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Otology

Paediatric otogenic sinus venous thrombosis: the role of *Fusobacterium necrophorum*

Trombosi del seno venoso su base otogena in pazienti pediatrici: il ruolo del Fusobacterium necrophorum

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SUMMARY

Objectives. Sinus venous thrombosis (SVT) is a rare complication of acute otitis media (AOM) with acute mastoiditis (AM), which during recent years has been associated with *Fusobacterium necrophorum* (Fn) infection. Our objective was to review clinical, microbiologic, and hematologic features of paediatric otogenic SVT, with a specific focus on the role of Fn.

Methods. A retrospective database review in a tertiary paediatric hospital between 2000-2019.

Results. Fifty children aged 6-155 months were treated for AM with SVT. Forty-seven (94%) underwent cortical mastoidectomy. Forty-six children received low-molecular-weight heparin (LMWH). Follow-up imaging revealed recanalisation in 92% of cases. No long-term neurologic or haematologic complications were observed. Since 2014, when anaerobic cultures and PCR were routinely used in our institute, Fn was isolated from 15/21 children with SVT. Their time to recanalisation was longer, and the rate of lupus anticoagulant antibodies (LAC) was higher than in the 6 non-Fn patients. Children positive for LAC also had a longer time to recanalisation.

Conclusions. Fn is a common pathogen in AM with SVT; its thrombogenic role was demonstrated by a higher prevalence of LAC and a longer time to recanalisation.

KEY WORDS: sinus thrombosis, mastoiditis, *Fusobacterium necrophorum*

RIASSUNTO

Obiettivi. *La trombosi del seno venoso (SVT) è una rara complicanza dell'otite media acuta (AOM) associata a mastoidite acuta (AM), che negli ultimi anni è stata associata all'infezione da Fusobacterium necrophorum (Fn). Il nostro obiettivo è stato rivedere le caratteristiche cliniche, microbiologiche ed ematologiche della SVT otogena pediatrica, con un focus specifico sul ruolo del Fn.*

Metodi. *Una revisione retrospettiva del database in un ospedale pediatrico terziario negli anni 2000-2019.*

Risultati. *Cinquanta bambini di età compresa tra 6 e 155 mesi sono stati trattati per AM con SVT. Quarantasette (94%) sono stati sottoposti a mastoidectomia corticale. Quarantasei bambini hanno ricevuto eparina a basso peso molecolare. L'imaging di follow-up ha rivelato una ricanalizzazione nel 92%. Non sono state osservate complicanze neurologiche o ematologiche a lungo termine. Dal 2014, quando nel nostro istituto sono state utilizzate di routine colture anaerobiche e PCR, il Fn è stato isolato in 15/21 bambini con SVT. Il tempo alla ricanalizzazione è stato più lungo e il tasso di anticorpi lupus anticoagulanti (LAC) è stato superiore rispetto ai 6 pazienti non Fn. Anche i bambini positivi per LAC hanno avuto un tempo più lungo per la ricanalizzazione.*

Conclusioni. *Fn è un patogeno comune in AM con SVT; Il suo ruolo trombogenico è stato dimostrato da una maggiore prevalenza di LAC e da un tempo più lungo alla ricanalizzazione.*

PAROLE CHIAVE: *trombosi sinusale, mastoidite, Fusobacterium necrophorum*

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Introduction

Otogenic sinus venous thrombosis (SVT) is a rare complication of acute otitis media (AOM) and acute mastoiditis (AM), with potentially serious consequences. SVT can result from direct extension or haematogenic spread of infection through emissary veins that connect the mastoid with the sinus. The disease may then propagate to the internal jugular vein or other dural sinuses. In the era of antibiotics and surgical treatment, the mortality rate from SVT has substantially decreased and while in the past a rate of 5% was described, in recent years mortality due to otogenic SVT has become rare [1-4].

The current treatment approach to AM with SVT includes broad spectrum antibiotics, introduction of a ventilation tube and cortical mastoidectomy with the removal of the bony plate covering the sigmoid sinus and epidural space. Anticoagulant therapy is usually administered postoperatively [3]. Other approaches can include sinus incision and thrombectomy or sinus ligation [5].

