Lemierre's Syndrome: A Thing of the Past?

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Abstract

Introduction: Lemierre's syndrome (LS), infectious thrombophlebitis of the internal jugular vein, is a rare, life-threatening complication of oropharyngeal infections underrepresented in literature. We reviewed the etiology, clinical characteristics, treatment regimens and prognosis of LS in pediatric patients.

Methods: PubMed and MEDLINE were searched from February 10, 2018 to July 28, 2018 for relevant studies. A systematic review was performed using the terms LS and pediatric case. Our criteria included reviews, case reports, and case series with patients under 18 years with a diagnosis of LS.

Results: 70 cases of pediatric LS were identified. The male to female ratio was 1:1.7 with an average age of 10.7 years (5 weeks to 17 years). The most common initial clinical presentations were fever (90.0%), sore throat (38.6%), and neck pain or tenderness (35.7%), while the most frequent findings on physical exam were fever (31.4%) and neck involvement (28.6%). *F. necrophorum* was the predominant organism cultured (62.9%). Septic emboli were seen in 51.4% of cases with the lungs affected in 40 patients. Most commonly used treatments were antibiotics (91.4%) followed by anticoagulation (50.0%) and the overall mortality rate was 8.6%. The average time from initial presentation to diagnosis was 4.9 days.

Conclusion: LS is a deadly condition with a staggering mortality rate despite the advent of antibiotic measures. Early identification and a high index of suspicion are necessary to prevent complications associated with LS. Despite its rarity it should remain on the differential for any patient with toxic signs and localized neck findings.

Introduction

Lemierre's syndrome (LS) was first described in early 1900s by Courmont and Cade. However, Andre Leimerre was the first to link the syndrome to an anerobic sepsis as a result of an oropharyngeal infection in 1936.[1] LS is a rare and possibly life-threatening complication that develops following oropharyngeal infection. The syndrome is characterized by internal jugular vein thrombosis, pulmonary emboli and bacteremia. Lemierre's is most commonly associated with the pleiomorphic gram-negative bacillus, *Fusobacterium necrophorum*, although the infection can be polymicrobial, especially in children. With the advent of antibiotics, the incidence of Lemierre's appeared to decrease dramatically in the 1940s and 1950s, dwindling down to as low as 1 in a million cases being reported.[1] Due to its rarity, it became known as the "forgotten disease." However, in the recent years there has been a considerable increase in reports about LS, especially in the last two decades.[2][3]

Previous studies have examined factors associated with the presentation and treatment of LS in population of primary adult patients. One study showed that the majority of the LS cases presented people in their second decade of life (51%). Of the cases that were studied, the most common sources of infections were the tonsils (37%) and the most common initial clinical presentation consisted of a sore throat (33%) and neck mass (23%).[4] In pediatric patients, LS has been reported to present similarly with fever, sore throat, neck masses or tenderness and/or tachycardia.[5][6][7]

Due to the rare nature of LS, most of the literature is limited to case reports or small case studies, which increases the difficulty in accessing a patient presenting with relevant symptoms and recognizing trends for the treatment of current patients. This is the first systematic review dedicated to pediatric patients. Due to the aggressive nature of this disease, LS can be fatal without adequate and timely antibiotic and anticoagulant measures. Thus, a thorough understanding of the various facets as well as management of the disease is essential for the care of patients. To develop a more comprehensive understanding of this rare condition in children, a systematic review was performed. This review strives to provide physicians with the etiology, clinical characteristics, treatment regimens and prognosis of LS in pediatric patients to help guide management and recognition of this disease.

Materials And Methods

PubMed and MEDLINE were searched through from February 10, 2018 to July 28, 2018 for relevant studies including case series, case reports, and systematic reviews. These databases were queried using the following search criteria:

1. PubMed: "Lemierre syndrome" AND "pediatric" AND "case"
2. Ovid MEDLINE: "Lemierre Syndrome" AND "pediatric" AND "case"

All studies were limited to the English language and PRISMA guidelines and checklist were used throughout. After September 2018, periodic surveillance of these databases was conducted to ensure no other research met inclusion criteria for this study.

