Title: Atypical Lemierre’s syndrome complicated by transcalvorial brain herniation.

Running Title: Lemierre’s syndrome and brain herniation

Authors: Nelson Yu Wang1, David P Burgner2,3,4, Katherine Ya-Hui Chen1,2

Corresponding author: Nelson Yu Wang

Corresponding author email: nywan3@gmail.com

Affiliations:
1. Department of General Medicine, The Royal Children’s Hospital, Melbourne, Australia
2. Murdoch Children’s Research Institute, The Royal Children’s Hospital, Melbourne, Australia
3. Department of Paediatrics, University of Melbourne, Parkville, Australia
4. Department of Paediatrics, Monash University, Clayton, Australia

Article Type: Case Report

Word Count: 1377

Key Words: Lemierre’s syndrome, thrombophlebitis, Fusobacterium necrophorum

Acknowledgements: The patient and their legal guardian has given informed consent for the writing and publication of the manuscript.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Funding Source: No funding was secured for this study.

Conflict of interest: The authors have no conflicts of interest to disclose.
Background
Lemierre’s syndrome was first described by French bacteriologist Andre-Alfred Lemierre in 1936 and includes oropharyngeal infection with progression to sepsis, internal jugular vein thrombosis and disseminated septic emboli, usually caused by *Fusobacterium necrophorum* and occasionally by other bacteria, including *Staphylococcus aureus*. Lemierre’s syndrome is rare, although the incidence may be increasing due to more judicious antibiotic prescribing for oropharyngeal infections. It is less common in younger children and therefore the diagnosis may not be considered until complications arise. We describe an atypical case of Lemierre’s syndrome culminating in septic thromboembolic disease.

Case Presentation
A previously well 11-year-old girl from Iran presented to an Australian tertiary hospital with a 10-day history of fever, worsening frontal headache and nasal congestion. In the three days prior to presentation, she reported visual disturbance and new generalised facial swelling. On presentation, she was febrile, tachycardic and had a borderline-low blood pressure. Her facial swelling was marked, worst over the right periorbital region, with associated pseudoptosis. She had intermittently blurred vision, but her extra-ocular movements were normal. She had bilar basal crackles on chest auscultation. Her remaining examination, including a full neurological assessment, was normal.

Her initial laboratory investigations were suggestive of an underlying severe bacterial infection with leukocytosis (white cell count of 18.7 x 10⁹/L), neutrophilia (neutrophil count of 12.16 x 10⁹/L), raised inflammatory markers (C-reactive protein >270 mg/L) and toxic changes on the blood film. An aerobic blood culture obtained prior to the administration of antibiotics was negative. Cerebral computer tomographical (CT) imaging on admission showed thrombus in the superior sagittal sinus, extending into the right transverse and sigmoid sinuses and superficial cortical vein (Figure 1a). There was opacification of the left maxillary, ethmoid, sphenoid and frontal sinuses consistent with sinusitis. A CT scan of her chest, abdomen and
pelvis showed multiple cavitating lesions throughout both lungs (Figure 1b). A transthoracic echo did not identify any features of infective endocarditis. A coagulation screen performed at the time excluded a hypercoagulable state, and showed an evolving coagulopathy, with an international normalised ratio (INR) of 1.7. On identification of significant sagittal sinus thrombosis, a heparin infusion was commenced targeting an activated partial thromboplastin time (APTT) of 60-80 seconds. Due to the initial clinical severity, the patient was commenced on broad-spectrum antimicrobials: intravenous meropenem and intravenous vancomycin.

Despite the fluid resuscitation, broad spectrum intravenous antibiotics and anticoagulation, her conscious state deteriorated. Magnetic resonance imaging (MRI) of her brain on day two demonstrated a new left frontal subdural empyema (Figure 1c). She underwent surgical drainage and washout of the subdural space, however due to the extensive intracranial thrombotic load and raised intracranial pressure, the craniotomy was converted to a craniectomy. A post-operative CT scan demonstrated transcalvarial herniation (Figure 1d). Multiple intra-operative samples were sent for Gram stain, culture and nucleic acid detection. The sinus washout cultured methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Fusobacterium necrophorum* was identified by 16SrRNA gene PCR from ethmoid and dural tissue.

