Background

Otogenic cerebral thrombophlebitis is a rare intracranial complication of otitis media in the modern age of antibiotics. It poses a danger that requires immediate diagnosis and urgent medical and surgical treatment. Complications are now more likely to arise from chronic ear disease or cholesterol, rather than acute otitis media.\textsuperscript{1} The mortality has significantly decreased but still range from 5\% to 10\%.\textsuperscript{2}

This study aimed to focus on clinical features, on diagnosis of this pathology and to review the most controversial aspect of management.
2 | METHODS

We conducted a retrospective study on 10 patients with otogenic cerebral thrombophlebitis diagnosed and treated in patients admitted in the ENT Department of Farhat Hached Hospital over a period of the period of 25 years (1995 to 2020). Our series included 10 patients; they were eight men and two women with a sex ratio (M/F) = 4. The mean age was 35 years (11 years old–77 years old). Neurologic signs (headache) were present in five patients and fever was noted in three other patients. All patients were assessed by cerebral CT scan, three among them benefits from a cerebral MRI also. The diagnosis was confirmed by radiographic examination in all cases. 90% of patients were anticoagulated.

3 | RESULTS

A total of 10 inpatients were identified. The clinical of our patient was summarized in the descriptive Table 1.

Four patients (40%) had poorly controlled diabetes. All patients had a history of otitis, either recurrent acute or chronic otitis media. The mean delay of consultation was 27 days (from 7 days to 3 months).

The most common symptoms were headache, reported in five patients (50%), otalgia in all patients, otorrhea in nine patients (90%), and fever in three patients (30%) (Table 2).

The etiology was related to an acute otitis media (AOM) in four cases (40%), cholesteatoma otitis media (COM) in three cases (30%), and necrotizing external otitis (NEO) in three cases (30%).

All patients had positive otoscopic findings, which included purulent ear discharge. Retraction pockets with cholesteatoma debris were present in two patients. Congested and retracted pars tensa was found in one patient (Table 2). The decreased visual acuity was found in one case (related to the extension of thrombophlebitis disease to the cavernous sinus).

All patients were assessed by cerebral CT scan with contrast (contrast-enhanced computed tomography CECT) of the brain and temporal bones. The “empty delta sign” (central non-enhancing clot surrounded by enhancing dural sinus wall) which is related to the presence of thrombus which has been objectified in seven patients (70%) (Figure 1A,B). Three patients (30%) underwent a Magnetic Resonance Imaging (MRI).

Thrombophlebitis disease was confined only to the lateral sinus in five patients (50%), extended to the internal

| Patient | Gender | Age | Diagnosis | Management |
|---------|--------|-----|-----------|------------|
| 1       | Male   | 11  | AOM+thrombosis of the lateral sinus | Cefotaxim+ofloxacin |
| 2       | Female | 34  | COM+thrombosis of lateral sinus | Amoxicillin+clavulanic acid+Antro-mastoidectomy+anticoagulant therapy |
| 3       | Male   | 18  | AOM+thrombosis of the lateral sinus and cavernous sinus+extradural empyema+meningitis+cerebral abcess | Cefotaxim+fosfomycin+metronidazole+Mastoidectomy+extradural empyema+anticoagulant therapy |
| 4       | Female | 50  | NEO+thrombosis of the lateral sinus | Ciprofloxacin+cefazitamide |
| 5       | Male   | 12  | AOM+thrombosis of the lateral sinus+extradural empyema | Cefotaxim+ofloxacin+Mastoidectomy+extradural empyema evacuation+anticoagulant therapy |
| 6       | Male   | 77  | Fungal NEO (candida)+thrombosis of the lateral sinus+internal jugular vein | Voriconazole |
| 7       | Male   | 21  | AOM+thrombosis of the lateral sinus+mastoiditis | Cefotaxime+ofloxacin |
| 8       | Male   | 38  | COM+thrombosis of lateral sinus+internal jugular vein+mastoiditis+meningitis+cerebral abcess | Cefotaxime+vancomycin+metronidazole+Incision of the sinus and evacuation of the clot+anticoagulant therapy |
| 9       | Male   | 59  | Fungal NEO (mucormycosis)+thrombosis of the lateral sinus+retropharyngeal abscess+cerebral abscess | Amphotericine B+anticoagulant therapy+the small size of the abscess does not require surgery |
| 10      | Male   | 30  | COM+thrombosis of lateral sinus+internal jugular vein+mastoiditis+extradural empyema | Cefotaxime+fosfomycin+metronidazole+Incision of sinus+evacuation of the clot+anticoagulant therapy |
jugular vein in four patients (40%) (Figure 2), and extended to the cavernous sinus in one patient (10%) (Figure 3).

