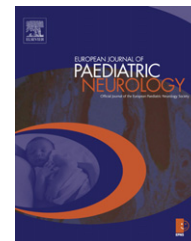**ELSEVIER**

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Original article

Cerebral sinovenous thrombosis in children: Clinical presentation and extension, localization and recanalization of thrombosis

J.P. Vieira[a,*], C. Luis[b], J.P. Monteiro[c], T. Temudo[d], M.M. Campos[e], S. Quintas[f], S. Nunes[g]

[a]Neurology Department, Hospital de Dona Estefânia, Rua Jacinta Marto, 1159-045 Lisbon, Portugal
[b]Pediatrics Department, Hospital Fernando Fonseca, Amadora, Portugal
[c]Pediatrics Department, Hospital Garcia de Orta, Almada, Portugal
[d]Pediatrics Department, Hospital de Santo António, Porto, Portugal
[e]Neurology Department, Hospital de São João, Porto, Portugal
[f]Pediatrics Department, Hospital de Santa Maria, Lisbon, Portugal
[g]Neurology Department, Instituto Português de Oncologia, Lisbon, Portugal

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ABSTRACT

Many important questions regarding pathophysiology and treatment of cerebral sinovenous thrombosis need clarification and may depend on further knowledge on the etiology, site, extension and recanalization of the thrombosis. We studied these variables in a cohort of children and adolescents from seven Portuguese Centers. We conclude from our results that the deep venous system and the superior longitudinal sinus are less frequently affected with thrombosis but have a greater potential for serious neurologic disease and for major sequelae. Non-recanalization, at least in the long term, is not an adverse prognostic factor. Extensive propagation of the thrombus from the initial site of origin seems to be common. The early identification of risk factors and their treatment coupled with an aggressive attitude towards diagnosis and treatment for thrombosis involving the deep venous system would be warranted.

1. Introduction

Children with cerebral sinovenous thrombosis (CSVT) are at risk for complications in the acute phase and may have long term sequelae.

In adults several factors affect adversely the prognosis in the acute phase: impaired consciousness, thrombosis of the deep venous system, right hemisphere hemorrhage and a posterior fossa lesion.[1–7] In the long term these factors retain prognostic significance. Idiopathic CSVT (absence of an etiologic or triggering factor) occurred in 15% of patients in the largest study in adults.[1]

The studies in children reached similar conclusions but the prognosis depends substantially also on the etiology of CSVT so the differences in prognosis are very likely also related to diverse etiologies.[8–16]

Recanalization has been studied in children and in adults with CSVT.[7,11,15,16,21] A total of 18–27% of adults and 11–16% of

children did not recanalize their thrombosis. Three pediatric studies also reported partial recanalization in up to 42%.[11,13,15,16]

Non-recanalization or partial recanalization is not associated with worse prognosis, very likely because transverse sinus thrombosis is more frequently associated with persistent thrombosis.

Treatment with anticoagulants in the acute phase, largely extrapolated from the current guidelines in adults,[17] became an accepted practice, but the decision to withhold anticoagulation in a subgroup of patients with good prognosis, instituting thrombolysis for those who continue to deteriorate despite anticoagulation or selecting patients who must prolong anticoagulation because they are at high risk for recurrence are still largely debated questions without a definite answer.

We tried to establish in our group of patients correlations between etiologic factors, the site and extension of thrombosis, the clinical picture in the acute phase, recanalization and long term sequelae.

2. Materials and methods

We included retrospectively in this study all children and adolescents (neonates to 18 years of age) with a diagnosis of sinovenous thrombosis, seen during the period of January/ 2001 to December/2007, at the Institutions participating in the study.

All patients underwent magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) in the acute phase to establish the diagnosis.

Clinical data (age, gender, underlying disease or triggering condition, neurologic symptoms and signs, long term neurologic deficits and treatment) were collected from the patient's records by their attending neurologist.

The clinical and imaging findings were evaluated considering the role played by the CSVT vs. the primary etiologic disorder.

We classified as possibly related to CSVT: headache, depressed consciousness, papilledema, VIth nerve palsy, IIIrd nerve palsy in cases of cavernous sinus thrombosis and focal neurologic signs and seizures attributed to brain lesions with a pattern consistent with venous infarction.

We also evaluated the symptoms and signs and imaging findings in order to establish alternatively or concomitantly a causal relationship with the disorder(s) implicated in the etiology of CSVT.

We had follow-up data for all children included in the study. The follow-up was done by the neurologist participating in the study. Median and mean follow-up duration were respectively 3.5 and 2.5 years.

