Lemierre’s and Lemierre’s-Like Syndromes in Children: Survival and Thromboembolic Outcomes

Neil A. Goldenberg, MD*‡; R. Knapp-Clevenger, MSN, CPNP*‡; Taru Hays, MD*; and Marilyn J. Manco-Johnson, MD*‡

ABSTRACT. Objective. Lemierre’s syndrome, or jugular vein thrombosis (JVT) associated with anaerobic infection of the head and neck and frequently complicated by septic pulmonary embolism (PE), has historically been described as a disease of young adults. In recent years, an increasing number of case reports of childhood Lemierre’s syndrome have been published, focusing mostly on the clinical and laboratory findings at disease presentation and the outcomes of infection. Given the potentially life-threatening thromboembolic complications of this disorder, we reviewed our single-institutional experience with pediatric Lemierre’s and Lemierre’s-like syndromes (LALLS) from within the context of a larger cohort study of thrombosis in children.

Methods. Children who were aged from birth to 21 years and had received a diagnosis of JVT and Lemierre’s syndrome at the Children’s Hospital (Denver, CO) between 2001 and 2005 were identified for inclusion. Case designation of LALLS required all the following: (1) radiologic confirmation of JVT, (2) clinical diagnosis of pharyngitis or other febrile illness, and (3) intraoperative evidence of loculated infection in the head and neck region or radiologic demonstration of bilateral pulmonary infiltrates. Isolation of a causative organism by microbiologic culture of blood, tissue, or purulent fluid was also a necessary diagnostic criterion among patients who had not been treated with antibiotics before culture. A designation of classic Lemierre’s syndrome was reserved for documented cases of anaerobic infection. Children in whom JVT was associated with the presence of an ipsilateral central venous catheter were excluded from the analysis. Analysis included information on underlying medical conditions, microbiologic and radiologic findings, and comprehensive hypercoagulability testing results from the time of diagnosis, as well as antimicrobial and anticoagulant therapies administered. In addition, clinical outcomes were evaluated via serial follow-up and included bleeding complications, thrombus resolution on serial radiologic studies, symptomatic recurrent venous thromboembolism (VTE), and mortality.

Results. From January 2001 to January 2005, 9 children with LALLS were identified. Median age was 15 years (range: 2.5–20 years). Clinical presentation was consistent with septic PE in 5 cases and septic shock in 2. Thrombophilia was present in 100% (7 of 7) of children tested, consisting principally of antiphospholipid antibodies and elevated factor VIII activity. Anticoagulation was given in 89% (8 of 9), for a median duration of 3 months (range: 7 weeks–1 year). After a median follow-up time of 1 year, all children had survived without recurrent VTE or anticoagulant-associated major hemorrhage. JVT failed to resolve at 3 to 6 months in 38% of anticoagulated children.

Conclusions. Our experience suggests that LALLS is an emerging pediatric concern with serious acute (eg, septic PE) and chronic (eg, persistent vascular occlusion) complications. Septic JVT may not be uniquely anaerobic, and the inflammatory prothrombotic state is often characterized by antiphospholipid antibodies and elevated factor VIII levels. Early diagnosis and aggressive antimicrobial and antithrombotic therapies in LALLS may be necessary for optimal long-term outcomes. PEDIATRICS 2005;116:e543–e548. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0433; Lemierre’s syndrome, outcome, thrombophilia, anticoagulation, thromboembolism.

ABBREVIATIONS. JVT, jugular vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; LALLS, Lemierre’s and Lemierre’s-like syndromes; FVIII, factor VIII; APLA, antiphospholipid antibodies; PTS, postthrombotic syndrome.

