

Lemierre's syndrome with double heterozygote status in the *methylenetetrahydrofolate reductase* gene

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Background: There are some risk factors being more vulnerable to Lemierre's syndrome such as a hypercoagulable state.

Methods: We report a rare case of Lemierre's syndrome with ethmoid and maxillary sinusitis, bilateral mastoiditis, and sigmoid sinus thrombosis.

Results: Genetic study revealed a double heterozygote status in the *methylenetetrahydrofolate reductase* gene including C677T and A1298C.

Conclusion: It is suggested to screen patients with Lemierre's syndrome for a hypercoagulable state to consider anticoagulant therapy.

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Key words: Lemierre's syndrome; mastoiditis; methylenetetrahydrofolate reductase; sigmoid sinus thrombosis

Introduction

Thrombosis of the internal jugular vein secondary to upper aerodigestive tract infections or Lemierre's syndrome is a rare entity since the advent of antibiotics.^[1,2] It usually presents in young adults with an estimated incidence of 0.6-2.3 per million population per year.^[3] Fever, severe

neck pain, tenderness along the anterior border of the sternocleidomastoid muscle, neck swelling, trismus and dysphasia are typical signs and symptoms of this syndrome.^[2] It could often lead to septicemia and pulmonary embolism. Anaerobic inhabitants of the oropharynx especially *Fusobacterium necrophorum* are known as the main cause of this syndrome but in children the infection is frequently polymicrobial.^[2] It seems that some conditions dispose patients to be more vulnerable to this syndrome, such as malignancy, preexisting viral or bacterial infection, IgA deficiency and a hypercoagulable state.^[2,4,5]

Herein, we report a rare case of Lemierre's syndrome with bilateral mastoiditis, ethmoid and maxillary sinusitis, sigmoid sinus thrombosis and double heterozygote status in the *methylenetetrahydrofolate reductase* (*MTHFR*) gene.

Case report

A 7-year-old boy was referred to Mofid children's Hospital because of 10 days of fever and persistent left earache and lateral neck pain. On physical examination, right tympanic membrane (TM) was erythematous, and left TM was perforated with copious purulent discharge in the left external ear canal. Both mastoids were tender in palpation without any swelling or redness. Leukocyte count, erythrocyte sedimentation rate (ESR) and C-reactive protein were increased but blood culture was negative. Computed tomography (CT) showed bilateral ethmoid and maxillary sinusitis as well as bilateral mastoiditis.

Antibiotic therapy with clindamycin and ceftriaxone was started. Fever subsided 24 hours later but left posterior auricular and severe neck pain persisted. The results of neurologic examination and lumbar puncture were normal.

Color doppler ultrasound revealed left jugular vein thrombosis and brain magnetic resonance venography (MRV) indicated left internal jugular vein and sigmoid sinus thrombosis as well (Fig.). Subcutaneous low molecular weight heparin (LMWH) was started for the patient according to otolaryngologist recommendation.

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Fig. Magnetic resonance venogram of the patient demonstrating absent left internal jugular vein and sigmoid sinus in favor of venous thrombosis.

His pain and neck tenderness were reduced significantly during the next 24 hours and no other complications were noted later. Two weeks after anticoagulant therapy color Doppler ultrasound showed regression of the thrombi and recanalization of the internal jugular vein. He was discharged with an oral antibiotic and subcutaneous LMWH three weeks later when his ESR and white blood cell count were dramatically decreased.

Genetic study revealed a double heterozygote status in *MTHFR* including C677T and A1298C despite a normal serum homocysteine level. However, no mutation was found in factor V leiden or prothrombin.

The coagulation profile results including serum protein C and S, anti-thrombin III, factor VIII and anti-thrombin activity were within normal limits. Anticardiolipin antibody and lupus anticoagulant levels were negative.

One month after discharge, a control brain MRV showed invisible left sigmoid sinus despite of complete clinical improvement. No sign or symptom indicating central nervous system involvement was shown during hospitalization and in a 6-month follow-up.

Discussion

Although Lemierre's syndrome is a rare condition in the antibiotic era, its incidence seems to be increasing in recent years. This increasing rate may be due to the common use of antibiotics as well as growing bacterial resistance. Therefore, it is important for general practitioners and pediatricians to be aware of this syndrome.^[1,5]

Generally, classic Lemierre' syndrome is characterized

by four findings: primary infection of the oropharynx, septicemia documented by at least one positive blood culture, clinical or radiographic evidence of thrombosis of the internal jugular vein, and at least one metastatic focus of infection.^[6] Our patient met two of the four criteria. Blood culture was negative and there was no documented infectious metastatic focus. Blood culture was not obtained for anaerobic organisms before antibiotic treatment, so it might be the reason of being negative in this case.

Most cases of Lemierre's syndrome are described secondary to pharyngeal infections but there are some reports including the present case that craniocervical infections from other sources such as sinus, mastoid, ear or tooth could also lead to this syndrome.^[2,4] There are few reports in the pediatric population that declares the association of a hypercoagulable state and Lemierre's syndrome or other forms of sepsis thrombophlebitis, but the exact prevalence of this association is not clear.^[1,2,5,7] Prothrombin gene mutation, antiphospholipid syndrome, protein C or S deficiency, factor XII deficiency, heterozygous mutation of factor V Leiden and *MTHFR* mutation are some types of thrombophilia associated with Lemierre syndrome which are reported in the literature.^[5,7,8]

Lemierre's syndrome is rare, so the association of these two is probably not random and hypercoagulable state may be a potential risk factor for this syndrome.^[7] Goldenberg et al^[2] found some thrombophilic abnormalities in all evaluated cases of Lemierre's and Lemierre's-like syndromes in their study which is another reason for hypercoagulable state being a risk factor not a random association for Lemierre's syndrome. *MTHFR* is a key enzyme in the folate cycle which catalyses the reduction of 5, 10 methylenetetrahydrofolate to 5-methyltetrahydrofolate and contributes to the generation of active form of folate required for remethylation of homocysteine to methionine.^[9] 677T and A1298C are two common missense mutations of *MTHFR* that are linked with cerebral thrombotic events and ischemic stroke.^[9]

Our patient had double heterozygote status in *MTHFR* including C677T and A1298C. Although the risk of thrombosis with a double heterozygote mutation is not clear in the literature, it might be probably the reason of thrombosis despite normal serum homocysteine level in our patient.^[10]

The mainstay of therapy is the proper use of antibiotics for an average of 6 weeks. Sometimes surgical ligation or excision of the internal jugular vein may be required but the role of anticoagulant therapy in this situation is not completely explained.^[1] It seems that two potential indications of anticoagulant therapy in this syndrome are: 1) Propagation or non resolution

of the thrombus despite of antibiotic therapy; 2) Patients with any form of predisposing thrombophilia.^[7]

Thus it is suggested to screen patients with Lemierre's syndrome for a hypercoagulable state so as to consider anticoagulant therapy after weighing its risks and benefits.^[7] The indication of anticoagulant therapy in our case was predisposing thrombophilia although we started LMWH according to otolaryngologist recommendation and before laboratory results are ready.

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