Regarding the patient with cavernous sinus extension, a CT scan revealed low-intensity cavernous sinus with bulging of its lateral edges, dilated ophthalmic veins, and bilateral exophthalmia, with the left eye having a more pronounced exophthalmia.

In three cases, the thrombophlebitis condition affected the right side, in six, the left side, and in one case, both sides. In four cases, the blockage was total and, in six cases, it was only partial.

Imaging had objectified other associated signs like mastoiditis which was identified in five patients (50%) (Figure 4), swelling neck in one case, and a retropharyngeal abscess in one case (Figure 5).

Other cranial complications were seen in 70% of patients, including cerebellar abscess (three patients), extradural empyema in two patients (20%), and meningitis in one patient (Figure 6).

Complete blood counts showed concentration of hemoglobin <10 g/dl in 2 (20%) patients, leukocytosis in 7 (70%) patients. All patients had normal plated counts. All patients had normal coagulation profiles.

Microbiologic cultures were produced from the middle ear of all patients and three of them had negative cultures. Among the positive cultures, Pseudomonas aeruginosa was isolated in two cases, Proteus mirabilis in one case, Streptococcus in one case, and streptococcus pneumonia in one case. Mycological cultures were positive in two cases: lichetmiae corymbiform in one case and Candida Albicans in the other case.

All patients received initially a broad-spectrum antimicrobial therapy, subsequently adapted according to the isolated germ. Antibiotic treatment lasted from 15 days to 3 months.

90% of patients were anti-coagulated: six patients were treated with subcutaneous low molecular weight heparin (enoxaparin) for an average period of 60 days, and

| Signs                                      | Number of patients |
|--------------------------------------------|--------------------|
| Fever                                      | 3                  |
| PDF (peripheral facial paralysis)           | 1                  |
| Exophthalmos with palpebral oedema         | 1                  |
| Torticollis                                 | 1                  |
| Cervical swelling                           | 1                  |
| Retroauricular tenderness with swelling of the ear lobe | 5 |
| Otorrhoea                                   | 5                  |
| Retracted tympanic membrane                 | 1                  |
| Narrowed external auditory canal            | 2                  |

FIGURE 1  (A) Lateral sinus thrombosis. (B) Lateral sinus thrombosis
three patients had intravenous unfractionated heparin for 15 days, then relayed with Sintrom (Acenocoumarol), for a mean period of 90 days.

Surgical management was performed in five cases (Table 1).

Except for one patient who experienced a loss of vision acuity, all patients made satisfactory recoveries, with all of their symptoms and problems completely resolved. In nine cases, the middle ear infection was under control. There was no mortality. One patient's thrombus significantly decreased, and four patients demonstrated recanalization. The follow-up period was 16 months long (range: 30 days to 36 months).
DISCUSSION

The prevalence of cerebral sinovenous thrombosis has significantly decreased with the development of antibiotics, and in recent decades, there have been very few reports of it.3 With an incidence of 0.7 per 100,000 kids per year, this rare ailment has been more frequently recorded in the pediatric population3–5. Most studies2,4,6 have found a definite male predominance.7 In our series, we also discovered the similar prevalence.

