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ORIGINAL ARTICLE

Clinical and radiological features of cerebral venous thrombosis in a children cohort

Características clínicas y radiológicas de una cohorte de niños con trombosis venosa intracraneal

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Abstract

Introduction: Cerebral venous thrombosis (CVT) is an uncommon and poorly studied condition in the pediatric population. **Objectives:** To describe and compare the clinical and radiological features of non-neonatal children with CVT according to age and to analyze their association with functional impairment or mortality at hospital discharge. **Methodology:** An observational cohort study of children older than 30 days with a first CVT diagnosed with imaging/venography by magnetic resonance (IMR/VMR). We measure functionality with the modified Rankin scale defining marked impairment with 3 to 5 points. We used U-Mann-Whitney test to compare ages averages between groups with and without the different studied variables (significance < 0.05). We used logistic regression analyses to estimate the risk of adverse outcome for each variable expressed in Odds Ratios (ORs) and 95% confidence intervals (CI). **Results:** Among 21 patients recruited, 42.8% were girls, median age 6.27 years (Interquartile range: 0.74-10). The average age was lower in children with diagnostic delay > 48 hours ($p = 0.041$), score < 12 in the Glasgow coma scale ($p = 0.013$), seizures ($p = 0.041$), sinus rectus thrombosis ($p = 0.011$), and intracranial hemorrhage ($p = 0.049$); while it was significantly higher in children with intracranial hypertension syndrome ($p = 0.008$). The presence of some chronic systemic condition (OR = 11.2; CI = 1.04-120.4), deep CVT (OR = 14; CI = 1.3-150.8), and brain ischemia (OR = 15.8; CI = 1.4-174.2) was associated with marked functional impairment or mortality at discharge. **Conclusions:** Clinical and radiological features of CVT are age-related. Chronic illnesses, deep venous system involvement, and brain ischemia predict adverse short-term outcomes.

Keywords:
Dural sinus thrombosis; brain infarction; intracranial hemorrhage; pediatric stroke; functional evaluation

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Introduction

Cerebral venous thrombosis (CVT) is a type of cerebrovascular disease characterized by partial or total occlusion of blood flow in the superficial or deep venous system, including involvement of cortical sinuses and veins, with or without secondary injury of the cerebral parenchyma due to ischemia or hemorrhage[1,2].

It is a rare condition in pediatric age, with an estimated incidence of 0.6 cases per 100,000 children per year[1-4]. Most cases occur in neonates (30 to 50%) with some acute or chronic systemic condition, causing non-specific clinical manifestations such as acute/subacute consciousness impairment or generalized seizures[5].

In children over one month of age, the diagnosis is usually delayed due to the high variability in manifestations and the low threshold of suspicion on the part of physicians[1,6]. Neurological symptoms of CVT are usually overall deficits, such as both quantitative and qualitative impairment of consciousness, progressive subacute headache, vomiting, and visual disturbances (usually nonspecific and characteristically decreased visual acuity or diplopia) secondary to cerebral edema and increased intracranial pressure. However, there is a high proportion of patients with focal neurological deficits, such as hemiparesis, aphasia, dysarthria, quadrantanopsia, and cerebellar ataxia due to ischemic or hemorrhagic involvement of the cerebral parenchyma[6,7].

A relatively recent, multicenter study assessing the acute clinical and radiologic characteristics of cerebral venous sinus thrombosis in 170 non-neonatal children found an association between (1) in-hospital mortality and absence of anticoagulation and (2) neurological status abnormalities at discharge or death and decreased level of consciousness at presentation and presence of a known prothrombotic state[6]. However, this study did not evaluate the neurological function at discharge or its relationship with concomitant acute diseases, cortical vein thrombosis, and cerebral infarction.

The objective of this study is to describe the clinical and neuroimaging characteristics of a first CVT in non-neonatal children, to differentiate them according to the age at presentation and to analyze their association with poor survival and functional outcome at hospital discharge.

Methodology

Study design

Observational analysis of a cohort of children recruited consecutively, with diagnosis of CVT through neuroimaging between 30 days and 18 years of age, admitted between January 2003 and March 2015 to the Department of Pediatrics of the Clinical Hospital of the Pontifical Catholic University of Chile and with evaluation by a pediatric neurologist of the institution during the hospital stay.

In order to reduce confounding variables, we exclude patients with neonatal CVT and other concomitant forms of cerebrovascular diseases, as well as children with a history of psychomotor developmental disturbances or known neurological pathology commonly associated with epilepsy.