The initial antibiotics were rationalised to intravenous ceftriaxone and oral clindamycin, however due to a recrudescence of fever and a rise in inflammatory markers after 72 hours, clindamycin was changed to intravenous flucloxacillin and oral metronidazole for six weeks. After completing her parenteral antibiotics, she was transitioned to oral amoxicillin/clavulanic acid until her autologous cranioplasty was completed 6 months after her initial craniectomy. She also continued on low-molecular-weight heparin for 6 months. She wore a helmet for impact-protection over the craniectomy site during this time. The patient made a complete neurological recovery with no residual deficits.
Discussion

Lemierre’s syndrome is a form of necrobacillosis; infection of necrotic tissue.\(^2\) It describes the constellation of head and neck infection, internal jugular vein thrombosis and subsequent septic emboli usually caused by *F. necrophorum*, although the term is often used to describe patients with only some of these features.\(^3\) A definition of Lemierre’s syndrome suggests a combination of: (i) history of head and neck infection in the preceding 4 weeks or compatible clinical findings; (ii) evidence of metastatic lesions in lungs and/or another remote site; and (iii) evidence of internal jugular vein thrombophlebitis or isolation of *F. necrophorum* or *Fusobacterium* spp. from blood cultures or a normally sterile site.\(^2\) The current case meets this definition if microbiological molecular identification is included. Progression from a localised oropharyngeal or in this case, sinus infection, to disseminated disease is due to invasion of local veins and spread into the internal jugular vein, with potential extension into the intracranial venous sinuses. Septic pulmonary emboli may occur.\(^2\)

Lemierre’s syndrome should be suspected in those presenting with signs of complications from local and intracranial thrombosis (painful swelling at the angle of the mandible, headache, altered conscious state) and emboli (chest pain, respiratory distress) following an oropharyngeal or sinus infection.\(^4\) The clinical features lack sensitivity and specificity and the diagnosis is often not made until *F. necrophorum* is identified or there are radiological findings suggestive of local venous thrombosis and/or septic embolic disease. It is important to consider Lemierre’s syndrome in patients, including younger children, with a protracted or unusual course of nasopharyngeal infection, or signs of complications.\(^2\) More recent reports include other bacterial aetiologies for Lemierre’s syndrome, especially *S. aureus*, which was also isolated from the sinus washout in this patient.\(^5\)

Transcalvorial cerebral herniation as a complication of an intracranial abscess and raised intracranial pressure from venous thrombosis in Lemierre’s syndrome has not been reported previously. This case was atypical as it was not preceded by the a sore throat or neck pain, instead originating from facial sinusitis.\(^3\) Although *F. necrophorum* is implicated in
oropharyngeal infection, sinusitis caused by this organism is unusual and progression from sinusitis to Lemierre’s syndrome is rare. It is important to consider *F. necrophorum* as a potential causative organism for head and neck infections regardless of the primary site and consider this possibility when selecting empiric antimicrobials in unwell patients.

Lemierre’s syndrome is rare and there are no randomised controlled clinical trials investigating treatment efficacy, thus management is solely based on published experience and in vitro data. In this case, initial empiric antibiotic choices were broad due to the clinical severity and diagnostic uncertainty. Although clindamycin is recommended as an alternative anti-anaerobic agent, there is some evidence that it may have somewhat poorer activity against *F. necrophorum* in vitro and there are occasional reports of treatment failure. Metronidazole is recommended as the treatment of choice and there was a good clinical response after its introduction in this case, with additional flucloxacillin for the MSSA identified from the sinuses. There is no consensus regarding treatment duration for Lemierre’s syndrome. Duration may depend on the site and extent of local and embolic septic foci; in this case the duration was based on the radiographical evidence of skull osteomyelitis and the complicated clinical course. The use of therapeutic anticoagulation for the treatment of thrombophlebitis in all cases of Lemierre’s syndrome is controversial, but anticoagulation is recommended if there is cerebral venous thrombosis.