Due to their anatomical proximity to the dural venous sinuses, the middle ear cavity and mastoid air cells are susceptible to thrombophlebitis brought on by infection and inflammation in these structures.8 The direct transmission of infection by erosive osteitis and retrograde thrombophlebitis are two pathogenic mechanisms of infection spread that have been proposed.9,10 The inflammatory process results in edema, a rise in local vascular pressure, and a hypercoagulable state. Consequently, it causes venous stasis and thrombosis to follow.11

Nowadays, headaches were the most often reported symptom. The clinical presentation included otorrhea, hearing loss, and fever, according to Raja.K in her series “Otogenic Lateral Sinus Thrombosis: A Review of Fifteen Patients and Changing Trends in the Management”.2 This result was replicated in both Sherer’s series and Bales’ study.4,12 Otalgia and vomiting were the commonest presenting features (63%) followed by fever (57%) and headache (43%) in Krishnan’s study.11

The primary signs and symptoms of cavernous sinus thrombosis included exophthalmos, decreased vision, ophthalmoplegia, ptosis, and palpebral edema along with headaches and fever.13–15 According to Zanoletti and coll, the existence of otogenic lateral sinus thromboses is not ruled out in the absence of the typical clinical indications of mastoiditis.16 Fever and headache were both present in 50% of the individuals in our series.

The most widely cultivated microorganisms before the invention of antibiotics were B-hemolytic streptococcus and pneumococcus. Previously, Pseudomonas and Proteus species were widespread.1

The profiles of microorganisms are evolving. A mixed flora, comprising Pseudomonas, Proteus, Bacteroides, Staphylococcus, Enterobacteriaceae, and other species, are frequently found in cultures of middle ear discharge. It could be often negative as a result of prior antibiotic use.2 (1). Six patients (about 40%) in Raja’s trial got negative cultures. Proteus mirabilis (four cases; 44%) and Pseudomonas aeruginosa (four cases; 44%) were the most common bacteria found in patients with positive cultures, followed by Enterococcus fecalis (one case; 11%) and Escherichia coli (one case; 11%). (2) Seven patients in our series had a positive culture. Five of them were associated with bacterial infections, two with mycologic infections, and one with an external ear infection. Pseudomonas aeruginosa was recovered in two of the positive bacterial cultures, Proteus mirabilis in one and Streptococcus in one.

The diagnosis of cerebral thrombophlebitis is based on radiographic imaging techniques. Contrast enhancing computed tomography of the head and neck is performed to investigate intra cranial complications of otitis media, especially the cerebral sinovenous thrombosis.5,9

Lateral Sinus thrombosis may be diagnosed by the presence of the pathognomonic empty delta sign which consists of an empty triangle appearance created by the thrombus within the sinus surrounded by contrast-enhanced dura.5,9,14,17 In our study, the lateral sinus was the most common location in our patients. It was confined in 70% of cases and spread to the jugular vein in four cases and the cavernous sinus in only one case.

Cavernous sinus thrombosis may be initially explored with non-contrast CT of the head which can show subtle abnormalities such as bulging of the lateral margins of the cavernous sinus, heterogeneous filling defect, and engorgement of the superior and/or inferior ophthalmic veins. In addition to the above-mentioned signs, contrast-enhanced CT/MRI, shows the presence of asymmetric filling defects, thrombosis in the superior ophthalmic vein, other venous tributaries, dural venous sinuses, and cerebral veins.18 In our case, a CT scan was able to diagnose the thrombus in the cavernous sinus by showing low-intensity cavernous sinus, with bulging of its lateral margins, dilation of the ophthalmic veins, and bilateral exophthalmos more marked in the left eye.

CT scan can misdiagnose the thrombus pathology because of bone-related artifacts.1 Therefore, M R I/M R V (magnetic resonance venography) is more sensitive in detecting this complication.5

FIGURE 6  Cerebral empyeme
To rule out other intracranial problems including nearby subdural empyema, cerebritis, or cerebral abscess, an MRI or MRV is helpful. Compared with CT scans, it can also reduce the danger of radiation exposure, especially for children. The thrombus appears isointense on T1-weighted images and hypointense on T2-weighted images, with increased intraluminal signal intensity on both T1 and T2 sequences, and the MRI does not require contrast injection to show it. Because it is a non-invasive approach, the MRV continues to be the gold standard for identifying cerebral sinus venous thrombosis. It also has the advantage of precisely determining the patency of the central venous sinuses. Additionally, it allows for the differentiation between a slow venous flow and an occlusive thrombus and can be done in conjunction with cerebral MRI. In three cases in our study when the MRI identified the thrombus, the scanner was negative.