We considered major sequelae major cognitive or motor deficits and epilepsy and defined as minor sequelae minor hyperactivity, minor motor incoordination and cranial nerve palsies (more frequently oculomotor nerve palsies).

Data from the prothrombotic studies were also collected. Not all studies were performed in all patients because knowledge in the field expanded. Most of the following investigations were performed: blood count, cholesterol, tryglicerides, fibrinogen, antithrombin III, proteins S and C,

serum homocysteine, factor VIII, antiphospholipid and anti-cardiolipin IgG antibodies, and a genetic study for Factor V Leiden, prothrombin gene 20210 mutation, thermolabile methyleno tetrahydrofolate reductase and plasminogen activator inhibitor gene 4G–5G polymorphism. Blood tests involving acute phase reactants (proteins C and S, fibrinogen and factor VIII) were repeated later to make sure that the abnormal values found initially were not transitory and secondary to acute thrombosis. The effect of warfarin and heparin on the blood tests (specifically on antithrombin III and proteins C and S blood levels) was also taken into account. The genetic investigations were performed, for all patients in a Molecular Genetics referral Laboratory (Instituto Ricardo Jorge, Lisbon, Portugal). The other studies were done at each Institution participating in the study. We confirmed previously that the techniques involved were accurate and comparable.

The MRI and MRV findings were reviewed, at each Institution, and followed the protocol design for this study established with the collaboration of a Neuroradiologist: sinuses or veins affected and parenchymatous brain lesions were recorded. Forty three patients were submitted later (within 1–24 months) to a follow-up MRI and MRV to evaluate both recanalization and residual brain lesions. We considered partial recanalization only when irregular and limited flow was present in the involved sinus with consideration of previously reports documenting certain areas of slow flow in the dural sinuses as a normal variant. In some cases we confirmed this finding on a subsequent study.

According to the updated version of the Declaration of Helsinki the study data were collected anonymously so that the investigators could not have access to the patients' identification.

Statistical analysis was made with SPSS for Windows® 14.0.

3. Results

3.1. Epidemiology

Fifty three children were included in the study, from seven different centers.

Thirty (56.6%) were male and 23 (43.4%) were female.

Median age was 4 years (minimum 3 days, maximum 17 years); six patients (11.3%) were newborns.

3.2. Underlying disease or triggering condition

Infection, especially mastoiditis, was the most frequent triggering factor, responsible for 30 cases (56.6%). In seven children (13.2%) idiopathic CSVT was diagnosed. Three out of the seven patients in the idiopathic group were neonates.

In Table 1 we list the triggering conditions or underlying diseases.

3.3. Affected dural sinuses and veins

Transverse and sigmoid sinuses were the most frequently affected, followed by the superior longitudinal sinus (Table 2).

Thirty children (52.6%) had multiple sinuses involved.

Table 1 – Triggering factors or underlying systemic diseases identified in our patients.

Etiologic factor	Number (%)
Infection	30 (56.6)
– Mastoiditis	23 (43.4)
– Meningitis	7 (13.2)
Hypercoagulable states	9 (16.3)
– Nephrotic syndrome	2 (3.8)
– Maternal autoantibodies	1 (1.9)
– Lupus	1 (1.9)
– l-asparaginase	5 (9.4)
Other	7 (13.2)
– Trauma	1 (1.9)
– AVM embolization	1 (1.9)
– Dehydration	1 (1.9)
– Surgery craneopharingioma	1 (1.9)
– Diabetes; dehydration	1 (1.9)
– NF1	1 (1.9)
– Sturge–Weber syndrome	1 (1.9)
Idiopathic	7 (13.2)

AVM: arteriovenous malformation; NF1: neurofibromatosis type 1.

3.4. Clinical presentation

Six patients (11.3%) had no neurologic symptoms or signs and CSVT was discovered when MRI was performed due to other symptoms and signs (more often these patients had mastoiditis).

CSVT was diagnosed on the 4th day of disease (median). Diagnosis was earlier when the venous thrombosis was associated with focal neurological signs (2 days vs. 10 days; $P = 0.046$).

Fifteen patients (28.3%) presented with combinations of headache, papilledema, vomiting and VIth nerve paralysis associated with lateral sinus thrombosis and mastoiditis.

CSVT associated with mastoiditis had a more uniform clinical presentation than thrombosis associated with other etiologies: papilledema (41.3% vs. 14.2%; $P = 0.038$) and VIth nerve palsy (44.8% vs. 0%; $P = 0.0001$).

Table 2 – Dural sinuses and veins involved in CSVT.

