LEMIERRE'S SYNDROME: A REVIEW

Vinayak M Gaware*,1, Manisha Bhandange1, Madhuri Mankar1, Kiran B Kotade2, Ramdas T Dolas3, Kiran B Dhamak1, Vikrant K Nikam3, Atul N Khadse1

2. Department of Pharmacology, College of Pharmacy Chincholi, Sinnar, Nashik, M.S, 422101.
3. Department of Pharmaceutics, College of Pharmacy Chincholi, Sinnar, Nashik, M.S, 422101.

Corresponding author*:
Vinayak Madhukar Gaware
Lecturer, Department of Pharmaceutical Chemistry,
College of Pharmacy, Chincholi, Sinnar, Nashik, M.S (422101)
E-mail: vins_gaware1@rediffmail.com.

Summary

Lemierre syndrome although today a rare disorder, it’s presenting symptoms and signs is characteristic. This syndrome must be considered in previously healthy young adults with recent oropharyngeal infections who have fever, neck pain, and pulmonary symptoms. Appropriate and prompt antibiotic therapy is the treatment of choice for this potentially life-threatening infection. In the present review we have highlighted the pathology, signs and symptoms, diagnosis and management of this syndrome.

Keywords: Fusobacterium necrophorum, Lemierre Syndrome, Oropharyngeal Infections

Introduction

Lemierre's syndrome or Lemierre's disease, also known as postanginal sepsis and human necrobacillosis is a form of thrombophlebitis usually caused by the bacterium Fusobacterium necrophorum, and occasionally by other members of the genus Fusobacterium and usually affects young, healthy adults1. Lemierre's syndrome develops most often after a sore throat caused by some bacterium of the Streptococcus genus has created a peritonsillar abscess, a pocket filled with pus and bacteria near the tonsils. Deep in the abscess, anaerobic bacteria (microbes that do not require oxygen) like Fusobacterium necrophorum can flourish. The bacteria penetrate from the abscess into the neighboring jugular vein in the neck and there they cause an infected clot (thrombosis) to form, from which bacteria are seeded throughout the body by the bloodstream. Pieces of the infected clot break off and travel to the lungs as emboli blocking branches of the pulmonary artery bringing deoxygenated blood from the heart to the lungs. This causes shortness of breath, chest pain and severe pneumonia. Fusobacteria are a normal part of the oropharyngeal flora. This is a very rare disease with only approximately 160 reported cases in the last 100 years2.
HISTORY

Sepsis following from a throat infection was described by Scottmuller in 1918. However it was Andre Lemierre, in 1936, who published a series of 20 cases where throat infections were followed by identified anaerobic septicemia, of whom 18 patients died.³

EPIDEMIOLOGY

Lemierre's syndrome is currently rare, but was more common in the early 20th century before the discovery of penicillin. The reduced use of antibiotics for sore throats may have increased the risk of this disease, with 19 cases in 1997 and 34 cases in 1999 reported in the UK. The incidence rate is currently 0.8 cases per million in the general population, ⁴ leading it to be termed the "forgotten disease". The disease is known to affect healthy young adults. The disease is becoming less rare with many cases being reported, however it is still known as "the forgotten disease" as many doctors are unaware of its existence, therefore often not even diagnosed which might considerably change the above mentioned statistics. The mortality rate was 90% prior to antibiotic therapy, but is now generally quoted as 15% once this illness is correctly diagnosed and cured with proper medical treatment, although one series of cases reported mortality as low as 6.4%.⁵

GENOME STRUCTURE

Two genomes have currently been sequenced: Fusobacterium nucleatum subsp. nucleatum ATCC 25586 and Fusobacterium nucleatum subsp. vincentii ATCC 49256. Both of these genomes were sequences by Integreated Genomics. A wealth of knowledge has already been discovered by these first two pioneer sequencings ⁶.

