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The association between otogenic lateral sinus thrombosis and thrombophilia – A long-term follow-up

Shay Schneider[a,*], Joseph Kapelushnik[b], Mordechai Kraus[a], Sabri El Saied[a], Itai Levi[c], Daniel Michael Kaplan[a]

[a] Department of Otolaryngology - Head and Neck Surgery, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva 8410501, Israel
[b] Department of Pediatric Hemato-Oncology, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva 8410501, Israel
[c] Department of Hematology, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University in the Negev, Beer-Sheva 8410501, Israel

ABSTRACT

Purpose: Otogenic lateral sinus thrombosis (OLST) is an intracranial, potentially life-threatening complication of acute and chronic otitis media. Since congenital thrombophilic disorders are risk factors for cerebral venous thrombosis, OLST may be related to thrombophilia. The aim of our study was twofold: to evaluate whether patients who suffered from OLST in childhood also have thrombophilia, and whether these patients experienced thromboembolic episodes in future years.
Study design: Retrospective case series.
Methods: The medical charts of all children hospitalized for OLST at Soroka University Medical Center of Israel, a tertiary referral hospital, from January 1983 to September 2014 were reviewed. The patients were invited for a follow-up visit and comprehensive medical history was taken along with a physical examination and laboratory work-up for thrombophilia.
Main findings: Seven patients were included in the study. Of these, 3 (43%) had results suggesting thrombophilic disorders manifested by elevated levels of factor IX and decreased levels of protein S activity (n = 1), decreased levels of proteins C and S activity (n = 1), and elevated levels of antibodies to cardiolipin (n = 1). No patients experienced clear thrombophilic events; however, 2 patients (29%) with later proven thrombophilia suffered neurologic sequelae, possibly suggesting thrombophilic events.
Conclusions: Pediatric OLST secondary to acute otitis media and mastoiditis may reflect an underlying thrombophilia. Laboratory work-up for thrombophilia should be performed, and anticoagulant treatment may be warranted in managing these patients.

1. Introduction

Otogenic lateral sinus thrombosis (OLST) is a rare, potentially life-threatening complication of acute and chronic otitis media. Traditionally, it had been considered a condition strictly related to local spread of infection and therefore managed primarily by surgery and antibiotics. More recently, studies have suggested that OLST may reflect underlying thrombophilia, and like other causes of sinus and vein thrombosis, should perhaps be managed mainly with anticoagulants [1–4].

The benefit of treatment with anticoagulants is still unclear, but it has been reported to be safe in children [5–7]. Congenital and acquired thrombophilic disorders are important risk factors for cerebral venous thrombosis [8]. Common congenital forms of the disorders include deficiencies of protein C, protein S, and anti-thrombin III; elevated levels of factors VIII, IX, and XI; elevated levels of antibodies to cardiolipin and beta2-glycoprotein (B2GP); activated protein C resistance (APCR); and lupus anti-coagulant (LAC) [9]. To date, the literature for OLST and thrombophilia consists of relatively small case series, and it is therefore very difficult to draw meaningful conclusions from the available evidence. Only two case series with five or more pediatric patients with OLST described abnormalities in their prothrombotic factors [10].

The aim of our study was twofold: (1) to evaluate whether patients who suffered from OLST in childhood also have thrombophilia and (2) to evaluate whether these patients experienced thromboembolic

* Corresponding author at: Department of Otolaryngology – Head & Neck Surgery, PO Box 151, Soroka University Medical Center, Beer-Sheva, 84101, Israel.
E-mail address: shayfr@clalit.org.il (S. Schneider).

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episodes in future years.

2. Materials and methods

The medical charts of all children hospitalized for OLST at Soroka University Medical Center of Israel, a tertiary referral hospital, from January 1983 to September 2014 were reviewed. Data were collected regarding patients' gender, age at diagnosis, involved side, and medical and surgical treatment. The patients were invited for a follow-up visit at our otolaryngology outpatient clinic and answered a survey regarding possible risk factors for thrombophilia. A comprehensive medical history was taken along with a review of the patients' complete medical files, and a laboratory work-up for thrombophilia was performed. The work-up included complete blood count, protein C, protein S, antithrombin III, factors VIII, IX, and XI, APCR ratio, screening tests for antiphospholipid antibody syndrome (APLS) measured by levels of IgM and IgG for cardiolipin and B2GP, as well as LAC measured by the Russell's Viper Venom Test (RVVT) and by Silica Clotting Time (SCT).

The protocol of this study was reviewed and approved by the hospital's Ethics Committee.

3. Results

Seventeen patients with a history of OLST were identified. An attempt was made to contact each of them. Six patients could not be reached and 4 did not show up to our clinic. Seven patients (n = 7, 5 females and 2 males) were included in the study (Table 1).

3.1. Patients during presentation

All patients presented with acute mastoiditis. Six patients (86%) underwent surgical treatment consisting of a cortical mastoidectomy. Four of them (67%) additionally underwent thrombectomy. All patients received antibiotics (I.V. ceftriaxone). One patient (14%) was treated conservatively without surgery owing to the rapid response to the antibiotic treatment, no evidence of suppurative disease, and his good general condition. Two patients (28.6%) received anticoagulation treatment with unfractionated heparin, followed by transition to oral warfarin for 3 to 6 months.