Affected Sinus	Number of sinuses or veins involved with thrombosis	Percentage in relation to number of patients (%)	Percentage in relation to number of "vessels" affected (%)
Transverse sinus	36	67.9	40.5
Sigmoid sinus	18	34	20.3
Superior longitudinal sinus	14	26.4	15.7
Straight sinus	10	18.8	11.2
Cavernous sinus	5	9.4	5.6
Jugular vein	5	9.4	5.6
Cortical vein	1	1.9	1.1

Depressed consciousness occurred in 19 patients and was more frequent in straight sinus thrombosis (80% vs. 30% $P = 0.09$).

The combination of depressed consciousness, seizures and focal signs was associated with longitudinal sinus thrombosis (68.8% vs. 32.4% $P = 0.019$).

Seizures were more common in newborns (83.3% vs. 17.1%; $P = 0.002$) and in association with longitudinal sinus (45.5% vs. 15.2%; $P = 0.042$) and with straight sinus thrombosis (50% vs. 16.3%; $P = 0.05$).

Headache, depressed consciousness, meningeal signs, cranial nerve palsies, focal signs and seizures were attributable, at least partly, to bacterial meningitis in five patients.

Depressed consciousness also occurred in one patient with hypernatremic dehydration, and peripheral facial palsy was a complication of acute otitis media and mastoiditis in another patient.

3.5. Treatment

Thirty six patients (67.9%) were submitted to anticoagulant therapy during the acute phase. Therapeutic regimens varied in different centers, but in all patients but one the treatment included heparin or a low molecular weight heparin initially. In 16 children anticoagulation with oral warfarin was started after the acute phase and maintained for several months.

Seventeen children were not anticoagulated and were treated only for the etiological factors (this group included six neonates).

3.6. Prothrombotic factors

Eighteen children were not investigated for associated prothrombotic factors. Most of these patients were the earliest to be diagnosed; in one child CSVT was associated with L-asparaginase treatment for leukemia and in another CSVT occurred in association with embolization of an arteriovenous malformation.

Of the remaining 35 children, 14 (40% of the patients studied) had a prothrombotic condition (Table 3).

3.7. Outcome

There were no deaths in our group of patients with CSVT. Overall 43.4% had long term neurologic deficits, major in 24.5% (13 patients) and minor in 18.8% (10 patients).

Table 3 – Prothrombotic factors identified in our patients.

Prothrombotic factor	Number
Mutations of the PAIi gene	6*
Anti-phospholipid/anti-cardiolipin antibodies	2
Homocistinemia	1
Deficits of antithrombin III	1
Mutations of factor VIII	2
Mutations of the MTHFR gene	1*
Leiden's factor V	1
Mutations of the prothrombin gene	1

PAIi: plasminogen activator inhibitor 1; MTHFR: methyleno tetra-hydrofolate reductase.
* 1 composite heterozygous for PAII/MTHFR mutations.

One patient with transverse sinus thrombosis had intracranial hypertension with a protracted course and needed surgical treatment (lumboperitoneal shunt and later a ventriculoperitoneal shunt because of occlusion of the lumboperitoneal shunt). We considered this a major sequela.

Not all patients' neurologic deficits were due to the CSVT. In four patients with bacterial meningitis we considered that the sequelae were more appropriately attributable to the underlying disease and in another patient with meningitis the sequelae were clearly due to multiple factors (CSVT, vasculitis, hydrocephalus).

Major sequelae occurred mainly in younger children (median age 1.67 years vs. 6 years; $P = 0.006$), and in children with seizures (50% vs. 11.1%; $P = 0.007$). Straight sinus thrombosis was associated with a higher risk of major sequelae (50% vs. 14.2%; $P = 0.037$).

A late diagnosis of venous thrombosis was associated with a better prognosis: children with major sequelae had a diagnosis on the 2nd day of disease (vs. 8th day; $P = 0.05$).

Transverse sinus thrombosis was associated with good outcome for both major and any sequelae ($P = 0.003$ and 0.001, respectively).

Major sequelae and any sequelae were significantly correlated with the clinical presentation of any combination of depressed consciousness, focal neurologic signs and seizures at presentation (43.7% vs. 10%; $P = 0.009$ and 60.8% vs. 30%; $P = 0.03$, respectively).

We have found no correlation between major sequelae and anticoagulation and with the presence of prothrombotic factors (Table 4).

3.8.   Recanalization

In ten patients a follow-up MRI/MRV was not performed.

In the remaining 43 patients MRI/MRV was repeated 1–24 months after the acute disease.