The syndrome of jugular vein thrombosis (JVT) associated with supplicative anaerobic infection of the upper aerodigestive tract, often complicated by septic pulmonary embolism (PE), was initially described in the early 20th century by Courmont and Cade,1 Goodman,2 Schottmüller,3 Mosher,4 and others and was delineated further in 1936 by Lemierre.5 Lemierre’s syndrome, as it has since become known, has commonly been associated with a pleomorphic Gram-negative bacillus (currently designated Fusobacterium necrophorum) identified from anaerobic culture of blood or purulent fluid.6,7 However, in children and perhaps adults, the infection frequently seems to be polymicrobial.8 JVT may arise from infection of the lateral pharyngeal space secondary to tonsillitis, pharyngitis, mastoiditis, and even odontogenic infection9 (including tooth abscess). In addition, both uncomplicated JVT and Lemierre’s syndrome can rarely be attributed to penetrating oropharyngeal trauma (“pencil-point injury”).10,11 From the perspective of Virchow’s triad, clot formation in Lemierre’s syndrome is likely the result of the combined effects of systemic hypercoagulability (caused or exacerbated by infection), ve-
Larger cohort study of pediatric thrombosis. Infection and thrombophlebitis in the anterior compartment of the lateral pharyngeal space often presents as neck pain, swelling, and tenderness along the anterior border of the sternocleidomastoid muscle; however, primary involvement of the posterior compartment may remain asymptomatic until the disease progresses systemically to include septic pulmonary embolism and, in some cases, sepsis syndrome with multisystem organ dysfunction. Lemierre's syndrome was particularly recognized in the preantibiotic era as a complication of pharyngitis with parapharyngeal abscess and was rarely reported in the literature during the 1960s and 1970s, when penicillin came into common use. In recent decades, however, an increasing number of reports of Lemierre's syndrome in childhood have been published, principally focusing on the presentation of illness, antimicrobial therapy, and clinical course of infection, with little attention to thromboembolic outcomes. To date, outcomes of thrombosis in children have been determined in at least 3 large pediatric thrombosis registries. Although these studies have in general suggested a low rate of clinically apparent recurrent venous thromboembolism (VTE), they have raised concern that the development of chronic venous insufficiency in the form of the postthrombotic syndrome may be a frequent sequela of thrombosis in children. In addition, in the registry report of Nowak-Gottlieb et al.14 and the recent cohort analysis of Goldenberg et al.,15 the incorporation of uniform radiologic assessment of thrombus evolution over time in the evaluation of pediatric VTE outcomes has led to the understanding that, in many cases, thrombosis may persist after standard anticoagulant therapy. However, the systematic evaluation of VTE outcomes in children, to our knowledge, has never been described separately for JVT or for Lemierre’s syndrome. Given the clinical severity of this disorder and its emergence as an important clinical entity in children, we sought to evaluate VTE outcomes of JVT associated with aerobic and anaerobic infection of the head and neck (Lemierre’s and Lemierre’s-like syndromes [LALLS]) from within the context of a larger cohort study of pediatric thrombosis.

METHODS

With the approval of the Colorado Multi-Institutional Review Board (05-0072), clinical and laboratory information from children who ranged in age from birth to 21 years and had received a diagnosis of JVT or Lemierre’s syndrome at the Children’s Hospital, Denver, and The Mountain States Regional Hemophilia and Thrombosis Center (Aurora, CO) between January 2001 and January 2005 was reviewed from the database of a larger cohort study of pediatric thrombosis. Case designation of LALLS required all of the following criteria: (1) radiologic confirmation of JVT, (2) a clinical diagnosis of pharyngitis or other febrile illness, and (3) intraoperative evidence of localized infection in the head and neck region or radiologic demonstration of bilateral pulmonary infiltrates. Isolation of a causative organism by microbiologic culture of blood, tissue, or purulent fluid was also a necessary diagnostic criterion among patients who had not been treated with antibiotics before culture but was not restricted to anaerobes. A designation of classic Lemierre’s syndrome was reserved for children who met the aforementioned criteria and in whom anaerobic infection was demonstrated microbiologically. Children in whom JVT was associated with the presence of an ipsilateral central venous catheter were excluded from the analysis.

In these patients, anticoagulant therapy consisted of either twice-daily subcutaneous low molecular weight heparin targeted to an anti-Xa activity level of 0.5 to 1.2 U/dL or initial continuous intravenous unfractionated heparin followed by daily oral warfarin with a goal international normalized ratio of 2.0 to 3.0. Radiologic assessment of JVT was repeated at 3 to 6 months after diagnosis and again at 1 year for persistent thrombosis, with additional interim assessment in some cases. Clinical follow-up had been undertaken by interview and examination at 3 months and yearly thereafter.

