

Venous sinus thrombosis in pediatrics. Case series of a tertiary hospital

Trombosis de senos venosos en pediatría. Serie de casos de un hospital terciario

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

In pediatrics, venous sinus thrombosis is an infrequent entity with a varied form of presentation and therefore often underdiagnosed. It is potentially serious with the risk of neurological sequelae, which decrease with early diagnosis and treatment.

What does this study contribute to what is already known?

This study suggests further studies to corroborate hypotheses such as the possibility of shortening the duration of anticoagulant treatment by performing earlier control neuroimaging, or the symptomatic treatment of intracranial hypertension with acetazolamide.

Abstract

Venous sinus thrombosis (VST) is a rare entity in pediatrics, probably under-diagnosed and potentially serious, described as a cause of stroke in childhood. **Objective:** To describe the clinical presentation, risk factors, treatment, and evolution of pediatric patients with VST. **Patients and Method:** Retrospective study of patients admitted to a referral hospital, diagnosed with VST, aged between one month and seventeen years, from January 2011 to December 2019. The following data were reviewed: age at diagnosis, sex, signs and symptoms of presentation, predisposing mechanisms, study of thrombophilias, treatment and duration of treatment, follow-up protocol, long-term sequelae, and mortality. Due to their differences in clinical presentation, the sample was divided into two age groups: young children between 1 month and 5 years and older children and adolescents between 6 and 17 years. **Results:** 17 patients were diagnosed with VST, 45% were women, with a median age of 4.5 years. The most frequent symptoms in older children (6-17 years old) were headache (80%) and diplopia (60%). In children under 5 years old, the most frequent clinical presentation was cerebellar ataxia (42%), asymptomatic (34%), and headache (25%). In 23.5% of the total, VST was a casual finding in neuroimaging. 13 patients presented relevant histories such as complicated otitis media with mastoiditis (53%), severe traumatic head injury (6%), and resection of a space-occupying lesion of the brain (6%). 23% of the cases were idiopathic and in 23% there were prothrombotic factors. The

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treatment of choice in all patients was low-molecular-weight heparin. During the short-term follow-up, 11.8% presented self-limited neurological symptoms. One patient presented long-term paresis of the sixth paired cranial nerve. There were no deaths or recurrences of the episode in our series. **Conclusions:** VST is a rare entity and it usually appears with signs and symptoms of intracranial hypertension. It is a potentially serious condition and early diagnosis and treatment can help minimize long-term sequelae.

Introduction

In pediatrics, venous sinus thrombosis (VST) is a little-known entity, possibly underdiagnosed. It is a potentially serious disease and is one of the causes of stroke in childhood¹⁻³.

The most frequent risk factors in children are infections of the otorhinolaryngological area, which produce continuity thrombophlebitis, and hematologic disease. Other less frequent associated factors are traumatic brain injury (TBI), the use of certain drugs, or hypercoagulability in the context of neoplasms¹⁻³.

Clinically, it may present with symptoms and signs of intracranial hypertension (ICH) (headache, vomiting, papilledema, sixth nerve palsy, or visual disturbances), neurological symptoms (monoplegia, hemiparesis, or epileptic seizures), and symptoms of encephalopathy (altered state of consciousness or coma)^{4,5}.

Magnetic resonance imaging (MRI) is the diagnostic test of choice because of its greater sensitivity; but, if there is no urgent possibility, a CT scan without contrast is usually the initial exploration allowing to rule out intracranial complications that are present in up to 70% of cases¹⁻³.

There is little evidence regarding treatment in children, but the same guidelines are recommended as in adults. Several studies show that anticoagulation is effective in reducing the risk of death, sequelae, and recurrences in children^{4,5}. A study that analyzed patients in the International Pediatric Stroke Study (IPSS)⁶ registry showed better results at discharge in children who received anticoagulation treatment compared with those who did not receive it, and these results persisted in the long term.

The treatment of choice consists of anticoagulation with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). There is evidence that suggests that LMWH is more effective than UFH and at least as safe, so LMWH is preferred unless in case of hemodynamic instability, planned invasive interventions, or contraindication. Control measures should be established in case of increased intracranial pressure^{4,5}.

A large international multicenter study⁷ found a short-term abnormal clinical status in 43% of pa-

tients. Regarding long-term evolution, there is a greater discrepancy, since some studies show that most patients recover without residual symptoms while others find greater alterations, such as residual epilepsy⁸. The most frequent acute cause of death is brain herniation^{4,5}.