All identified study titles were reviewed by two members of the research team to ensure that the selected cases discussed patients < 18 years of age with Lemierre's syndrome. Studies marked for inclusion by either reviewer underwent thorough full-text analysis by both members independently. If the reviewers disagreed, conflicts were resolved through discussion and consultation with another member of the team.

Data abstraction forms were created to extract uniform data from each study, including the following variables: race, gender, age, co-morbidities, physical examination findings, radiologic review, length of symptoms prior to seeking treatment, site of preceding infection, organ involvement, thrombosis, site of culture, intervention (incision and drainage, internal jugular vein ligation), antibiotic regimen, anticoagulation, length of stay, mortality, complications, site of septic emboli, and disposition.

Results

Using PubMed and MEDLINE, 63 case studies and reports published between 1998 and 2018 met our study criteria (**Table 1**). From these studies, 70 cases of Lemierre's syndrome were identified for review. 47 of the cases in our study were published in the last decade. The male to female ratio of patients was 1.7:1 and the average age was 10.7 years with a range of infants at 5 weeks to adolescents at 17 years.

Most the cases presented over the age of 12 (51.4%), followed by children between the ages of 2 and 12 (47.1%) and then infants under 2 (18.6%). The demographics are further detailed in **Table 2**.

Patients had presenting symptoms prior to diagnosis ranging from 1 to 21 days, averaging 4.9 days to confirmation of diagnosis by a medical professional. The most common clinical presentations were fever (90.0%), sore throat (38.6%) and neck pain/swelling (35.7%). Other clinical presentations that were less common included cough, headache, nausea/vomiting, earache, dyspnea, chest pain and dysphagia (**Table 2**). Most patients were demonstrated fevers (31.4%), swollen/tender at the neck (28.6%), tachycardic (27.1%) and were toxic-appearing (25.7%). Other findings on examination include tachypnea, enlarged tonsils, lymphadenopathy, lung findings and joint involvement (**Table 2**). The most common initial radiologic technique was computed tomography of the head/neck in 46.3% of patients, commonly revealing IJV thrombosis and chest x-ray in 34.7% of patients, commonly showing some form of consolidation. Other initial radiological techniques reported were magnetic resonance imaging (8.70%), ultrasonography (7.24%), and echocardiogram (4.3%).

Further evaluation of the patient's presentation include sources of infection prior to development of Lemierre's syndrome. The ear/mastoid (15.7%), throat/upper respiratory tract infection (10.0%) and lungs (7.1%) made up a majority of sources of the infection. Oral sites, lower extremities, tonsils, appendix, brain and blood made up the remaining specified sources; however, 51.4% of cases did not have specified sites (**Table 3**). *F. necrophorum* was the predominant organism cultured (62.9%), followed by Group A *Streptococcus* and MRSA (7.1%). Although most cases were culture positive, 11.4% of patients yielded negative bacterial cultures (**Table 4**).

Sixty-three of the patients had other organ involvement; the lungs (57.1%), the brain (27.1%) and the heart (22.9%) were the organs primary affected (**Table 5**). Lung manifestations include septic emboli, cavitating pulmonary nodules, pneumonia, respiratory failure, and pulmonary effusions. Brain manifestations include meningitis, epidural and subdural abscesses and sinus thrombosis. Cardiomegaly, decreased ejection fraction, systolic murmurs, and tachycardia were some of the complications seen with cardiac involvement. In 36 of 70 cases, septic emboli were observed with the most common location being the lungs (42.8%) organ followed by the brain (2.9%). Other less common sides of emboli were the bones, renal, cutaneous, lateral sinus, and femoral (**Table 5**).

Treatments for Lemierre's were very patient specific and dependent on the presenting symptoms and physical exam findings. The most common treatment interventions were nonsurgical. Despite the great variability in cases, most patients were treated with antibiotics (91.4%) and anticoagulative therapy (50%). The most common anticoagulants were Heparin/LMWH (51.4%), Enoxaparin (20%) and Warfarin (11.4%) and the most common antibiotics were Cephalosporins (60.9%), Clindamycin (21.9%), Penicillins (21.9%), and Vancomycin (20.3%). **Table 6** provides a complete list of all anticoagulant and antibiotic therapies that were initiated in patients. The overall mortality rate was 8.6% for this rare syndrome.