Anaerobic culture is not routinely performed on throat swab isolates and so *F. necrophorum* (an anaerobic Gram negative bacillus) may be missed. It is also common in the paediatric setting to collect blood cultures in a single aerobic paediatric culture bottle, reducing the diagnostic yield for anaerobic bacteria. The use of 16SrRNA molecular detection, a culture-free method relying on the stability of the 16SrRNA gene for prokaryotic pathogen identification, has previously been suggested as an alternative to anaerobic culture for fastidious organisms. Detection of pathogens via this method has been demonstrated on samples taken from the ear, oro-nasopharyngeal cavity, pleural fluid, blood and gastrointestinal tract, although the sensitivity of 16S rRNA PCR is still limited if the Gram stain or culture are negative. This
case demonstrates the potential adjunctive utility of 16SrRNA gene detection in the identification of culture-fastidious organisms such as *F. necrophorum* and other obligate anaerobes in the paediatric population. Furthermore, if deep head and neck infections are suspected in children, an anaerobic (in addition to aerobic) blood culture may aid diagnosis.

**Conclusion**

Here, we highlight the importance of considering potentially life-threatening thrombo-embolic complications of head and neck infections, especially when the clinical course is severe and atypical. As *F. necrophorum* is fastidious, anaerobic blood culture should be considered prior to antimicrobial therapy and there may be clinical utility in molecular diagnosis of operative samples.

**Key Points**

- Lemierre’s syndrome is a rare constellation of internal jugular vein thrombosis and disseminated septic thromboembolism following head and neck infection usually caused by *Fusobacterium necrophorum*.

- Although typically following pharyngitis or tonsillitis, it is important to consider this as a differential for sinusitis which does not follow the expected clinical course.

- Molecular detection methods, such as 16SrRNA PCR, may a useful adjunct in the identification of culture-fastidious anaerobic organisms.
References:


Figure 1. A summary of the patient’s significant radiological findings. (a) Sagittal view of a computerised tomography (CT) scan of the patient’s brain with arrows highlighting significant superior sagittal sinus thrombosis. (b) Axial view of a CT-chest and arrow highlighting a cavitating lung lesions as a result of septic emboli. (c) Sagittal view of a magnetic resonance imaging (MRI) scan of the patient’s brain with an arrow indicating a left frontal subdural empyema. (d) Coronal view of the patient’s post-operative CT-brain showing transcalvorial herniation of the brain.
Title: Atypical Lemierre’s syndrome complicated by transcalvorial brain herniation.

Running Title: Lemierre’s syndrome and brain herniation

Authors: Nelson Yu Wang¹, David P Burgner²,³,⁴, Katherine Ya-Hui Chen¹,²

Corresponding author: Nelson Yu Wang
Corresponding author email: nywan3@gmail.com

Affiliations
1. Department of General Medicine, The Royal Children’s Hospital, Melbourne, Australia
2. Murdoch Children’s Research Institute, The Royal Children’s Hospital, Melbourne, Australia
3. Department of Paediatrics, University of Melbourne, Parkville, Australia
4. Department of Paediatrics, Monash University, Clayton, Australia

Article Type: Case Report

Word Count: 1377

Key Words: Lemierre’s syndrome, thrombophlebitis, Fusobacterium necrophorum

Acknowledgements: The patient and their legal guardian has given informed consent for the writing and publication of the manuscript.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Funding Source: No funding was secured for this study.

Conflict of interest: The authors have no conflicts of interest to disclose.
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Wang, NY; Burgner, DP; Chen, KY-H

Title:
Atypical Lemierre's syndrome complicated by transcalvarial brain herniation

Date:
2021-02-18

Citation:

Persistent Link:
http://hdl.handle.net/11343/298245