Six patients (13.9% of the patients evaluated) did not recanalize their thrombosis and ten had partial recanalization (23.2% of the patients evaluated).

Transverse sinus thrombosis associated with mastoiditis (but not with other etiologies) was statistically associated with non-recanalization ($P = 0.051$).

Jugular vein thrombosis with sigmoid and transverse sinus thrombosis was also correlated inversely with recanalization ($P = 0.022$).

A longer duration of symptoms at the time of diagnosis of CSVT was also correlated with non-recanalization ($P = 0.051$).

In Table 5 we present data from correlation between recanalization and other variables.

Table 4 – Major sequelae (study of other possible risk factors).

		p	OR (CI)
Anticoagulation	14.3% vs. 38.1%	0.25	0.2 (0.05–1.5)
Prothrombotic factors	19.4% vs. 35.3%	0.3	0.4 (0.1–1.6)

Table 5 – Recanalization (study of other possible risk factors).

		p	OR (CI)
Age	5.6 years vs. 6 years	0.77	–
Transverse sinus (any etiology)	66.7% vs. 60%	0.75	0.77 (0.2–2.8)
Straight sinus	61.8% vs. 66.7%	1.0	1.23 (0.2–5.8)
Sup. longitudinal sinus	62.1% vs. 64.3%	1.0	1.1 (0.3–4.1)
Meningitis	71.4% vs. 61.1%	0.69	1.5 (0.2–9.3)
Anticoagulation	54.8% vs. 83.3%	0.15	0.2 (0.04–1.3)
Prothrombotic factors	66.7% vs. 37.5%	0.25	1.02 (0.3–3.6)
Sequelae (any)	62.5% vs. 63.2%	1.0	1.5 (0.3–6.9)
Major sequelae	70% vs. 60.6%	0.7	0.3 (0.09–1.2)

4.   Discussion

We have found a higher proportion of male (56.6%) vs. female (43.4%) patients, concordant with previous reports.[9–11,13–15]

The majority of these reports on CVST in children found a peak incidence of CSVT in neonates[8,9,12–14,16] but our patients distributed uniformly across all age groups.

In seven of our patients (13.2%) no underlying disease or triggering condition was identified. Idiopathic cases were less frequent in other series as reported by Sébire (no idiopathic CSVT),[13] Bonduel (three idiopathic cases in 38 patients)[14] and deVeber (only 2% of 160 children did not have a clinical risk factor).[9] Nevertheless Heller et al.[11] did not identify a clinical risk factor for CSVT in 29.5% of 149 patients and Carvalho et al.[10] reported on 31 children (seven out of 31 patients had no clinical risk factor). While this discrepancy may be due to referral bias; idiopathic CSVT in children is probably slightly less frequent than in adults (15% idiopathic CSVT were reported in the International Study on Cerebral Vein and Dural Sinus Thrombosis).[5]

The triggering factor(s) for thrombosis in our patients included a greater proportion of mastoiditis (43.4%). This is probably related to epidemiological factors that are outside the scope of this work.

As a consequence of this predominance of mastoiditis, transverse sinus thrombosis is disproportionately represented in our group of patients (40.5% of all "vessels" involved and 67.9% of all patients).

We have found that various combinations of transverse, cavernous, sigmoid sinus and jugular vein thrombosis were frequently found in this setting. The particular combination of transverse plus cavernous sinus thrombosis was not reported previously and was found in four of our patients with mastoiditis; possibly in these cases the thrombus propagated from the lateral to the cavernous sinus through the petrous sinus.

Sébire et al. reported, in a series of 42 patients, transverse sinus thrombosis in 47% and mastoiditis was also the triggering factor in a significant number of their patients (42%).[13]

Transverse sinus thrombosis, isolated or associated with thrombosis of other sinuses, was less frequently seen in other pediatric series: 20.7%, 31% and 12% were reported respectively by Heller,[11] Bonduel[14] and Kenet.[15]

All studies found that besides the underlying disease or triggering condition a prothrombotic state was also frequently found. We had similar results with our group of patients.

Symptoms and signs in our patients were concordant with those reported by other studies.

Our patients with thrombosis of the straight sinus (80%) or longitudinal sinus (56.3%) had significantly more often depression of consciousness compared to patients with lateral sinus thrombosis (38.9%).

Seizures were more common in newborns and in association with straight and longitudinal sinus thrombosis while lateral sinus thrombosis characteristically had a subacute presentation with symptoms and signs of intracranial hypertension.

