multiple CSVT which affected the superior sagittal and straight sinuses, the most frequently affected ones.\(^1,4\) Among the associated lesions (≈50%) in CSVT, specifically in straight sinus thrombosis, stand out unilateral thalamic hemorrhagic

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**Figure 2. A-B.** The MRI study on T1W and T2W shows a hemorrhagic infarction in the right thalamus. Additionally, it shows a thrombosis in the SSS. Besides this, congestion of the medullary veins in the periventricular frontal white matter is present. **C.** Middle sagittal image T2W shows thrombosis in the SSS, of the straight sinus (SS) and of the vein of Galen (VOG), and the internal cerebral vein (ICV). **D.** TOF image shows lack of venous flow in the straight sinus and marked reduction in the SSS.
infarction, intraventricular hemorrhage, or parenchymal hemorrhage infarction. Our patient presented the first on along with medullary veins congestion, especially in the frontal periventricular white matter, which is another frequently observed finding (Figure 1 and 2).

We must rule out a CSVT in the presence of ventricular hemorrhage along with unilateral thalamic hemorrhage and lesions easily detected through brain ultrasonography. In our case, the diagnosis was also supported by an asymmetric aEEG with predominant epileptic seizures on the right side.

A wide range of maternal, perinatal, and neonatal factors can contribute to the development of CSVT. However, in our patient, the only potential risk factor was the homozygous C677T mutation in the MTHFR gene. This gene produces the enzyme methylenetetrahydrofolate reductase (MTHFR) which turns the 5,10 methylenetetrahydrofolate into 5-methylene-tetrahydrofolate. The C677T polymorphism of the MTHFR gene is thermolabile and, when both alleles (homozygous) are mutated, it represents a risk of early thrombotic disease.

Although isolated cases have been published, as well as studies without a control cohort in which several patients with CSVT had an MTHFR mutation, a study that compared genetic thrombophilia among 25 infants with CSVT and their mothers to 85 mother-child control pairs, did not establish that the C677T MTHFR mutation was a risk factor. The only prothrombotic risk factor observed was FII G20210A, which showed an OR 6.70 (95% CI 0.65-69.22). Based on this study, we cannot confirm the role of the MTHFR C677T mutation in the genesis of the CSVT in our patient. However, until there are more studies, all the newborns with CSVT should be studied for thrombophilia, including at least FVG169A, FII G20210A, and MTHFR C677T and any of these mutations should also be considered potential causal factors.

Currently, anticoagulant treatment is recommended in adults with CSVT and also in the non-lactating child, however, the use of such treatment in the neonate is controversial. On the one hand, there is the possibility that if thrombosis is not treated, it will spread, and, on the other hand, there is the fear that if it is treated, the intracranial hemorrhage (ICH), so frequent in
this pathology, will worsen. A recent meta-analysis that studies the influence of ICH on CSVT in treated versus untreated infants did not find that anticoagulant treatment was associated with higher pre-discharge mortality or bleeding complications. In contrast, anticoagulant therapy reduced the risk of thrombosis spreading.

Although there is a lack of evidence on the benefit of the treatment and it comes from international registers and not from studies specifically aimed at answering whether or not anticoagulant therapy is necessary or effective, the available data suggest that anticoagulation treatment is safe and prevents CSVT spreading. In our patient, the second MRI at two months of age showed adequate repermeabilization, and, most importantly, there was no extension of thrombosis.

Conclusions

Despite it is a rare pathology, neonatal cerebral sinovenous thrombosis is often serious, requiring early diagnosis and an appropriate management plan. In the case of a full-term newborn with seizures and no clear cause, we must complete the imaging study through brain ultrasonography and MRI. If there is intraventricular or thalamic hemorrhage, we must rule out CSVT. Although controversial in neonates, anticoagulant treatment has shown to be safe and to prevent the thrombosis spreading.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.
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