This study was approved by the Scientific Ethics Committee of the Faculty of Medicine of the Pontifical Catholic University of Chile (Project ID: 160907008).

Definitions and data collection

We define CVT as any obstruction, partial or total, to blood flow from the cerebral parenchyma to the superior vena cava by a thrombus[8]. The used definition of epilepsy is the suggested by the International League Against Epilepsy (ILAE) at the time of study initiation[9]. The definitions used to define cerebral ischemic involvement and intracranial hemorrhage are those suggested by the American Heart Association/American Stroke Association (AHA/ASA)[10].

Prospective recruitment was made in a pre-built database, according to the criteria and protocols of the International Pediatric Stroke Study (IPSS)[6]. Demographic data, clinical presentation, and risk factors for CVT were recorded: gender, age at onset of CVT, days between symptoms onset and diagnosis, intracranial hypertension syndrome (headache, vomiting, vertigo, photophobia, diplopia, or ataxia; without other detected cause), quantitative impairment of consciousness (defined with a score < 12 points on the Glasgow Coma Scale (GCS) adapted to pediatric age), epileptic manifestations (symptomatic generalized seizures, symptomatic focal seizures or convulsive status epilepticus), focal deficits (paresis, acute language and visual impairment; with evidence of compatible brain injury), chronic systemic conditions (known prothrombotic conditions, including antithrombin deficiency, nephrotic syndrome, antiphospholipid syndrome, thrombocytosis, and iron deficiency anemia; heart disease, hematologic malignancies, use of procoagulant drugs, ulcerative colitis), acute systemic conditions (infections, febrile syndrome, dehydration, anoxia, central venous line), chronic local conditions (intracranial neoplasia), acute local conditions (upper respiratory infection, acute bacterial meningitis), use/type of anticoagulant therapy (unfractionated heparin (UFH), low molecular weight heparin (LMWH)). Demographic, clinical and laboratory data were obtained using a pre-designed form according to institutional data collection protocols.

All patients with magnetic resonance imaging (MRI) and cerebral MR venography (MRV) evaluated and reported by a neuroradiologist at the time of diagnosis (1.5 T Philips Achieva; diffusion-weighted images, Fluid-Attenuated Inversion Recovery, Double Inversion Recovery and T1; axial, coronal and parasagittal cuts of 5 mm thickness and 2.5 mm separation between cuts).

Functional impairment at discharge was measured using the modified Rankin scale score (mRS) for children and categorized as absent (mRS score 0), mild (mRS score 1 or 2, with neurological impairments that do not interfere with the performance of daily living activities) and marked (mRS score 3, 4 or 5, with neurological impairments that interfere with the performance of daily living activities)[11,12]. We define poor outcome as in-hospital death or marked functional impairment at discharge.

Data analysis

All statistical analyses were performed using IBM SPSS Statistics software version 20 (IBM Corp., Somers, NY). The demographic, clinical and radiological characteristics of the study subjects were summarized in absolute and relative frequencies. We ruled out the hypothesis of normal age distribution at the time of CVT (Shapiro-Wilk $p = 0.061$). Continuous variables were expressed as median and interquartile ranges (IQR) or mean. We compared the age distribution of each clinically significant dichotomous variable with the nonparametric U-Mann-Whitney test (bilateral exact significance set at $p < 0.05$). We performed univariate binary logistic regression analysis to identify the association between each clinical/radiological characteristics and the chance of marked functional impairment or death in the acute period (expressed as Odds Ratios (ORs) and their corresponding 95% confidence interval (CI)).

Results

Demographics and clinical characteristics

21 patients with CVT were identified during the study period. 12 boys (57.2%) and 9 girls (42.8%). The median age at the time of the acute event was 6.27 years (IQR, 0.74 and 10 years). CVT was detected in six infants (< 2 years), four preschoolers (2 to 5 years), six schoolchildren (6 to 10 years), and five adolescents (10 to 18 years).

Table 1 summarizes the clinical characteristics at the time of diagnosis and the differences in the age distribution of each variable. The average time between the onset of symptoms and the diagnosis through MRI/MRV of CVT was 3.5 days. The average age was significantly lower in the group of patients diagnosed after 48 hours of the onset of symptoms compared to those diagnosed early. Risk factors for the development of CVT were identified in 20 patients (95.2%). There were no statistically significant differences in the age distribution for the different categories of risk factors; however, the average age of children with heart disease tended to be lower than that of patients without heart disease. The average age of patients with impairment of consciousness and seizures was significantly lower than that of children without these manifestations, while the average age was significantly higher in patients with intracranial hypertension syndrome.