Computerised tomography (CT) and magnetic resonance imaging (MRI) are indispensable in the diagnosis, management and follow-up of patients with SVT. Contrast enhanced CT has a major role in diagnosis of SVT and surgical planning. The duration of anticoagulant treatment is directly influenced if recanalisation is demonstrated in imaging follow-up with MRI [6,7].

The incidence of *Fusobacterium necrophorum* (Fn) mastoiditis has been shown to increase in the last two decades and is strongly associated with an increased risk of developing SVT [8-12].

The study reviewed our 20-year experience with SVT treatment and outcomes and to compare clinical characteristics of patients with Fn SVT and non-Fn SVT. The current study is a follow-up of our previous publication from 2014 that described our experience with a limited cohort of 24 children [13].

Materials and methods

Patients

We reviewed the records of all patients hospitalised and treated for otogenic SVT at a university-affiliated tertiary paediatric care centre from 2000 to 2019. Data collected from medical charts included: symptoms and signs, microbiologic evaluation, thrombophilic evaluation, radiologic findings, medical and surgical treatments and clinical outcome.

Treatment approach for AM

Children were diagnosed with AM by a paediatric otolaryngologist in the presence of otalgia, fever, signs of AOM, and retro-auricular redness and swelling. Tympanocentesis was performed in cases without spontaneous discharge, and culture was taken for microbiology. If retro-auricular fluctuation was diagnosed, needle aspiration of the pus was performed at admission. According to our departmental imaging protocol for AM, CT was not routinely performed at admission. CT was performed only in patients with a septic appearance at presentation (including high fever, inflammatory indices, haemodynamic instability, or altered mental status), subperiosteal abscess with no response to needle aspiration, or when no clinical or laboratory improvement was observed during 48 h of treatment. CT was always performed with intravenous contrast enhancement. CT findings determined the extent of surgical intervention which included ventilation tube insertion and one of the following options: 1) If CT demonstrated a confined, small abscess without intracranial involvement, we performed incision and drainage of the subperiosteal abscess; 2) If CT demonstrated SVT by signs of dural enhancement and a filling defect of the involved lateral sinus or epidural abscess, the preferred surgical option was cortical mastoidectomy with unroofing of the bony plate covering the sigmoid sinus and epidural space; and 3) all other cases that failed to improve underwent cortical mastoidectomy with drainage of the subperiosteal abscess. MRI is not performed in our institute at the diagnostic stage of AM with SVT and is used mainly as the follow-up imaging modality of choice.

Imaging follow-up

Follow-up imaging was mostly performed with MRI including an MR venography (MRV) protocol at 3 months after hospitalisation and at 3-month intervals until recanalisation was demonstrated. Until 2010, follow-up imaging was performed mainly with CT venography (CTV). Time to recanalisation was defined as the time (days) between initiation of anticoagulation treatment and the date of the imaging exam showing complete or partial recanalization.

Thrombophilic work-up

Of 50 children included in the study, 46 had a documented haematologic work-up including: prothrombin time (PT), partial thromboplastin (PTT), international normalised ratio (INR), factors IX, X, XI, XII, antithrombin, Lupus anticoagulant (LAC), antiphospholipid antibodies (APLA) [anticardiolipin (ACL) and β-2 glycoprotein], protein C, protein S, activated protein C resistance, lipoprotein (a), factor V Leiden, methylenetetrahydrofolate reductase (MTHFR) mutation and homocysteine. Children with partial data were included only for the tests available. This work-up was performed during or shortly after hospitalisation, and all were followed in our haematology clinic after discharge.

Microbiologic work-up

Microbiologic cultures were performed on middle ear fluid

samples obtained from all children either by tympanocentesis or by collection of spontaneous discharge at admission, and during the surgical procedure. Our institutional policy until the year 2013 was to obtain only aerobic cultures for children with AM, unless anaerobic infection was suspected. Since 2014, both aerobic and anaerobic cultures have been routinely performed in children with AM. For patients with sterile cultures who undergo surgical intervention, a broad-range 16S rRNA polymerase chain reaction (PCR) and sequencing panel are performed to identify the causative pathogen. Fn-SVT and non-Fn SVT characteristics were only compared for patients treated since 2014 to avoid the inclusion of patients who might have previously been misdiagnosed as non-Fn SVT.