3.2. Patients at follow-up visit

At follow-up visit, a comprehensive medical history was taken, along with a physical examination and laboratory work-up for thrombophilia. Patients were recalled on average 13 years after the initial OLST (range 5–23 years post-OLST).

Patients 3 and 6 didn't complete the full protocol for thrombophilia markers (Table 2) and declined to repeat the blood test.

Of these 7 patients, 3 (43%) had results suggesting thrombophilic disorders (Tables 2 and 3), manifested by elevated levels of factor IX and decreased levels of protein S activity (n = 1, patient No. 2 in Tables 1–3), decreased levels of protein C and S activity (n = 1, patient No. 3 in Tables 1–3), and elevated levels of antibodies to cardiolipin (n = 1, patient No. 7 in Tables 1–3). Two of these 7 patients had decreased levels of factor VIII and no elevation of thrombophilic markers (patient Nos. 1 and 5 in Table 2). One patient had decreased levels of factor VIII and elevated levels of factor IX (patient No. 3 in Table 2).

Based on the follow-up interview, health questionnaire, and medical file review, no patient had experienced apparent thrombophilic events in the intervening years. Two patients (29%) had experienced long-standing neurologic symptoms. One patient (No. 2 in Tables 1–3) suffers from severe hearing loss of the involved ear, inability to close the eye on the same side, and multiple, severe mental and verbal disturbances. The other patient (No. 3 in Tables 1–3) suffered from persistent headaches for more than a decade. Notably, both of these patients exhibited abnormal results on the thrombophilia laboratory workup. Patient No. 2 had elevated levels of factor IX and patient No. 3 had decreased levels of both proteins C and S.

Table 1
Demographics and treatment in 7 children with OLST.

Patient number	Age at onset[a]/ Gender	Year of onset	Side	Treatment
1	6.5/Female	1991	R	Ab (Cef)
2	0.5/Female	1991	L	M, Ab (Cef)
3	6/Female	2002	L	M, T, and Ab (Cef)
4	1/Male	2003	R	M, T, and Ab (Cef)
5	8/Female	2005	L	M, T, and Ab (Cef)
6	1.5/Male	2005	L	M, T, AC, and Ab (Cef)
7	4/Female	2009	L	M, AC, and Ab (Cef)

[a] Years; R/L, Right/Left; Ab, Antibiotics; Cef, I.V. Ceftriaxone; M, Mastoidectomy; T, Thrombectomy; AC, Anticoagulants.

4. Discussion

Only a fraction of children with acute mastoiditis develop OLST. We sought to investigate whether thrombophilia can be considered a predisposing factor for developing OLST. However, the rarity of OLST makes it hard to obtain a broad sample of patients to investigate this. In a review of the literature to date, there have been 21 studies reporting series of five or more pediatric patients with OLST, with a total of 153 children considered [10–15]. Screening for thrombophilia was performed in 6 of those 21 studies on a total of 39 patients [1,2,10,16–18]. Abnormal results were reported in 2 studies, totaling 10 out of 39 children (26%). Oestreicher-Kedem et al. [1] found prothrombotic disorders in 5 out of 7 children (71%), manifested by elevated levels of lipoprotein apolipoprotein [Lp (a)] (n = 4; 57%), elevated levels of antibodies to B2GP or cardiolipin (n = 4; 57%), homozygosity for the methyltetrahydrofolate reductase mutation (MTHFR, C677T) (n = 2; 29%) and factor V Leiden heterozygote (n = 1; 14%). [Lp (a)] competes with plasminogen for its binding site, leading to reduced fibrinolysis. Antibodies to B2GP are involved in sclerosis and are strongly associated with thrombotic forms of lupus [19]. The role of MTHFR in thrombophilia is controversial [20]. Fifty percent of unselected patients are heterozygous for this mutation and 15% are homozygous [21]. All 5 children (100%) with OLST in the Zangari et al. study were found to be heterozygous for the C677T MTHFR mutation and 1 child also presented heterozygosity for factor V Leiden mutation [2].

From 11 studies in the literature (with any number of cases) examining OLST and thrombophilia, 28 (56%) of a total of 50 patients underwent thrombophilia testing, and were found to have a coagulation abnormality [24].

In our study, prothrombotic tendencies were identified by decreased levels of serum proteins C and S, elevated levels of factor IX, and elevated levels of antibodies to cardiolipin. Heterozygous protein C deficiency occurs in 0.14–0.50% of the general population [22]. A deficiency of protein C results in a loss of the normal cleaving of coagulation factors Va and VIIIa [23]. Elevated levels of antibodies to cardiolipin are markers of APLA syndrome, and can be found in 6.5% of the population [9]. Elevated factor XI is a risk factor for venous thrombosis through sustained generation of thrombin, which leads to the protection of fibrin from proteolysis [25]. In our series we found a higher rate of thrombophilic factors compared with their expected prevalence in the general population.

We administered anticoagulants to two of the children and they did not develop adverse reactions. Chronologically these were patients treated in later years and the decision to add anticoagulants to their treatment was based on the previously mentioned reports. In addition, Ropposch et al. found that if anticoagulants are administered correctly and the dosing is monitored in short-term intervals, the risk of side