The analysis involved data on underlying medical conditions, microbiologic and radiologic findings, and comprehensive thrombophilia (ie, hypercoagulability) laboratory testing from the time of diagnosis, as well as antimicrobial and anticoagulant therapies administered. The thrombophilia panel included plasma testing for native anticoagulant levels (protein C activity, free and total protein S antigen, and antithrombin activity); factor VIII (FVIII) activity; concentrations of homocysteine, D-dimer, and lipoprotein(a); and antiphospholipid antibodies (APLA; anticardiolipin immunoglobulin G and immunoglobulin M, as well as lupus anticoagulant by dilute Russel viper venom test). FVIII activity levels >132 IU/dL were considered elevated, and a lupus anticoagulant ratio of 1.3 or greater was considered positive, in accordance with institutional clinical laboratory reference ranges defined in healthy children. The presence of genetic thrombophilia mutations (factor V Leiden and prothrombin 20210 mutations) was also evaluated. In addition, clinical outcomes were analyzed, including mortality, symptomatic recurrent VTE, bleeding complications, and thrombus resolution on serial radiologic assessments (consisting of a repeat of the initial diagnostic imaging test, either computed tomography of the neck with intravenous contrast or compression ultrasound of the neck with duplex Doppler). Given a small sample size, nonparametric descriptive statistics were reported (median and range).

RESULTS

From January 2001 to January 2005, 9 children who met all criteria for LALLS were identified from our cohort. The clinical characteristics at presentation, infectious causes, other underlying clinical conditions, and durations of antibiotic therapy in these patients are given in Table 1; Table 2 displays the sites of VTE, abnormalities on thrombophilia testing, degree of vaso-occlusion of JVT at diagnosis, the types and durations of anticoagulation, radiologic evidence of JVT at 3–6 months, and the times to thrombus resolution. The median age at diagnosis was 15 years (range: 2.5–20 years), and no clear gender predisposition was evident. Underlying conditions in addition to head and neck infection were present in 4 patients, including congenital anomaly of the carotid artery, type 1 diabetes, relapsed acute lymphoblastic leukemia, and Rubenstein-Taybe syndrome with large B-cell lymphoma.

Infections and Antimicrobial Therapy

The clinical foci of infection in these 9 pediatric patients with LALLS included pharyngitis in 6 children, accompanied by parapharyngeal abscess in 2, dental abscesses and bilateral pleural effusions in 1, and multiple bilateral cavitary pulmonary infiltrates in 3. In addition, sinusitis was the underlying infection in 2 children, and mastoiditis with abscess associated with bilateral pleural effusions was the underlying infection in 1. Infectious causes were diverse,
including anaerobic and aerobic organisms, and frequently were polymicrobial. \textit{α}-\textit{Streptococcus} and \textit{Staphylococcus aureus} were most commonly identified, with \textit{Fusobacterium necrophorum} isolated in 2 cases. Septic shock with disseminated intravascular coagulation and multiorgan dysfunction was manifest at presentation in 2 children, each of whom required intensive care supportive measures during the early hospitalization period. Parenteral antimicrobial treatment involved consultation with the Infectious Disease team and typically was prescribed for at least 6 weeks, sometimes followed by an additional course of oral therapy. The antibiotic regimens were tailored to the microbiologic culture results and potential pathogenic involvement of oral anaerobes; hence, clindamycin was commonly used. The median duration of total antimicrobial therapy was 6 weeks (range: 6 weeks–1 year).

### VTE Characteristics and Anticoagulant Therapy

Among the 9 cases of LALLS, JVT was left-sided in 7 and was completely vaso-occlusive in 5 (56%). The clinical presentation included findings consistent with septic PE in 5 (56%) patients. A comprehensive laboratory panel of hypercoagulability revealed the presence of thrombophilia at diagnosis in all 7 (100%) children tested. Thrombophilic abnormalities consisted of APLA in 3 cases and elevated FVIII in 4; the factor V Leiden mutation was present in only 1 patient. Combined thrombophilia traits were present in 3 of the 7 (43%) children studied. Assays for the lupus anticoagulant and FVIII level were repeated between 2 and 6 months after diagnosis in 6 of 7 patients in whom this testing had been positive at presentation; factor VIII normalized in all cases, and the lupus anticoagulant was no longer present in 2 (67%) of 3 cases at follow-up, suggesting epiphenomena of the acute inflammatory prothrombotic state rather than intrinsic hypercoagulability in these patients.

Anticoagulant treatment was administered in 8 (89%) of 9 children with LALLS. Primary therapy consisted of twice-daily administration of the low molecular weight heparin enoxaparin (sometimes followed by extended therapy with warfarin) in all except 1 treated child, who received daily oral warfarin as primary therapy. The median duration of anticoagulation was 3 months (range: 7 weeks–1 year) and was prescribed for at least 1 week beyond completion of the antibiotic regimen.