The objective of this study is to analyze the clinical presentation, risk factors, treatment, and short- and long-term evolution of this entity.

Patients and Method

Design

Retrospective study, by review of medical records of patients, admitted to a referral hospital with a diagnosis of VST, aged between one month and seventeen years, from January 2011 to December 2019.

The following data were reviewed: age at diagnosis, sex, presenting signs and symptoms, predisposing mechanisms, testing for thrombophilias, treatment and duration of treatment, follow-up protocol, long-term sequelae, and mortality.

Statistics

The data were analyzed with the SPSS software. A descriptive analysis of the data was performed, expressing quantitative variables as median and interquartile range (IQR) and qualitative variables as number and percentage.

Due to their differences in clinical presentation, the sample was divided into two age groups: the first one of young children aged between 1 month and 5 years and the second one of older children and adolescents between 6 and 17 years of age.

This study has been approved by the Ethics Committee for Drug Research of the *Hospital Universitario y Politécnico La Fe*.

Results

Seventeen patients with a diagnosis of VST were included. The median age was 4 years (IQR 2-6) and 45% of the sample was female.

In the group of older children (5 patients), 4 (80%) presented with headache, and 3 (60%) presented with diplopia due to sixth nerve palsy. The other patient presented with status epilepticus.

In the group of young children (12 patients), there was greater variability in symptomatology, with 5 patients with cerebellar ataxia (42%), 3 with headache (25%), 2 with sixth nerve palsy (17%), 2 with vomiting (17%), and one patient with epileptic seizure. Four children (34%) were asymptomatic and the diagnosis of VST was a chance finding on neuroimaging.

The most frequent associated risk factor was complicated acute otitis media (AOM) with mastoiditis in 9 cases (53%). Figure 1 shows other related risk factors. Cases secondary to AOM occurred in younger patients, with a median age of 3.4 years, and the oldest patient was 7 years old. In 23.5% of the patients, there was no associated usual risk factor. Of these, 50% had ulcerative colitis, thus it was suspected that a prothrombotic state secondary to this disease may contribute.

All patients underwent a study of prothrombotic risk factors, showing alterations in 4 of the patients (23.5%), one case of heterozygous prothrombin mutation, and 3 cases of lipoprotein(a) elevation. These 4 patients had other risk factors mentioned above (3 mastoiditis and one case of ulcerative colitis).

All patients received treatment with LMWH (subcutaneous enoxaparin), including the case secondary to TBI with a small epidural hematoma.

Treatment was initiated at a dose of 1mg/kg/12 hours and then adjusted according to anti-Xa levels. The regime was maintained until resolution was confirmed in the neuroimaging, which was performed 2-3 months after the start of treatment. In two cases, the control test was requested between 15 days and one month as part of the evolution control of complicated mastoiditis, observing in both cases resolution of the thrombosis.

After resolution was observed in neuroimaging, enoxaparin treatment was reduced to prophylactic doses of 1 mg/kg/24 hours. The mean total duration of treatment was 4 months (range between 3 and 7). In 2 patients, anticoagulation was maintained for up to 48 months with acenocoumarol, given the suspicion of high prothrombotic risk (patients with ulcerative colitis)^{9,10}. Patients with confirmed thrombophilia (heterozygous prothrombin mutation or lipoprotein(a) elevation) did not require prolonged anticoagulation for this reason alone.

In two patients who presented with clinical symptoms of ICH, the initial suspicion was benign ICH due to normal CT scan and increased opening

pressure in lumbar puncture, with normal CSF cytochemistry. They were treated with acetazolamide, with clinical improvement. The control MRI showed a VST.

Follow-up at discharge was performed in the neuropsychiatry office to monitor the long-term evolution of the possible neurological deficits and the lesions observed in the neuroimaging. Follow-up was also performed in the pediatric hematology office, where anticoagulant treatment was monitored and a control brain imaging test was requested, which in our center is performed between 2 and 3 months after the event.

In 88.2% of the cases, complete resolution of the acute thrombosis was observed in the control MRI at 2-3 months (Figure 2). In 5 patients (29.4%), chronic changes secondary to thrombosis persisted (fibrosis of the sinus wall, hemorrhagic transformation of ischemic stroke), without clinical relevance.

During follow-up, 2 patients (11.8%) presented short-term neurological deficits. One of them presented repeated and difficult to control epileptic seizures, with generalized tonic-clonic characteristics, requiring continuous perfusion of midazolam, and a venous infarction with hemorrhagic transformation in the right frontal area was evidenced in the control MRI performed four days later. The other patient presented a clinical picture of left hemiparesis and difficult-to-control seizures. Both had a rapid recovery after treatment with complete disappearance of symptoms in a few weeks. One patient (5.8%) presented with chronic sixth nerve palsy.