Discussion

Although literature is riddled with mentions of LS dating back to the early 1900s, Andre Lemierre was the first to report 20 cases of the syndrome in 1936 and link it to *Fusobacterium necrophorum*.^[8] LS is characterized as infectious thrombophlebitis of the internal jugular vein, is a rare, life threatening complication of oropharyngeal infections. The incidence of Lemierre's fell dramatically in the 1940s and 1950s with the introduction of antibiotics that it became dubbed the "forgotten disease." Nonetheless, there is evidence of a recent rise in the number of LS cases in recent years.^[9] This is supported by our analysis which found that 67.1% of our cases of LS were published in the last decade alone. Although the exact cause of the rise of LS remains unknown, many attribute this rise to increased antibiotic resistance or changes in regional alterations in antibiotic usage by physicians.^[10] Another explanation is the fact that antibiotic prescription practices have become more conservative, especially in children.^[11] This could potentially lead to more infections not being treated properly and having a higher likelihood of subsequent complications such as Lemierre's. The recent resurgence of LS suggests physicians need to keep the disease in their minds when treating head and neck infections in patients.

LS is specifically a disease of the young with 89% of the patients being between 10 and 35 years of age.^[9] The majority of our patients (51.4%) were between the ages of 12–17. The syndrome typically presents as an infection in the head and neck with 80–90% of cases originating in the oropharynx and parapharyngeal space.^[12] Our study showed similar results with the ear and mastoid as the most common sources of infection (15.7%), followed by the oropharynx (10.0%). The clinical presentation of LS is nonspecific and is typical of a bacterial infection with symptoms such as fever, sore throat, and neck pain as found in our analysis. On physical exam, most children were febrile, had some sort of neck involvement such as abscess, swelling, or tenderness, and were tachycardic. Due to the ambiguity of these symptoms, initially diagnosing LS can be difficult and can lead to treatment delays.^[13] This is supported by our study, which showed the average time from presentation in a hospital to diagnosis of LS to be 4.9 days. LS is a life-threatening condition with mortality rates between 5–18% in treated patients.^[13] The average mortality rate in our analysis fell in this range at 8.6%, higher than that seen in a systematic review of adults which reported a 5% mortality rate.^[4] The diagnosis of LS should be considered in patients that are otherwise healthy who present with an oropharyngeal infection with worsening symptoms.

F. Necrophorum was the most commonly cultured bacteria (62.9%) in our analysis, followed by Group A Strep (7.1%) and MRSA (7.1%) *F. Necrophorum* is a gram-negative non-spore-forming anaerobic rod. It has the potential to cause a range of diseases in its patients from tonsillar abscess to LS.^[10] Antibiotics were used in 65 of 70 cases in our analysis. The most common antibiotics used in our analysis to effectively treat LS were beta-lactams such as cephalosporins and penicillin, as well as clindamycin. Moreover, we found that if cephalosporins and clindamycin were not used in the antibiotic regimen initially, they were the most added antibiotics either after culture results or diagnosis of LS was made. This is consistent with other studies which have shown *F. Necrophorum* is most susceptible to antibiotics such as metronidazole, clindamycin, and beta-lactams due to good penetration and oral bioavailability.^{[3][14]}

Studies maintain that clinicians should begin treatment with broad-spectrum therapy with anaerobic coverage.[15]

Conversely, anticoagulative therapy was only used in 35 cases, half of the cases analyzed. Heparin or LMWH (51.4%) was most commonly used followed by enoxaparin (20.0%). The use of anticoagulants in LS is case and/or physician dependent. Campo et al recommended anticoagulation should be carried out in the absence of any contradictions and only in patients that responded poorly to antibiotic therapy, had thrombophilia or intracranial thrombosis.[15] The benefits of anticoagulation therapy in LS has not been properly studied. A common complication of the IJV thrombosis in LS is septic thrombosis brought on by inflammation from the disease.[16] 51.4% of the cases analyzed in our study reported septic emboli, with 42.8% of the emboli being pulmonary in origin. Pulmonary involvement precipitated by septic emboli has been well cited in literature with some studies reporting emboli in 79–100% of cases.[16][17][18] Other common sites of septic metastasis were the central nervous system and bone or more specifically the joints. Nevertheless, further research is required to establish evidence for the consensus of anticoagulative therapy in LS. Surgical therapy is considered in LS on a case by case basis.