Radiological characteristics

MRI/MRV was performed as the initial diagnostic method in 19 children (90.4%). In the remaining two patients, non-contrast cerebral computed tomography (CT) scan was initially performed, and MRI/MRV was performed within the first week of the initial neuroimaging. CT scan failed to detect one in two patients, which was studied with MRI/MRV.

Most patients had superficial venous thrombosis (20/21, 95.2%). 12 patients (57.1%) with multiple sinus thrombosis. The most frequently affected venous sinuses were the superior sagittal one (Figure 1), the transverse one and the sigmoid one (Figure 2). There was concomitant cortical vein involvement in ten cases (47.6%) and deep venous system involvement in four cases (19%). 12 patients (57.1%) were detected with a brain injury (ischemic or hemorrhagic) associated with CVT, 11 (52.4%) with infarction and nine (42.9%) with intracranial hemorrhage. The average age of patients with straight sinus thrombosis and intracranial hemorrhage was significantly lower compared to children without these characteristics (Table 2).

Anticoagulant therapy

Out of 17 patients (81%) who received anticoagulant therapy during the acute episode, 14 (66.7%) were treated with UFH and three (14.3%) with LMWH. Out of the four patients who did not receive anticoagulant therapy, two had congenital heart disease with severe hemodynamic instability, one child had bacterial meningitis and thrombocytopenia, and one patient had active gastrointestinal bleeding. No patients received thrombolysis with alteplase or thrombectomy.

Functional impairment at discharge

Regarding functional status at discharge, nine patients (42.9%) had no impairments, four children (19%) had mild functional impairment, five children (23.8%) showed marked functional impairment, and three patients (14.3%) died before hospital discharge (two of them due to the underlying pathology: con-

Table 1. Demographics, clinical presentation, risk factors for thrombosis and anticoagulant therapy of 21 pediatric patients with cerebral venous thrombosis

		Average age (years)		
	N (%)	Present	Absent	P-Value*
Demographics				
Sex (female)	9 (42.9)	7.17	5.15	0.422
Delay in diagnosis (> 48 hours)	9 (42.9)	3.73	7.74	0.041
Clinical presentation				
Intracranial hypertension syndrome**	13 (61.9)	8.18	2.51	0.008
Impairment of consciousness (GCS < 12 points)	13 (61.9)	3.69	9.81	0.013
Epileptic manidestations at onset	9 (42.9)	3.11	8.21	0.041
Focal deficits	5 (23.8)	7.59	5.53	0.495
Risk factors for thrombosis***				
Acute conditions				
Local (head and neck)	8 (38.1)	3.89	7.33	0.268
Upper respiratory infections	4 (19)	5.96	6.04	0.897
Acute bacterial meningitis	4 (19)	2.78	6.78	0.275
Systemic	9 (42.9)	5.15	6.68	0.862
Fever	7 (33.3)	5.43	6.32	0.971
Sepsis	8 (38.1)	4.83	6.76	0.697
Other^	3 (14.3)	-	-	-
Chronic conditions				
Systemic	12 (57.1)	7.38	4.22	0.345
Prothrombotic conditions ^^	5 (23.8)	8.86	5.14	0.179
Antithrombin deficiency	2 (9.5)	-	-	-
Nephrotic syndrome	3 (14.3)	9.86	5.38	0.185
Other^^^	2 (9.5)	-	-	-
Heart disease	4 (19)	2.66	6.82	0.065
Hematologic malignancies	2 (9.5)	-	-	-
L-asparaginase	2 (9.5)	-	-	-
Ulcerative colitis	1 (4.8)	-	-	-
Local (head and neck)	1 (4.8)	-	-	-
Anticoagulant therapy				
Any therapy	17 (80.9)	6.59	3.59	0.237
Unfractionated heparin	14 (66.6)	5.08	7.91	0.585
Low molecular weight heparin	3 (14.3)	12.8	4.88	0.035

GCS: Glasgow Coma Scale. *P-value of the non-parametric Mann-Whitney U test for age. **Includes headache, vomiting, vertigo, diplopia, photophobia, and ataxia. ***Risk factors are not mutually exclusive. ^Includes dehydration (1), anoxia (1), central venous catheter (1). ^^Includes congenital and acquired alterations. ^^^Includes antiphospholipid syndrome (1), thrombocytosis/iron deficiency anemia (1).

genital heart disease and bacterial meningitis, and one case attributable to cerebral infarction associated with a transtentorial herniation).