Antibiotics treatment protocol

In our institute, children hospitalised with AM are generally treated with a second-generation cephalosporin (cefuroxime). In a severe clinical presentation with high fever and high inflammatory markers, empiric coverage is wider and includes a third-generation cephalosporin (ceftriaxone) and an antibiotic covering anaerobic bacteria (clindamycin or metronidazole).

Statistical analysis

Continuous variables are presented as medians with range, and compared between groups using the Mann-Whitney test. Categorical variables were compared between groups using the Fisher exact test. Time to recanalisation was evaluated from the initiation of anticoagulation treatment to the date of the MRI showing recanalisation and compared using Kaplan-Meier survival curves. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp. Armonk, NY) was used for all analyses.

Results

During the study period, 1280 children with AM were hospitalised in our institution. Fifty children (3.9%), aged 6-155 months (median 25 months), had SVT. Of these, 37 (74.0%) were younger than 3 years (Fig. 1). Twenty-five (50%) were male.

Symptoms and signs of available data in 42 cases are presented in Table I. Redness and swelling of the mastoid were reported in 78.6% and 76.2% of cases, respectively. Discharge from the ear was reported in 20 cases (47.6%) and bilateral otitis in 9 cases (21.4%). When comparing Fusobacterium and non-Fusobacterium cases diagnosed since 2014, we found no significant difference in symptoms and signs.

The incidence of thrombosis propagation to other sinuses and epidural space abscess is presented in Figure 2. In all, 40% of children had transverse sinus involvement, and the same number had internal jugular vein involvement.

All children were treated with broad-spectrum antibiotics (mainly ceftriaxone, and either metronidazole or clindamycin). Forty-seven children (94%) underwent ventilation tube insertion and cortical mastoidectomy with the removal of the bony plate over the sigmoid sinus and epidural space,

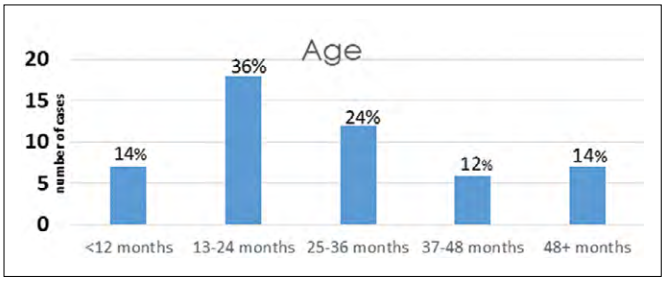

Figure 1. Age distribution at the presentation of 50 children with sinus venous thrombosis.

Table I. Symptoms and signs of 42 children with mastoiditis with sinus venous thrombosis, and comparison between *Fusobacterium* and non-*Fusobacterium* cases diagnosed since 2014.

Symptom/Sign	Number of children (%) (n = 42)	Fusobacterium (n = 15)	Non-Fusobacterium (n = 6)	*P-value*
Pain	18 (42.9%)	7 (46.7%)	3(50%)	p = 0.69
Discharge	20 (47.6%)	8(53.3%)	2(33.3%)	p = 0.64
Bilateral otitis	9 (21.4%)	6(40%)	1(16.7%)	p = 0.61
Retro auricular erythema	33 (78.6%)	12(80%)	4 (66.7%)	p = 0.6
Retro auricular swelling	32 (76.2%)	11(73.3%)	4 (66.7%)	p = 1
Retro auricular fluctuation	12 (28.6%)	5 (33.3%)	1 (16.7%)	p = 0.44
Protrusion of auricle	31 (73.8%)	10 (66.7%)	4 (66.7%)	p = 1
Headache	2 (4.8%)	0	0	
Cranial nerve palsy	3 (7.1%)	1(6.7%)	0	p = 1