### VTE Outcomes at Follow-up

The median duration of follow-up in these 9 children with LALLS was 1 year (range: 4 weeks–3 years). All patients survived, without any symptomatic recurrent VTE or anticoagulant-associated major hemorrhage observed.

Serial radiologic follow-up of JVT revealed no cases of thrombus progression over time. Complete thrombus resolution was demonstrated at 3 to 6 months (the standard duration of anticoagulation for pediatric thrombosis\textsuperscript{16}) in 4 patients. Among these children, the median time to thrombus resolution was 5 weeks (range: 3–7 weeks).
TABLE 2. Thromboembolic Findings, Treatment, and Outcomes in 9 Children (Age 21 Years) With LALLS

<table>
<thead>
<tr>
<th>Case</th>
<th>Site</th>
<th>Vaso-occlusion</th>
<th>Septic PE</th>
<th>Anticoagulation</th>
<th>TE Outcome (3–6 Mo)</th>
<th>Time to Thrombus Resolution</th>
<th>Thrombophilic Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L IJ</td>
<td>Yes</td>
<td>No</td>
<td>7 wk (LMWH)</td>
<td>Persistent</td>
<td>N/A</td>
<td>↑ FVIII</td>
</tr>
<tr>
<td>2</td>
<td>L IJ</td>
<td>Yes</td>
<td>No</td>
<td>N/A (none)</td>
<td>Persistent</td>
<td>N/A</td>
<td>LA, ACA IgM</td>
</tr>
<tr>
<td>3</td>
<td>L IJ</td>
<td>Yes</td>
<td>No</td>
<td>12 mo (LMWH)</td>
<td>Persistent</td>
<td>N/A</td>
<td>↑ FVIII</td>
</tr>
<tr>
<td>4</td>
<td>L IJ</td>
<td>No</td>
<td>Yes</td>
<td>3 mo (VKA)</td>
<td>Resolved</td>
<td>6 wk</td>
<td>Factor V Leiden, heterozygous</td>
</tr>
<tr>
<td>5</td>
<td>R IJ</td>
<td>No</td>
<td>Yes</td>
<td>9 wk (LMWH)</td>
<td>Resolved</td>
<td>4 wk</td>
<td>↑ FVIII</td>
</tr>
<tr>
<td>6</td>
<td>L IJ</td>
<td>No</td>
<td>Yes</td>
<td>7 wk (LMWH)</td>
<td>Resolved</td>
<td>7 wk</td>
<td>LA, ACA IgG</td>
</tr>
<tr>
<td>7</td>
<td>R IJ</td>
<td>No</td>
<td>No</td>
<td>6 mo (LMWH)</td>
<td>Resolved</td>
<td>3 wk</td>
<td>NE</td>
</tr>
<tr>
<td>8</td>
<td>L IJ</td>
<td>Yes</td>
<td>No</td>
<td>9 mo (LMWH, then VKA)</td>
<td>Persistent</td>
<td>N/A</td>
<td>LA, ↑ FVIII</td>
</tr>
<tr>
<td>9</td>
<td>L IJ</td>
<td>Yes</td>
<td>Yes</td>
<td>3 mo</td>
<td>Resolved</td>
<td>6 wk</td>
<td>NE</td>
</tr>
</tbody>
</table>

TE indicates thromboembolic; L, left; R, right; IJ, internal jugular vein; LMWH, low molecular weight heparin (enoxaparin); N/A, not applicable; VKA, vitamin K antagonist (warfarin); ↑ FVIII, elevated factor VIII activity; LA, lupus anticoagulant positive; ACA, anticardiolipin antibody positive; NE, not evaluated.

By contrast, persistent thrombosis was observed on radiologic follow-up at 3 to 6 months in 4 (44%) of 9 children. This represented 4 (80%) of 5 patients in whom JVT had been completely vaso-occlusive at diagnosis, 1 of whom had received no anticoagulant therapy. In 2 of the children with persistent thrombosis at initial follow-up, results were available from subsequent radiologic evaluation at 1 year; in both cases, the thrombus remained persistent and unchanged.