Additional intracranial complications must be investigated in the presence of cerebral sinus thrombosis. The high association of cerebral sinus thrombosis with other cranial complications is well documented. Concurrent complications were prevalent in 80% of cases in the pre-antibiotic period. Since the discovery of antibiotics, complications are now 20% less common. Meningitis, otitis hydrocephalus, internal jugular vein thrombosis, and intracranial abscesses were a few of the concurrent intracranial and extracranial problems.

Symms and coll reported a group of patients who all had concomitant intracranial problems, including three patients with hydrocephalus and four patients with cerebral abscesses. Twelve of the thirteen patients in the Kaplan et al. study experienced concomitant problems, such as meningitis, cerebral abscesses, epidural abscesses, and development of the thrombus to the transverse sinus and the internal jugular vein. We have objectified 70% of the related cranial complications, including meningitis in one patient, extradural empyema in two patients, and cerebellar abscess in three patients.

Broad-spectrum intravenous antibiotics should be started at the earliest and must be adjusted later according to bacterial cultures. Antibiotics have led to a reduction of incidence of complications from 80% to 20% in cerebral sinus venous thrombosis, and intracranial abscesses were a few of the concurrent intracranial and extracranial problems.

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Anticoagulation therapy’s purpose in the management of LST is uncertain. In cases of cerebral sinus venous thrombosis, the clinician should consider the risks and advantages of anticoagulant medication. Although Au. JK et al. showed a trend in the usage of anticoagulant treatment, they did not find a statistically significant difference.

Anticoagulation has evolved to have the benefit of stopping the thrombus from spreading to distal sinuses. In special instances of thrombus propagation, embolic events, and neurological alterations, it may therefore be indicated. The American Stroke Association advises Low molecular weight heparin (LMWH) for kids with Cerebral sinus venous thrombosis (CSVT) outside of the newborn period, even if there is proof of cerebral hemorrhage. It is recommended over other anticoagulants because it reduces the risk of long-term neurological sequelae, increases the rate of recanalization, and prevents thrombus propagation. However, it can also lead to thrombocytopenia, bleeding, hemorrhagic skin necrosis, and an increased risk of septic emboli. Antibiotherapy combined with anticoagulation resulted in complete recovery in 74% of patients, with complete symptom relief and recanalization.

Nine patients recovered, and only one patient experienced complications after receiving anticoagulation, antibiotics, and surgical treatment for all of the patients.

Surgery is an essential part of the management of this entity, it improves prognosis. A better prognosis is ensured. However, controversies on the best surgical approach persist. A cortical mastoidectomy is used successfully to treat noncholesteatoma ear disease. It confirms the diagnosis of LST and allows the drainage of the initiating infection. A modified radical mastoidectomy is sufficient treatment for cholesteatomatous ears presenting acutely with cerebral sinus thrombosis. Nowadays, routine ligation of the internal jugular vein is no longer performed. It is usually reserved for unresponsive cases with persistent septicemia, lung thromboembolism, and deep neck infection.

In our study, we realize a mastoidectomy isolated in four patients (40%), it was associated to an internal jugular vein ligation in one case, and to an extradural empyema evacuation in two patients (20%). We performed an antromastoidecomy with incision of the sinus and evacuation in two cases (20%).

5 Conclusion

Otogenic cerebral sinus venous thrombosis is a rare complication of otitic pathology. It is associated with significant morbidity and mortality. In the era of antibiotics, classic clinical signs of mastoiditis (pain, swelling, and erythema posterior to the pinna) are not always present at the presentation. A clinical presentation might be subtle, which requires clinicians to maintain a high index of suspicion of this entity. Imaging (CT, MRI) is a key component in diagnosing and managing this complication. Treatment of otogenic CSVT consists of conservative surgery, antibiotics, and anticoagulation.
AUTHOR CONTRIBUTIONS
MA and GA charged of data collection, follow-up the case and writing the paper; BH and MO formulated the idea and supervised the manuscript preparation; BM and HJ participate in analyzing and interpreting data; KW and AM revising and approved the final version.

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None.

CONFLICT OF INTEREST
We have no competing interests.

DATA AVAILABILITY STATEMENT
All data and material of this case are available.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

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