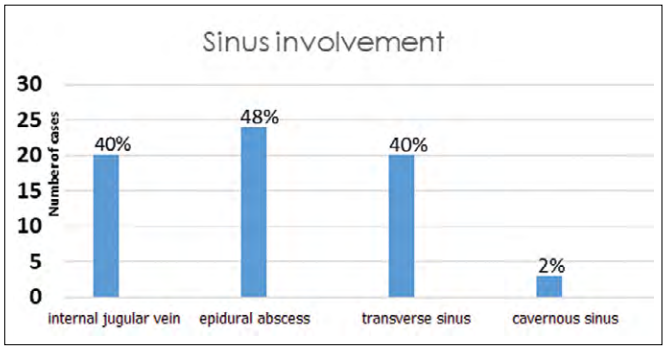

Figure 2. Site involvement among 50 children with sinus venous thrombosis based on radiological and surgical findings.

without sinus aspiration, thrombectomy, or sinus ligation. Two other children underwent ventilation tube insertion only because the SVT was detected by CT after AM had responded clinically to conservative treatment.

Forty-six children (92%) received LMWH for a median time of 4 months (range: 2-12 months). The few cases that were not treated with LMWH were from earlier years when the standardised treatment approach that includes anti-coagulant treatment and imaging follow-up was not yet completely embedded in our institute. Out of these four cases, only one had documented follow-up imaging which demonstrated complete recanalisation.

Follow-up imaging was documented in 36 children, and all received LMWH. The median time from hospitalisation to first follow-up imaging was 99 days (range 39-227 days). A second follow-up imaging was performed in 10 cases, (all without recanalisation at the first imaging) with a median time from first to second imaging of 117.5 days (range 63-222 days). Four patients without recanalisation had a third follow-up imaging performed. The median time from second to third imaging was 165 days (range 39-371 days). No significant difference was observed between children who had documented imaging at follow-up and those who did not, considering age at diagnosis, mean body temperature, maximal white blood cell count (WBC), C-reactive protein (CRP), sinus involvement on primary CT imaging during hospitalisation and microbiologic profile. In 26 patients, imaging follow-up was performed with MRV; in 10 patients, all treated before 2010, the imaging was by CTV. Recanalisation was demonstrated in 33 patients (91.6%) (complete recanalisation in 58.3% and partial recanalisation in 33.3%). For 3 patients, the haematologist decided to stop anticoagulant treatment due mainly to clinical and laboratory exams, even though recanalisation was not demonstrated on follow-up imaging.

No long-term neurologic or haematologic sequelae were observed in any children during a mean haematologic follow-up of 9.8 months.

Of 46 children who underwent haematologic thrombophilic work-up (Tab. II), 38 (83%) had at least one positive pro-thrombotic factor. Three patients had 3 pro-thrombotic factors (6.5%), 9 had 2 factors (19.6%) and 26 had one factor (56.5%, positive LAC and APLA was considered 1 factor). In total, 28 children (62% of those examined) were positive for LAC, 12 of them were also APLA positive (of 41 examined, 29%) while 5 patients were APLA positive without LAC (12.2%).

Fn mastoiditis with SVT versus non-Fn mastoiditis with SVT

Since 2014, when anaerobic cultures were routinely taken, 21 children were diagnosed with AM and SVT. Of these, 15 (71.4%) had Fn infections. Of those negative to Fn, four (19%) were positive to group A streptococcus; one had co-infection of group A streptococcus with *Pseudomonas aeruginosa*, and another co-infection of group A strepto-

Table II. Hypercoagulability factors among children with otogenic sinus venous thrombosis during 2000-2019.