Figure 1: Structure of Fusbaacterium nucleatum subsp
CELL STRUCTURE AND METABOLISM 7, 8

This spindle-shaped or fusiform rod-shaped bacterium varies in size, motility, and form. Fusobacterium cells have been identified both as motile and non-motile. When rod-shaped, Fusobacterium cells have parallel walls with rounded or tapered ends (Integrated). Fusobacterium cells gain energy through fermenting carbohydrates and certain amino acids. This fermentation creates butyrate and in some cases acetic acids as major metabolic by-products (Oral).

Figure 2: Cell Structure and Metabolism

SIGNS AND SYMPTOMS 9, 10

The symptoms vary, but usually start with a sore throat, fever, and general body weakness. These are followed by extreme lethargy, spiked fevers, rigors, swollen cervical lymph nodes and a swollen, tender or painful neck. Often there is abdominal pain, diarrhea, nausea and vomiting during this phase. These symptoms usually occur several days to 2 weeks after the initial symptoms. Symptoms of pulmonary involvement can be shortness of breath, cough and painful breathing (pleuritic chest pain). Rarely there is hemoptyisis. Painful or inflamed joints (arthritis or arthralgia, respectively) exist when the joints are involved. Septic shock can occur which presents as hypotension, tachycardia, oliguria and tachypnea. Nuchal rigidity, headache and photophobia occur in case there is meningitis. Hepatomegaly and splenomegaly (enlarged liver and spleen, respectively) can be found, but are not always associated with hepatic or splenic abscesses.

Other signs and symptoms that may occur:
- Headache (not related to meningitis)
- Muscle pain
- Jaundice
- Trismus
- Crepitations are sometimes heard over the lungs
- Pericardial friction rubs as a sign of pericarditis (rare)
- Cranial nerve paralysis and Horner's syndrome (both rare)

CAUSES 11, 12

*Fusobacterium necrophorum* is the causative agent in most people with Lemierre's syndrome. However only 1 in 400 cases of *Fusobacterium necrophorum* results in Lemierre's syndrome and 81% of cases of Lemierres's syndrome have been infected with *Fusobacterium necrophorum*,
while in 11% of people it was caused by other Fusobacterium species. MRSA might also be an issue in Lemierre infections. Rarely Lemierre's syndrome is caused by other (usually Gram-negative) bacteria, which include *Bacteroides fragilis* and *Bacteroides melaninogenicus*, *Peptostreptococcus* spp., *Streptococcus microaerophile*, *Staphylococcus aureus*, and *Eikenella corrodens*.

**PATHOPHYSIOLOGY**

Lemierre's syndrome is initiated by an infection of the head and neck region. Usually this infection is pharyngitis but it can also be initiated by an otitis, mastoiditis, a sinusitis or a parotitis. During the primary infection, *F. necrophorum* colonizes the infection site and the infection spreads to the parapharyngeal space. The bacteria then invade the peritonsillar blood vessels where they can spread to the internal jugular vein. In this vein, the bacteria cause the formation of a thrombus containing these bacteria. Furthermore, the internal jugular vein becomes inflamed. This septic thrombophlebitis can give rise to septic microemboli that disseminate to other parts of the body where they can form abscesses and septic infarctions. The first capillaries that the emboli encounter where they can nestle themselves are the pulmonary capillaries. As a consequence, the most frequently involved site of septic metastases is the lungs, followed by the joints. In the lungs, the bacteria cause abscesses, nodular and cavitary lesions. Pleural effusion is often present. Other sites involved in septic metastasis and abscess formation are the muscles and soft tissues, liver, spleen, kidneys and nervous system (intracranial abscesses, meningitis). Production of bacterial toxins such as lipopolysaccharide leads to secretion of cytokines by white blood cells which then both lead to symptoms of sepsis. *F. necrophorum* produces hemagglutinin which causes platelet aggregation that can lead to diffuse intravascular coagulation and thrombocytopenia.