Patients with a poor outcome had more frequent chronic underlying conditions, deep vein thrombosis and cerebral parenchymal infarction compared to survivors with mild or absent functional impairment (Table 3).

Discussion

This study provides detailed information on clinical manifestations, predisposing conditions, and neuroimaging findings during the acute period in a group of children with CVT after neonatal age. The clinical presentation, the time between the onset of symptoms and diagnosis, and some radiological characteristics of the lesion are dependent on the age at which the event occurs, and there are factors related to the index episode that predict poor vital and function prognosis in the short term.

The age of the cohort was similar to that described in previous studies, with a high occurrence of CVT in patients under two years of age[6]. Although the incidence appears to be inversely related to age, there is an increase in the frequency of diagnosis in schoolchildren and adolescents, probably associated with the presence of a higher number of prothrombotic conditions.

Despite finding a higher proportion of male pa-

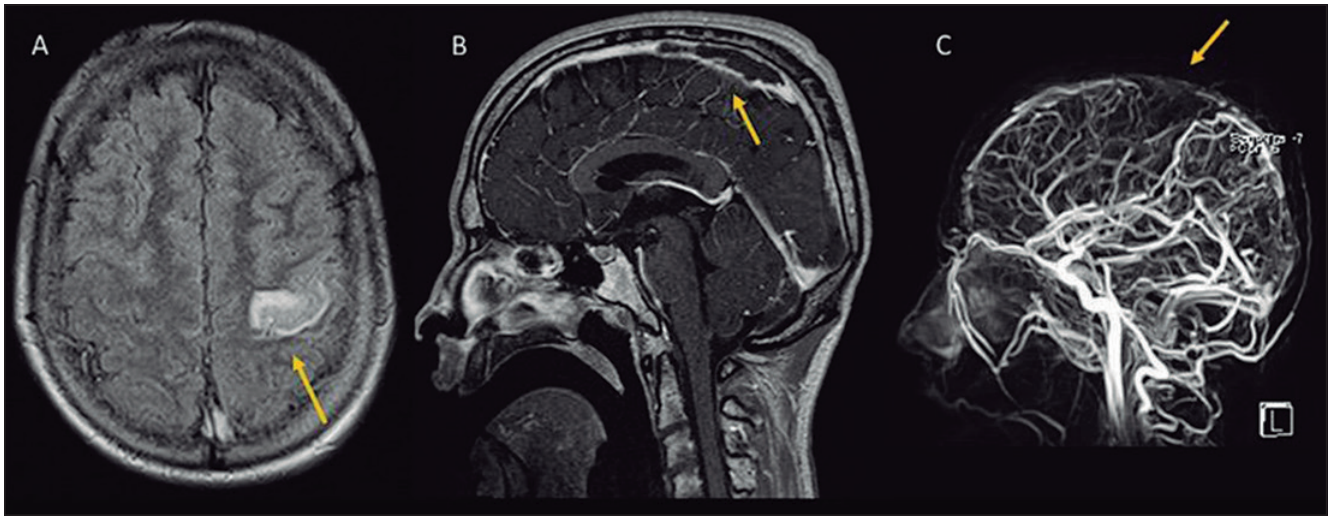

Figure 1. MRI of the brain of a fifteen-year-old patient with acute lymphoblastic leukemia. **(A)** Axial T2 FLAIR-weighted image show a hyperintense lesion concordant with a cortical ischemic stroke of the left postcentral gyrus. **(B)** Lateral sagittal gadolinium-enhanced T1-weighted image, and **(C)** MRV show signs of thrombosis of the middle and distal thirds of the superior sagittal sinus and adjacent cortical veins. A diffuse hypo intensity of the bone marrow compatible with infiltration by base pathology is observed.