As with any study, systematic review studies are not without their limitations. Each case is investigated individually and inputted into a standardized form, which can result in human errors of interpretation and analysis. Moreover, the quality of the data available is another limitation of this study. LS is a rare disease with relatively few cases reported in the pediatric population and no consistent reporting of patient demographics, clinical presentation, disease progression, and treatment. Therefore, there may be discrepancies in the information attained from each report. Also, the cases included in this study spanned from 1998 to 2018, thus preferred treatment modalities and disease diagnosis may have changed over time. Despite these limitations, this study represents the only systematic review in literature on pediatric cases of LS. It provides essential information on patient demographics and clinical trends of LS that can help guide physicians with the awareness and management of this fatal disease.[19]

Conclusion

Physician awareness and a high index of suspicion are an essential part of diagnosis and management of LS. LS is a difficult to recognize disease that can prove to be fatal if not identified early. Antibiotic therapy is key in the management of LS. Anticoagulant and surgical therapy are utilized on a more case to case basis and physician discretion. This study strives to recognize the symptoms and presentation of LS in pediatric cases and establish clinical trends to help guide recognition and treatment and of this rare disease.

Declarations

Financial Disclosures: None

Conflicts of Interest: None

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Tables

Table 1. Studies Meeting Criteria for Systematic Review

First Author	Year	Number of Cases
Dhawan[20]	1998	1
Duong[21]	2001	1
Hoehn[22]	2002	1
Bentham[23]	2004	1
Busko[24]	2004	1
Litterio[25]	2004	1
Hong[26]	2005	2
Masterson[27]	2005	1
Schmid[28]	2005	2
Trapp[29]	2005	1
Veldhoen[30]	2007	2
Waterman[31]	2007	1
Westhout[32]	2007	1
Aspesberro[33]	2008	2
O'Dwyer[34]	2008	1
Abourazzak[35]	2009	1
Bonhoeffer[36]	2010	1
Dirks[37]	2010	1
Hoehn[22]	2010	1
Ridgway[38]	2010	3
Shah[39]	2010	1
Al-Sayyed[19]	2011	1
Bababeygy[40]	2011	1
Frizzola[41]	2011	1
Singhi[6]	2011	1
Davies[42]	2012	1
Phan[43]	2012	1
Teng[44]	2012	1

Wasilewska[45]	2012	1
Wu[46]	2012	1
Blessing[47]	2013	1
DeGaffe[7]	2013	1
Hawes[48]	2013	1
Horwitz[49]	2013	1
Khan[50]	2013	1
Kizhner[5]	2013	2
LoVerme[51]	2013	1
Root[52]	2013	1
Soh[53]	2013	1
Behpour-Oskooee[54]	2014	1
Cardenas-Garcia[55]	2014	1
Duke[56]	2014	1
Ratnasingham[57]	2014	1
Udassi[58]	2014	1
Benevides[59]	2015	1
Dalen[60]	2015	1
He[61]	2015	1
Jacob[62]	2015	1
Macao[63]	2015	1
Pinheiro[64]	2015	1
Sarma[65]	2015	1
Shiber[66]	2015	1
Garcia-Salido[67]	2017	3
Jariwala[68]	2017	1
Kumral[69]	2017	1
Mattke[70]	2017	1
Rafati[12]	2017	1

Raggio[71]	2017	1
Sinatra[72]	2017	1
Vogt[73]	2017	1
Held[74]	2018	1
Ibrahim[8]	2018	1
Unic[75]	2018	1