There were no deaths or serious complications due to thrombosis or treatment, and no recurrences during the follow-up period (between 1 and 9 years).

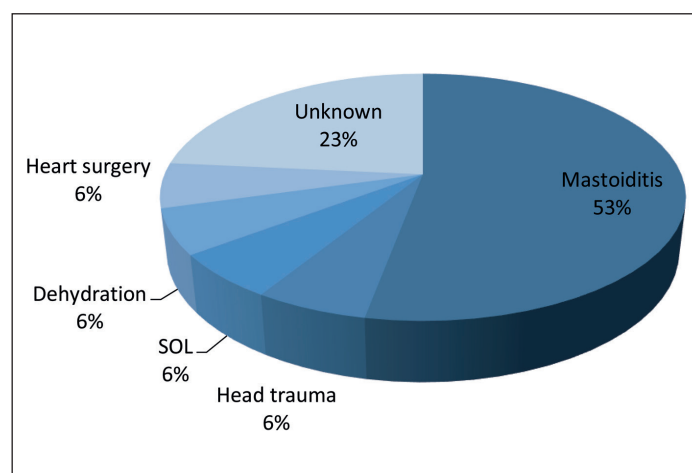


Figure 1. Predisposing factors for cerebral venous thrombosis in 17 patients. SOL: space-occupying lesion, at the brain level.

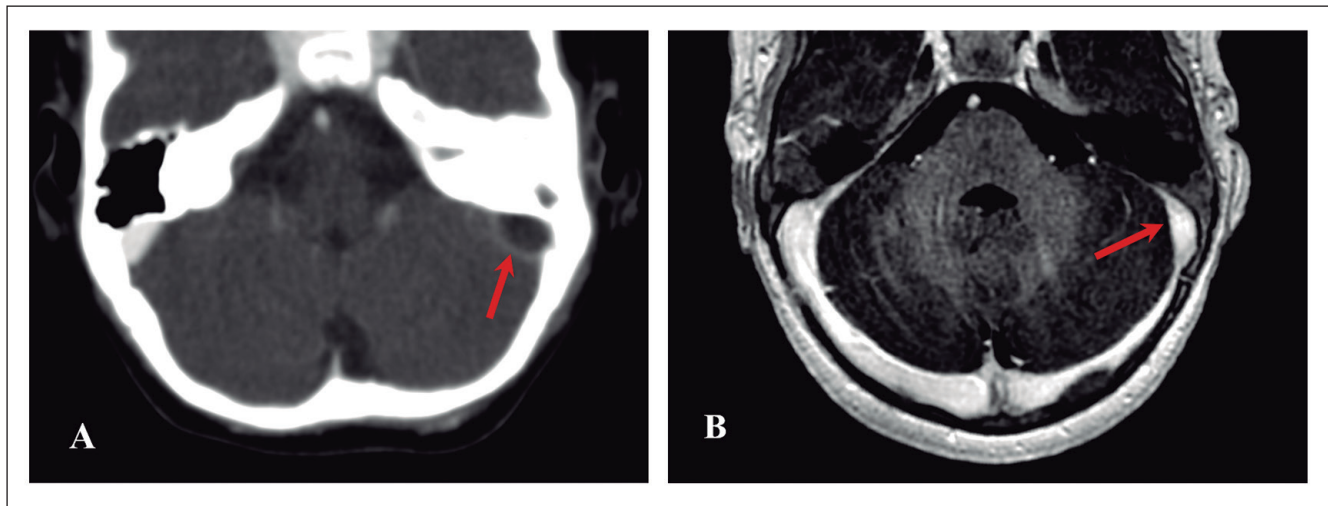


Figure 2. 2-year-old woman with left AOM and sigmoid sinus thrombosis that extends to the jugular gulf. In CT after administering contrast (A), otomastoid occupation and ectasia with a filling defect of the left sigmoid sinus were observed. Control at 3 months with contrast-enhanced MRI (B) shows repermeabilization of the sigmoid sinus.

Discussion

VST is an infrequent entity, which usually manifests with signs and symptoms of ICH, with a wide variety of clinical manifestations that makes diagnosis difficult¹⁻³.

Among the risk factors in children, complicated AOM was the most frequent cause in our series, coinciding with the literature.