Long term major neurologic deficits in our patients were associated with younger age, seizures, decreased level of consciousness, focal neurologic signs and with thrombosis of the straight sinus. This was also reported by other studies in children.[9,13] Studies in adults besides similar clinical risk factors identified worse prognosis with age greater than 37.[1]

We also found that the prognosis depends significantly, in some cases, on the etiologic factor for thrombosis. In four patients the sequelae were more likely due to bacterial meningitis and in another the residual neurologic deficits were of multifactorial origin (bacterial meningitis, hydrocephalus, venous thrombosis and arteritis).

MRV is a technique dependent on blood flow and slow flow occurs normally in parts of the intracranial venous system. Non-visualization of part of a sinus on MRV may therefore occur without thrombosis. This was reported at the origin of the lateral sinus[18–20] and, in neonates, in the posterior part of the longitudinal sinus.[20] In addition a normal hypoplastic sinus (usually the left lateral sinus) can also be mistakenly interpreted as partially thrombosed.[19] Therefore we did not consider non-recanalization or partial recanalization any patient's MRV presenting one of these normal variants.

Recanalization was investigated in five studies in adults[7] but one study did not distinguish between partial recanalization and absent flow. Globally 16% of adult patients did not recanalize their thrombosis.[7] Lateral and sigmoid sinuses were more frequently affected with persistent thrombosis and non-recanalization at 4 months usually was incompatible with later resolution of the thrombosis.[7,21,22]

Three reports on CSVT in children investigated recanalization and reported non-recanalization in 11–16%[11,13,15] and partial recanalization in 41% and 42% of patients.[11,15]

The total number of patients in our series with persistent thrombosis or with partial recanalization is slightly lower (37.1%), and we had a smaller proportion of cases with partial recanalization (23.2%).

In our series transverse sinus thrombosis associated with mastoiditis (but not with other etiologies) was statistically associated with a greater risk for non-recanalization.

Doppler studies documented that flow is slower in the transverse sinus[23] and the greater volume of this sinus and longer duration of symptoms before diagnosis of thrombosis may predispose to propagation and to organization of the thrombus. In addition, septic thrombophlebitis may cause a more aggressive endothelial injury.

In theory recanalization could be viewed as an important goal in the treatment of venous thrombosis but, as others have reported previously, we have found that recanalization in the long term did not correlate positively with a better prognosis.

Transverse sinus thrombosis secondary to mastoiditis was frequently compatible with recovery without sequelae regardless of the recanalization status.

The prognosis is apparently more dependent on the localization of thrombosis. Thrombosis affecting the deep venous system may have more serious consequences in the acute phase and is associated with a greater risk for long term sequelae. Nevertheless the deep venous system recanalizes more frequently and probably earlier.

The events in the acute phase are largely unknown at present. Venous stasis, endothelial injury and genetic and acquired prothrombotic factors may play a role in the processes of thrombus formation, propagation, organization and dissolution.

Doppler studies in peripheral vein thrombosis concluded that thrombus propagation is a rare and usually limited event[24] but peripheral veins have valves that probably limit propagation. Thrombus propagation is probably more extensive and more frequent in the dural sinuses.

We think that the imaging data from our patients with transverse sinus thrombosis secondary to mastoiditis support the notion that thrombosis in the intracranial venous sinuses carries a significant risk of extension from the initial site of thrombus formation. In 14 of 23 (60.9%) of our patients with mastoiditis and lateral sinus thrombosis other sinuses were also affected.

Recurrence of SVT in the adult population is infrequent (2.2% reported in the ISCVT study, five/100 patients-years reported by Gosk-Bierska).[1,25]

The Canadian study from DeVeber et al. in 160 children with CSVT identified 12 children with recurrent thrombosis.[9]

The study by Kenet et al. in 266 children with CSVT found that venous thrombosis recurred in 3%. In this study non-recanalization significantly increased the likelihood of recurrence of thrombosis.[15]

In our study there were no cases of recurrence of the CSVT after a period of follow-up from 13 months to 6 years.

As final conclusions we point out that in CSVT depressed state of consciousness, thrombosis of the deep venous system and/or of the superior longitudinal sinus and extensive thrombosis should be viewed as ominous prognostic factors. The predisposing conditions should be aggressively treated and the patients clinically monitored for neurologic complications. Thrombus propagation may be a frequent occurrence. Recanalization in the long term is not a significant factor for outcome but we believe that in the short term it could be relevant and repeating MRI in the acute phase could give additional information to guide the clinical management of a selected group of patients that present with clinical and imaging findings linked to a greater risk for complications and to poor prognosis.

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