Hypercoagulability factor	Non-Fn SVT (%) since 2014 (n = 6)	Fn SVT (%) since 2014 (n = 15)	All cases (n = 46)	*P-value*
LAC	2/6 (33%)	10/15 (67%)	28/45 (62%)	p = 0.038
APLA	3/5 (60%)	8/15 (53%)	17/41 (41%)	p = 0.77
APCR	1/5 (20%)	2/15 (13%)	4/36 (11%)	p = 0.43
Lipoprotein a	1/4 (25%)	3/15 (20%)	14/39 (36%)	p = 1
Factor V Leiden (Heterozygote)	0/1	2/4 (50%)	5/23 (22%)	
Protein C	0/6	0/13	0/39	
Protein S	0/6	0/15	0/39	
Homocysteine (homozygote)	0/3	0/13	1/40 (2.5%)	
Factor II	0/4	0/14	1/41 (2.4%)	
Factor VIII	0/6	0/13	0/46	
Anti Thrombin III	0/6	0/13	0/39	

Fn: Fusobacterium necrophorum; LAC: Lupus antianticoagulant; APLA: antiphospholipid antibodies; APCR: Activated protein C resistance.

Table III. Clinical characteristics of 21 children with sinus venous thrombosis diagnosed from 2014 according to the presence of *Fusobacterium necrophorum* infection.

Clinical characteristic	Non-Fusobacterium (n = 6)	Fusobacterium (n = 15)	*P-value*
Age (months)	30.3	29.1	p = 0.9
Male	67%	60%	p = 0.79
Bacteraemia	0	6.7%	p = 1
Max. WBC (K)	18.32 (16.39-29.28)	19.14 (9.91-36.66)	p = 0.88
Max. CRP	14.2(6.8-27.5)	19.5 (7.2-32.3)	p = 0.38
Hospitalisation (days)	15.5 (13-31)	19 (11-35)	p = 0.57
IV Ab (days)	25 (17-45)	26(11-51)	p = 0.85
Anticoagulation (months)	4 (3-6.5)	4.5 (3-12)	p = 0.47

WBC: white blood cells count; CRP: C-reactive protein; IV Ab: intravenous antibiotic.

coccus with *Staphylococcus aureus*. Two children had sterile cultures with negative PCR for Fn.

Among children with SVT, the mean ages of those with and without Fn were similar (29.1 and 30.3 months, respectively, p = 0.9), as was the male to female ratio (60% males in the Fn mastoiditis sub-group *vs* 67% in the non-Fn mastoiditis sub-group, p = 0.79). Significant differences were not found between children with Fn SVT and non-Fn SVT in median hospitalisation time (19 days *vs* 15.5 days, p = 0.57), median maximal WBC count (19,140 *vs* 18,320, p = 0.88), mean maximal CRP level (19.5 *vs* 14.2, p = 0.38) and mean duration of intravenous antibiotic treatment (26 *vs* 25 days) (Tab. III).

The mean time to recanalisation was 120 days (78 to 187) for patients with Fn and 88 days (86 to 90) for patients without Fn (Kaplan-Meier analysis, log rank test, p = 0.027) (Fig. 3). Children with Fn infection were treated with LMWH for a median of 4.5 months (range 3-12) compared to 4 (range 3-6.5) months among those without Fn infection; this difference was not significant (p = 0.42).

Table II compares haematologic factors among the 21 patients diagnosed since Fn infection was routinely tested. Of the 15 children with Fn infection, 10 (67%) were positive for LAC; this compares to 2 (33%) of the 6 children without Fn infection (p = 0.038). APLA antibody positivity was similar in the two groups. Positivity for APLA was detected in 8/15 (53%) of the children with Fn infection and 3/5 (60%) of the children tested without Fn (p = 0.77). No correlation was found between the number of pro-thrombotic factors and Fn (p = 0.69).

We analysed the effect of LAC on the time to recanalisation regarding the 21 children diagnosed since 2014. Children positive for LAC (12 cases, with data regarding time for recanalisation for 11 of them) had a significantly longer time to recanalisation compared to those negative for LAC (9 cases) with a log rank p-value of 0.041 (Fig. 4).