The hematological disorders with the greatest impact associated with VST are the presence of factor V Leiden, prothrombin gene mutation, and antiphospholipid syndrome^{4,5,11,12}. In our series, four patients with thrombophilia were identified, one with prothrombin mutation in heterozygosis and three cases of lipoprotein(a) elevation. However, given the presence of other concomitant prothrombotic factors, it is difficult to confirm that the presence of coagulation alterations is sufficient for the development of VST.

Two patients in our series had ulcerative colitis. Inflammatory bowel disease is a multisystem disease that conditions a proinflammatory state that can be directly related to a state of procoagulability and activate the coagulation cascade with consequent thrombosis. Further studies are needed in patients with inflammatory disease to determine the risk of thrombosis they are exposed to^{9,10}.

Early diagnosis and treatment minimize the risk of cerebral ischemia and long-term sequelae^{1,6,12,15}. In our series, all patients received treatment with LMWH. There is little evidence in the literature regarding anticoagulant treatment in children, and therefore the same treatment as in adults with LMWH is recom-

mended. The published studies advise, once the acute phase has ended, to maintain LMWH or continue with vitamin K antagonists for at least 3 months^{12,14,15}. In our series, the mean duration of treatment was 4 months, in line with that described in the literature. If recanalization of the venous sinuses is incomplete or symptoms persist after 3 months, prolongation of treatment is suggested. The presence of hemorrhagic venous infarction, ICH, or isolated subarachnoid hemorrhage are not contraindications for treatment with anticoagulants in VST^{14,15}. Prospective and case-control studies are needed to better clarify the role of anticoagulant therapy.

It should be noted that two cases were initially diagnosed as benign ICH because they presented symptoms of ICH with diplopia due to sixth nerve palsy and persistent headache, normal brain CT and increased opening pressure in CSF, so treatment with acetazolamide was started. In the control MRI, venous sinus thrombosis was observed and later it was classified as secondary ICH. In both patients, the clinical condition improved after lumbar puncture and the start of medical treatment with acetazolamide. These data suggest that, in addition to etiological treatment with LMWH, patients with symptoms of ICH could be treated symptomatically with acetazolamide.

During follow-up, a control neuroimaging is recommended to assess venous sinus recanalization. There is no consensus in the literature on when this should be performed^{12,13}. In our series, most patients underwent monitoring between 2 and 3 months from the start of anticoagulant treatment, and adequate repermeabilization was observed in 88.2%. In 2 cases,

a brain MRI was performed during the first month of treatment and complete resolution of the thrombosis was observed. This suggests that it may be possible to perform early monitoring after one month of treatment, which could shorten the anticoagulation time of the patients. However, further studies are needed to establish the optimal time frame for neuroimaging monitoring.

This study presents percentages similar to other studies in the literature regarding forms of presentation and risk factors. Our study also coincides with others in that the patients presented short-term neurological alterations, such as seizures or neurological deficits⁷.

On the other hand, there is a discrepancy regarding long-term evolution, since most of our series presented clinical normality, except for one patient with sixth nerve palsy, and there were no serious sequelae or death. However, other studies have found a higher percentage of long-term sequelae, such as the study by Mineyko A. et al⁸, in which 25% of patients with VST presented epilepsy one year later. This appeared in patients without presenting seizures at the acute moment, nor having lesions on neuroimaging. Early diagnosis and treatment could be key to reducing long-term sequelae.

The study is limited by the sample size because it is an infrequent entity with great age variability, where etiology and therefore the behavior of the disease is different in younger and older children.

In our experience, symptomatic treatment with acetazolamide in patients with ICH symptoms has been effective without adverse effects.

Neuroimaging monitoring one month after the episode could contribute to assessing the early resolution of sinus thrombosis, thus shortening the duration of anticoagulant treatment. In addition, it is suggested that the coexistence of pathologies such as inflammatory bowel disease increases the risk of venous sinus thrombosis and could be a factor to consider increasing diagnostic suspicion in these patients and to establish the duration of treatment.

With the current evidence, it is not possible to es-

tablish solid recommendations regarding the duration of anticoagulant therapy, the timing of radiological controls, or the benefit of symptomatic treatment with acetazolamide in patients with symptoms of ICH, so we suggest further studies.

In conclusion, VST is an infrequent entity in children with risk of severe sequelae, it usually manifests with signs and symptoms of ICH although the clinical manifestations are varied. Complicated AOM is the most frequent predisposing factor in our series. Early diagnosis and treatment with LMWH could minimize the risk of cerebral ischemia and long-term sequelae.

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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