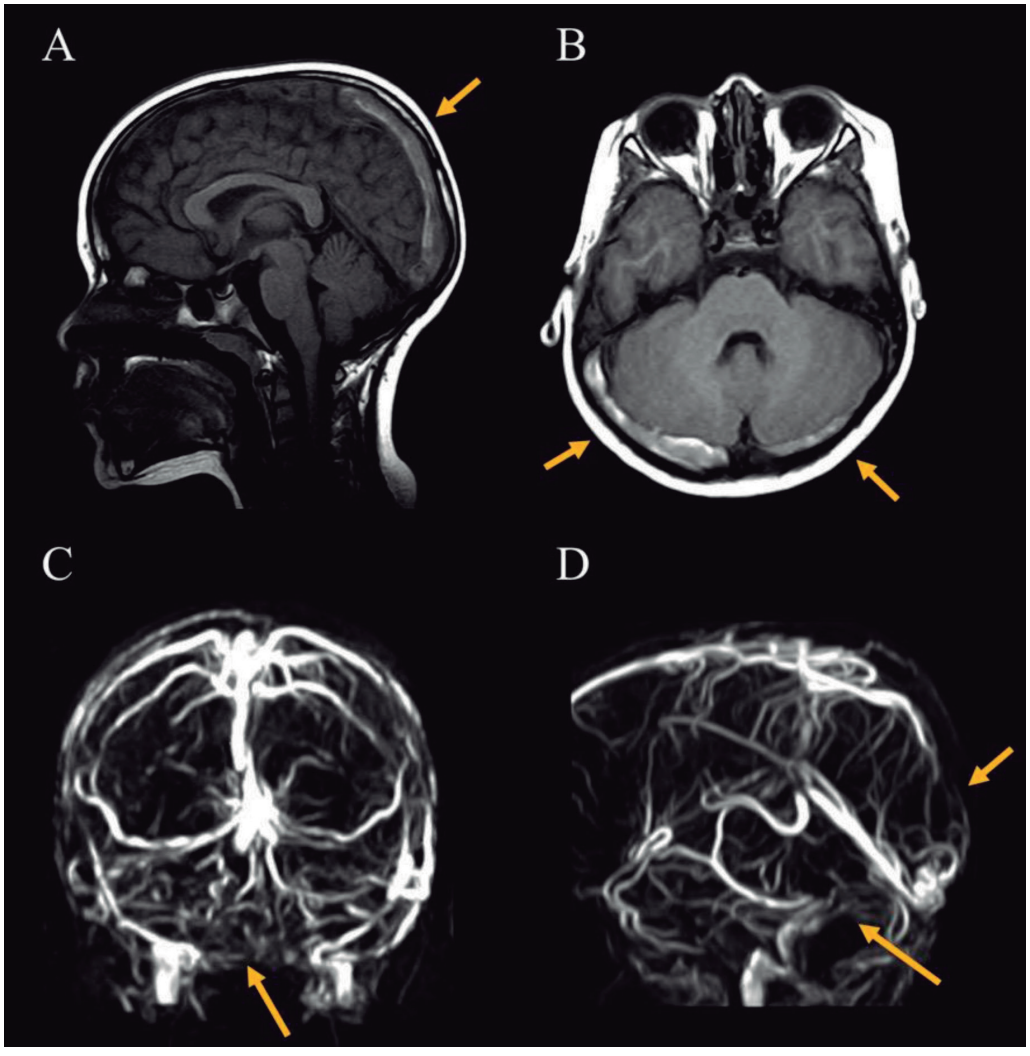

Figure 2. IMRI of the brain of a six-year-old patient with bilateral mastoiditis. Lateral sagittal and axial gadolinium-enhanced T1-weighted images show signs of thrombosis of the distal third of the superior sagittal sinus **(A)** and both transverse sinuses **(B)**. MRV show signs of thrombosis of the distal third of the superior sagittal sinus, both transverse sinuses (**C** and **D**, arrow above), and right sigmoid sinus (**D**, down arrow).

Table 2. Radiological Characteristics of the cerebral venous thrombosis and brain ischemic and hemorrhagic parenchymal lesions