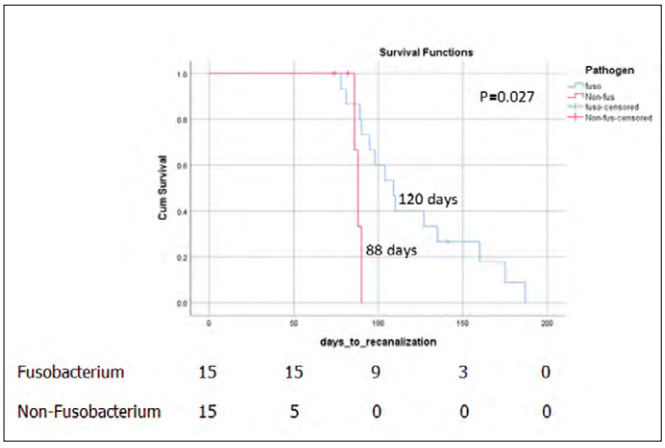

Figure 3. Kaplan-Meier survival curves comparing mean time to recanalisation in children with sinus venous thrombosis and with and without Fn infection.

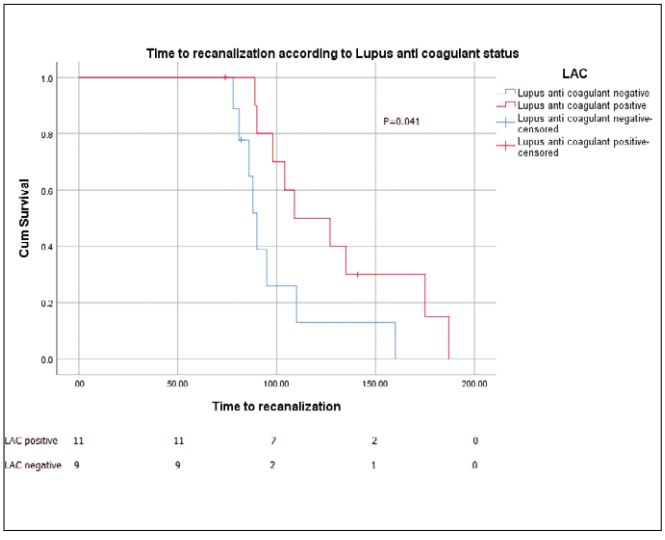

Figure 4. Kaplan-Meier survival curves comparing mean time to recanalisation in children with sinus venous thrombosis and positive and negative for Lupus anticoagulant.

Discussion

The current study highlights the thrombogenic role of Fn infection in the pathogenesis of SVT in AM. We herein confirmed the very good short- and long-term outcomes presented in our earlier study [13]. These outcomes followed conservative surgical treatment with ventilation tube insertion, cortical mastoidectomy and unroofing of the sigmoid sinus and epidural space (as performed in 94% of the patients) combined with broad spectrum antibiotics and anticoagulation treatment. No long-term neurologic or haematologic sequelae were recorded for children.

A significantly longer time to recanalisation was demonstrated among patients with Fn infection compared to non-Fn patients. However, we found no differences between these groups in other clinical and laboratory factors assessed. These included WBC count, CRP level, hospitalisation time and duration of intravenous antibiotics.

In contrast to our findings, a multicentre study of children with AM and SVT reported longer mean hospitalisation time among 28 children with Fn infection than among the 24 without (19.8 *vs* 13.7 days, p = 0.02) [12]. Similar to our results, they showed no difference in the duration of antibiotic therapy (31.3 *vs* 31.5 days, p = 0.97). The protocols of the two studies were similar. They performed a first MRI follow-up after a mean of 2.2 months and a second MRI after an average of 5.1 months. We performed a first MRI 3 months after hospitalisation and a second after 6 months if recanalisation was not demonstrated. In their study, a difference in the rate of complete recanalisation was demonstrated by the end of the radiologic follow-up in favour of non-Fn cases; however, this difference was not statistically significant (61.5% in Fn *vs* 84.2% in non-Fn, p = 0.18). In contrast, our study demonstrated a significantly longer time to recanalisation among children with Fn infection (120 *vs* 88 days, p = 0.027).