Table 2. Patient Demographics and Findings on Presentation

Demographics	Totals
Sex, No. (%)	
Male	26 (37.1)
Female	44 (62.9)
Race, No. (%)	
White	7 (10.0)
Hispanic	4 (5.7)
Black	3 (4.3)
Asian/ Pacific Islander	1 (1.4)
Not Specified	55 (78.6)
Age Groups, No. (%)	
Children over 12	40 (51.4)
Children 2 to 12	33 (47.1)
Infants under 2	13 (18.6)
Clinical Presentation, No. (%)	
Fever	63 (90.0)
Sore Throat	27 (38.6)
Neck Pain/ Swelling	25 (35.7)
Cough	17 (24.3)
Headache	15 (21.4)
Nausea/Vomiting	15 (21.4)
Earache	11 (15.7)
Dyspnea	7 (10)
Chest Pain	7 (10)
Dysphagia	4 (5.7)
Physical Exam Findings, No. (%)	
Febrile	22 (31.4)

Neck Involvement (Swelling/Tenderness/Abscess)	20 (28.6)
Tachycardia	19 (27.1)
Toxic Appearing	18 (25.7)
Tachypnea	11 (15.7)
Enlarged Tonsils	8 (11.4)
Lymphadenopathy	8 (11.4)
Lung Findings	7 (10.0)
Joint Involvement	5 (7.1)

Table 3. Source of Infection for Lemierre's Syndrome

Source of Infection	N (%)
Not Specified	36 (51.4)
Ear/Mastoid	11 (15.7)
Throat/URI	7 (10.0)
Lungs	5 (7.1)
Oral	3 (4.3)
Lower Extremity (Gluteal/Knee/Calf)	3 (4.3)
Tonsils	2 (2.9)
Appendix	1 (1.4)
Brain	1 (1.4)
Blood	1 (1.4)

Table 4. Culture results by case

Culture	N (%)
F. necrophorum	44 (62.9)
Group A Strep	5 (7.1)
MRSA	5 (7.1)
MSSA	4 (5.7)
Gram Negative Rods	3 (4.3)
S. Aureus	1 (1.4)
S. Epidermis	1 (1.4)
Culture Negative	8 (11.4)

Table 5. Other organs Affected and Sites of Septic Emboli

	N (%)
Organs Affected	
Lungs	40 (57.1)
Brain	19 (27.1)
Heart	16 (22.9)
Bone	9 (12.9)
Kidney	6 (8.6)
Liver	5 (7.1)
Ear/ Mastoids	2 (2.9)
Spleen	1 (1.4)
Larynx	1 (1.4)
Tonsils	1 (1.4)
Sinuses	1 (1.4)
Skin	1 (1.4)
Rectus Abdominis	1 (1.4)
Sites of Septic Emboli	
Lungs	30 (42.8)
Brain	2 (2.9)
Bone	1 (1.4)
Renal	1 (1.4)
Cutaneous	1 (1.4)
Lateral Sinus	1 (1.4)
Femoral	1 (1.4)
No Septic Emboli	34 (48.6)

Table 6. Anticoagulative and Antibiotic Therapy Use

Treatment Methods	Totals
Anticoagulative Therapy, No. (%)	N = 35
Heparin//LMWH	18 (51.4)
Enoxaparin	7 (20)
Warfarin	4 (11.4)
Aspirin	3 (8.6)
Lovenox	3 (8.6)
Fraxiparine	1 (2.9)
Tinzaparin Sodium	1 (2.9)
Initial Antibiotic Therapy, No. (%)	N = 64
Cephalosporins	39 (60.9)
Clindamycin	14 (21.9)
Penicillins	14 (21.9)
Vancomycin	13 (20.3)
Metronidazole	9 (14.1)
Gentamycin	5 (7.8)
Meropenem	4 (6.2)
Piperacillin/ Tazobactam	3 (4.7)
Levaquin	1 (1.6)
Levofloxacin	1 (1.6)
Rifampin	1 (1.6)
Altered Antibiotic Therapy, No. (%)	N = 64
Cephalosporins	39 (60.9)
Clindamycin	14 (21.9)
Surgical Intervention, No. (%)	N = 34
Incision and Drainage	24 (70.6)
Mastoidectomy	9 (26.5)
Debridement	6 (17.6)
Myringotomy	4 (11.8)

Figures

PRISMA 2009 Flow Diagram

Figure 1