	N (%)	Average age (years)		P-Value*
		Present	Absent	
Number of involved sinuses				
1	9 (42.9)	6.79	5.44	0.464
2	4 (19)	5.18	6.22	0.829
3 o more	8 (38.1)	5.57	6.31	0.595
Localization of thrombosis				
Superior sagittal sinus	14 (66.6)	6.74	4.58	0.443
Transverse sinuses	11 (52.4)	6.06	5.98	0.863
Right	7 (33.3)	5.06	6.51	0.287
Left	8 (38.1)	4.74	6.81	0.301
Sigmoid sinuses	7 (33.3)	4.78	6.64	0.322
Right	6 (28.6)	3.96	6.85	0.154
Left	3 (14.3)	3.31	6.47	0.185
Straight sinus	3 (14.3)	0.45	6.95	0.011
Cortical veins (superficial)	10 (47.6)	6.22	5.84	0.756
Deep venous system	4 (19)	4.67	6.34	0.574
Intracranial associated lesion				
Any lesion	12 (57.1)	4.85	7.58	0.193
Brain infarct	11 (52.4)	5.04	7.11	0.314
Intracranial hemorrhage	9 (42.9)	3.61	7.84	0.049
Parenchymal hemorrhage	8 (38.1)	4.03	7.25	0.161
Intraventricular hemorrhaga	3 (14.3)	3.68	6.41	0.471

*P-value of the non-parametric Mann-Whitney U test for age.

tients, there were no differences in prognosis or age distribution when comparing by sex. Prospective multicenter studies in the adult population have determined that the female gender is an independent risk factor (correcting for oral contraceptive use, pregnancy and puerperium) for the development of CVT, and women have better long-term neurological prognosis than men[13]. In contrast, the available pediatric literature shows a higher frequency of this condition in boys and the short and long-term prognosis is similar regardless of gender[6,14]. The reason for the predominance of pediatric CVT in boys is unknown, it is thought that estrogens may play a protective role, but studies comparing pre-pubertal and adolescent subjects have not shown differences in the gender ratio of those affected[15,16].

There are significant differences in the clinical presentation of CVT at different ages. At a younger age, it is more frequent to find quantitative impairment of consciousness and epileptic seizures; on the other side, it is less frequent to detect symptoms suggestive of intracranial hypertension. This finding is important since most of the studies evaluating age-dependent differences in CVT include newborns and there is no clarity of the clinical manifestations in the different non-neonatal pediatric age groups[5-8]. Possibly, the presence of permeable cranial sutures, lower seizure threshold, communication difficulties, and high frequency of intracranial hemorrhages in infants (5/6; 83%), similar to that described in neonates, may be associated with the clinical characteristics exposed[17].

We found a significant delay in the diagnosis of pediatric CVT at younger ages. This finding emphasizes the need to have a high rate of suspicion in the presence of predisposing factors, especially in children under two years of age, in which it is difficult to detect the impairment of consciousness and focal neurological symptomatology.

Consistent with the literature, most patients have at least one risk factor for CVT, mainly systemic conditions[6]. Although it is described that acute triggers, including infections and hydroelectrolyte imbalances, are more common in neonates and infants, we found no significant differences in the distribution of risk factors for CVT by age[8,18,19].

Children with a chronic condition have a greater chance of having a poor short-term survival and functional outcome, possibly due to the mortality of the underlying condition and the high frequency of ischemic brain lesions seen in this group (9/12; 75%).

The detected proportion of prothrombotic states was similar to that described by IPSS (23.8% vs. 20%), however, unlike this study, we did not find an increase in the risk of adverse prognosis when presenting any

Table 3. Clinical and radiological variables associated with marked functional impairment at discharge or in-hospital mortality

Clinical variables	OR (CI 95%)	Radiological variables	OR (CI 95%)
Age (increase per year)	1.05 (0.88-1.25)	Deep venous thrombosis	14 (1.3-150.8)
Delay in diagnosis (> 48 hours)	0.7 (0.12-4.23)	Without deep venous thrombosis	Ref.
Delay in diagnosis (< 48 hours)	Ref.	Cortical vein thrombosis	1.17 (0.2-6.81)
GCS < 12 points	2.57 (0.37-17.8)	Without cortical vein thrombosis	Ref.
GCS 12-15 points	Ref.	Involvement of multiple sinuses	0.29 (0.04-1.98)
Intracranial hypertension syndrome	2.57 (0.37-17.8)	Single venous sinus thrombosis	Ref.
Without intracranial hypertension syndrome	Ref.	Superior sagittal sinus thrombosis	0.3 (0.05-1.99)
Epileptic manifestations at onset	0.7 (0.12-4.23)	Without superior sagittal sinus thrombosis	Ref.
Without epileptic manifestations at onset	Ref.	Transverse sinuses thrombosis	1.94 (0.32-11.8)
Focal deficit	3.3 (0.41-26.3)	Without transverse sinuses thrombosis	Ref.
Without focal deficit	Ref.	Sigmoid sinuses thrombosis	3.33 (0.5-22.1)
Any chronic systemic condition	11.2 (1.04-120.4)	Without sigmoid sinuses thrombosis	Ref.
Without chronic systemic condition	Ref.	Straight sinus thrombosis	4 (0.29-53.5)
Known prothrombotic conditions	3.3 (0.41-26.3)	Without straight sinus thrombosis	Ref.
Without a known prothrombotic condition	Ref.	Intracranial associated lesion	
Any acute systemic condition	0.7 (0.12-4.23)	Brain infarct	15.8 (1.4-174.2)
Without acute systemic condition	Ref.	Without brain infarct	Ref.
Any head or neck acute infection	0.12 (0.01-1.3)	Intracranial hemorrhage	3.75 (0.6-23.9)
Without a head or neck acute infection	Ref.	Without intracranial hemorrhage	Ref.
Acute bacterial meningitis	0.48 (0.04-5.57)	Parenchymal hemorrhage	5.56 (0.81-38.2)
Without acute bacterial meningitis	Ref.	Without parenchymal hemorrhage	Ref.
Absence of anticoagulant therapy	1.83 (0.2-16.5)	Intraventricular hemorrhage	4 (0.29-53.5)
Presence of anticoagulant therapy	Ref.	Without inrtaventricular hemorrhage	Ref.