**DIAGNOSIS**

Diagnosis and the imaging (and laboratory) studies to be ordered largely depend on the patient history, signs and symptoms. If a persistent sore throat, with the symptoms is found, physicians are cautioned to screen for Lemierre's syndrome. Laboratory investigations reveal signs of a bacterial infection with elevated C-reactive protein, erythrocyte sedimentation rate and white blood cells (notably neutrophils). Platelet count can be low or high. Liver function tests and renal function tests are often abnormal. Thrombosis of the internal jugular vein can be displayed with sonography. However, thrombi that have developed recently have low echogenicity and thus will not show up on ultrasound. A CT scan or an MRI scan is more sensitive in displaying the thrombus. Chest X-ray and chest CT may show pleural effusion, nodules, infiltrates, abscesses and cavitations. Bacterial cultures taken from the blood, joint aspirates or other sites can identify the causative agent of the disease.

Other illnesses that can be included in the differential diagnosis are:

- Q fever
- Tuberculosis
- Pneumonia
TREATMENT 17, 18

Lemierre's syndrome is primarily treated with antibiotics given intravenously. However, because sore throats are most commonly caused by viruses, for which antibiotic treatment is unnecessary, such treatment is not usual in the first phase of the disease. Lemierre's disease proves that, rarely, antibiotics are needed for 'sore throats'. *Fusobacterium necrophorum* is generally highly susceptible to beta-lactam antibiotics, metronidazole, clindamycin and third generation cephalosporins while the other fusobacteria have varying degrees of resistance to beta-lactams and clindamycin. Additionally, there may exist a co-infection by another bacterium. For these reasons is often advised not to use monotherapy in treating Lemierre's syndrome. Penicillin and penicillin-derived antibiotics can thus be combined with a beta-lactamase inhibitor such as clavulanic acid or with metronidazole. Clindamycin can be given as monotherapy. If antibiotic therapy does not improve the clinical picture, it may prove useful to drain any abscesses and/or perform ligation of the internal jugular vein where the antibiotic cannot penetrate. There is no evidence to opt for or against the use of anticoagulation therapy. The low incidence of Lemierre's syndrome has not made it possible to set up clinical trials to study the disease. The disease can often be untreatable, especially if other negative factors occur, i.e. various diseases occurring at the same time, such as meningitis, pneumonia.

MANAGEMENT 19

In patients with Lemierre syndrome, therapy is directed toward eliminating *F. necrophorum*, a strictly anaerobic gram-negative bacillus; the infection, however, can be polymicrobial, involving anaerobes and streptococcal species. Increased documentation of β-lactamase–producing *Fusobacterium* species will most likely rule out penicillin G as the antibiotic of first choice. Other antibiotics that have been used successfully to treat Lemierre syndrome include clindamycin, metronidazole, cefoxitin, and chloramphenicol. A favorable response to treatment occurs, in most cases, within 2 to 6 weeks of initiating antibiotic therapy. Ligation of the internal jugular vein is reserved for cases of recurrent septic emboli. Anticoagulation has not been shown to be necessary, unless there is propagation into the cavernous sinus. Although the case patient was initially treated with antibiotics, administered orally, the infection most likely had already spread to the lateral pharyngeal space and internal jugular vein. Consequently, intravenous administration of antibiotics was necessary.

PROGNOSIS 20

When properly diagnosed, the mortality of Lemierre's syndrome is about 4.6%. Since this disease is not well known and often remains undiagnosed, mortality might be much higher.

Conclusion

Lemierre's syndrome though is the rare disorder today but if proper care is not taken can cause serious problems which may lead to various complications. This disorder is mostly seen in healthy young adults with recent oropharyngeal infections who have fever, neck pain, and pulmonary symptoms. Thus with proper treatment and management technique one can stay away or protected from this syndrome.
References

1. Lemierre syndrome" at Dorland's Medical Dictionary