We observed haematological abnormalities at diagnosis in 83% of children with SVT. Overall, 33/46 (72%) of patients had positive LAC and/or APLA; this compares with an estimated prevalence of positive LAC and APLA in 1-5% of the general population [14,15]. Outstandingly, we found that the prevalence of LAC was 67% in children with Fn SVT compared to 33% in the non-Fn SVT group. This difference was significant (p = 0.038). Based on this finding, we can cautiously presume that the strong thrombogenic effect of Fn infection is associated with LAC elevation. Furthermore, we were able to demonstrate by Kaplan-Meier curves that children who were LAC positive had a significantly longer time to recanalisation, suggesting a key role for LAC as a thrombogenic factor in these cases. Our study demonstrated a high prevalence of APLA antibodies both among children with Fn SVT (53%) and with non-Fn SVT (60%). No significant association was found between the other thrombophilic factors and Fn infection.

Fn infection is well known for its possible severe inflammatory and thrombogenic potential, especially in Lemierre syndrome, in which tonsillitis results in thrombophlebitis of the internal jugular vein. Holm et al. [16] showed that Fn activates an inflammatory response that results in bradykinin release and activation of the intrinsic coagulation pathway by binding to factor XI.

Our finding of at least one pro-thrombotic factor in 83% of our cohort concurs with the report of at least one pro-thrombotic factor in 24 (96%) of 25 children with otogenic SVT in a study by Scorpecci et al. [17]. Only 64% of the children in that study were treated surgically. All patients were treated with LMWH and the recanalisation rate was slightly lower than observed in the present cohort: with 68% recanalisation after 6 months and 80% after 12 months of MRI follow-up.

Our study demonstrates a strong tendency for thrombophilia among children with SVT, especially LAC/APLA. These hypercoagulability factors are often transient in children and associated with infectious processes. In the absence of follow-up data on the perseverance of the LAC/APLA, we cannot unequivocally determine whether this thrombogenic tendency is the result of the infection, or whether these children are at continued risk for thrombogenic events due to inherited conditions. To answer these questions, further long-term follow-up studies are needed in larger cohorts.

Our thrombogenic work-up included inherent factors such as factor V Leiden and homocysteine levels. Zangari et al. [18] published a study of 5 children who had otogenic SVT, all of whom were heterozygote for the MTHFR mutation. One of the children was also Factor V Leiden heterozygote, similar to the rate of 22% positive cases for Factor V Leiden in our cohort. All 5 children were treated with LMWH and showed full or partial recanalisation in follow-up MRI, also in agreement with our high rate of recanalisation of 91.6%. Schneider et al. [19] attempted to examine the prevalence of thrombophilia in a long-term follow-up of children with otogenic SVT. A total of 7 patients were recalled for work-up after an average of 13 years after the SVT episode. Three patients (43%) were positive for at least one pro-thrombotic factor, including elevated factor IX, decreased protein C and S and elevated ACL. Two patients had long-term sequelae including hearing loss and headache.

Even in patients with Fn infection and positive hypercoagulability work-up, no long-term haematologic or neurologic sequelae were recorded in our series.

Limitations of this study include its retrospective nature and the absence of data on the possible long-term thrombogenic effect of Fn infection, in the context of positive LAC and APLA antibodies. Hence, we cannot reach any conclusions

regarding the long-term relation between Fn infection and the prothrombotic state. Furthermore, due to the dominance of Fn as the pathogen among AM with SVT cases, our control group of non-Fn was relatively small.

Conclusions

A combination of broad-spectrum antibiotics, anticoagulation, and a conservative surgical intervention with ventilation tube insertion, cortical mastoidectomy and unroofing of the bony plate over the sinus yields good outcomes in children with both Fn and non-Fn otogenic SVT.
Most children in our cohort had haematological abnormalities. The availability of anaerobic cultures and PCR exams in the past few years demonstrated that Fn infection is a major pathogen in SVT, followed by group A Streptococcus. SVT with Fn infection demonstrated a longer time to recanalisation and a higher rate of LAC. The role of Fn infection in the induction of LAC, and the consequent influence of LAC on SVT secondary to AM, is an interesting field for further study.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Conceptualisation: EY, OH, DU. Data and material acquisition: EY, MS, ER. Data Analysis: JY, ER. Writing and editing: EY, OH, DU. Reviewing: MS, ER, JY.

Ethical consideration

The study was approved by the local institutional review board with waiver of informed consent (approval number/ protocol number(IRB-0242-17-RMC).
The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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