GCS: Glasgow Coma Scale. Ref.: reference.

of these conditions[8]. Although it is recommended to perform thrombophilia studies on all CVT of unspecified etiology, the long-term therapeutic management in these cases is the subject of discussion[6,8,20].

The MRI/MRV study confirmed diagnostic suspicion in all cases, while CT scan did not detect CVT in one of the two patients in whom it was chosen as initial examination. Although digital subtraction angiography in venous phase is considered the gold standard in the detection of CVT, non-invasive imaging methods such as MRI/MRV and venous phase angiography (a non-invasive method of choice in the absence of MRI) have a high diagnostic sensitivity and are recommended as initial study[21,22].

Comparable to that observed in multicenter studies, the preferred location of thrombosis was in the superficial venous system[6]. Deep venous involvement is infrequent and is associated with poor outcome at discharge. Studies in the pediatric population show no association between adverse outcomes and deep CVT, however, this is an independent predictor of acute mortality in the adult population[23].

The percentage of associated brain injuries is similar to that described in the literature[6]. An important finding is that the presence of cerebral ischemia is associated with poor short-term outcome. Although IPSS found no association between the existence of brain parenchyma lesions and neurological alterations at discharge or acute mortality, previous studies in the non-neonatal pediatric population associated neurological normality at one year of a CVT with absence of ischemic or hemorrhagic brain damage during the acute period[7]. It is very likely that some characteristics of the associated brain injury, including the location and volume of the infarction, have prognostic implications similar to those observed in arterial ischemic stroke[24].

Most patients received anticoagulation therapy during hospitalization, mainly with UFH. LMWH was used only in three cases (all diagnosed after 2011, ol-

der than five years, and managed in a low complexity room). Although there are significant differences in the average age of children treated with UFH and LMWH, the different criteria for the indication of anticoagulants used throughout the study period make this finding clinically irrelevant. Currently, most patients are treated with LMWH, however, there is no evidence of efficacy or differential safety between the two anticoagulation alternatives[6,8]. In our patients, the decision depended on the underlying condition and the experience of the treating team. Unlike IPSS data, we found no association between absence of anticoagulation and brain parenchyma lesions or poor outcome in the short-term[6].

The low number of patients recruited in the cohort, the lack of multivariate analysis, the wide range of the study period (with differences in the criteria and type of anticoagulant treatment used), and the selection bias when conducting the study in a single center, are the main limitations recognized in the study. However, the presence of MRI and VRM images reported by a neuroradiologist in all subjects, the serial evaluation by a pediatric neurologist, and the systematization of data collection are strengths that allow the information provided to be considered valid evidence.

In conclusion, children with CVT have important clinical and age-related neuroimaging differences. The high proportion of patients with delayed diagnosis reflects the low rate of suspicion, especially at younger ages. Both the deep location of the thrombus and the presence of brain infarctions significantly increase the risk of adverse survival and functional at discharge. Since early detection of CVT may decrease the occurrence of secondary brain injuries, it is recommended to request neuroimaging (MRI/VRM or Angio-TC with venous phase) early in risk groups, in the face of the appearance of neurological symptomatology of variable expression and intensity.

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.

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

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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