DISCUSSION

Although incidence data from epidemiologic studies in children are lacking, the increasing number of reports of childhood Lemierre’s syndrome in the recent literature suggests, in the absence of observer or publication biases, that this syndrome may be reemerging as an important clinical entity. A prospective study of anaerobic infections at a large pediatric center during 1974 revealed only 1 possible case of Lemierre’s syndrome.17 In the late 1990s, Hagelskjaer et al18 found 24 cases over the course of a 6-year retrospective analysis in Denmark and noted a trend toward increase in the diagnosis of Lemierre’s syndrome in later years; however, the retrospective design of the study is suboptimal for establishing incidence. Regardless of true epidemiologic trend, the severe and sometimes life-threatening nature of LALLS in children necessitates an enhanced awareness of this syndrome by the pediatrician.

To date, the mechanisms of hypercoagulability in LALLS remain incompletely understood. It has been suggested that the anaerobic infection may play an important causative role in thrombus formation and embolization, especially in the classic Fusobacterium-associated Lemierre’s syndrome. In vitro studies have suggested that direct cell-to-cell contact of virulent strains of F necrophorum with platelets results in platelet aggregation, which can be inhibited in the presence of aspirin.19 In addition, animal experimentation has shown that intravenous injection of bacterial cultures of Bacteroides and Fusobacterium species or their culture filtrates or lipopolysaccharide and lipid A components significantly shortened the whole-blood clotting time in mice.20 However, this effect was not reproduced consistently in rabbits, and neither lipopolysaccharide nor lipid A preparations from these anaerobes produced aggregation of human platelets in vitro.

Our finding that thrombophilic abnormalities were present in all investigated cases of LALLS in this series is worthy of additional investigation. Among children with acute VTE, underlying thrombophilia has been found to be most prevalent in the absence of a central venous catheter or other clinical risk factors for VTE.16 Hence, if not simply attributable to chance, then it is surprising to find pervasive thrombophilia in a syndrome of septic thrombophlebitis such as LALLS, wherein the underlying infection seems to be a potent mediator of thrombosis. However, in the present series, APLA and elevated FVIII activity levels that were present at presentation of JVT were rarely persistent on reevaluation at 2 to 6 months after diagnosis. These results are reminiscent of previous findings of APLA and protein S antibodies in acute varicella infection21 and suggest that APLA and elevated FVIII levels in LALLS may often represent epiphenomena of the underlying inflammatory prothrombotic process rather than a pre-existing hypercoagulable state.

Fundamental and prerequisite to the optimal management of LALLS is an adequate understanding of its underlying risk factors and disease associations, as well as of the long-term outcomes of both the infectious and thromboembolic processes. Siauve et al22 in 1989 reported their experience with Lemierre’s syndrome in adults and children, including 3 patients who were younger than 21 years. Although clinical findings of neck tenderness and swelling were present in these patients, radiologic confirmation of JVT was not performed. The authors included their experience in a comprehensive review of 38 published cases of Lemierre’s syndrome from 1974 through 1989, in which microbiologic diagnosis of bacteremia and clinical presentation consistent with the syndrome were required for inclusion. It is likely that numerous additional cases of Lemierre’s syndrome were not reported during this period and that others remained occult because of the insensitivity of imaging modalities at the time, particularly before the availability of high-resolution computed tomography for the enhanced recognition of septic pulmonary emboli.23 It is interesting that in several cases, septic arthritis was among the manifestations of sep-
tic embolism. Among a total of 27 patients who had Lemierre’s syndrome and were younger than 21 years in the retrospective analysis by Sinave et al,22 overall mortality was 7% (2 of 27).

A separate review of the pediatric literature during this period, in 1988, by Goldhagen et al,24 who added their experience of 3 children who were younger than 18 years and had Lemierre’s syndrome, concurrently revealed an overall mortality of 8% (1 of 12). Radiologic confirmation of JVT was reported in one third of cases (4 of 12) in this series. Neck pain was part of the clinical presentation in 83% (10 of 12) of children, and dyspnea was a complaint in 50% (6 of 12). *F. necrophorum* grew from anaerobic blood culture in 82% (9 of 11) of patients with proven bacteremia.

More recently, in 1995, Alvarez et al25 reviewed the English literature on pediatric Lemierre’s syndrome from 1980 to 1994. Among 12 published cases in their analysis, the mean duration of antibiotic treatment was 6 weeks, and anticoagulant therapy was administered to 25% (3 of 12) of patients. Overall mortality was 8% (1 of 12). Importantly, the mean delay to diagnosis of Lemierre’s syndrome from the time of admission was 5 days; in previous work, the occurrence of septic embolization has been associated with a prolonged delay to diagnosis.18

The present study of 9 children who had a diagnosis of LALLS at the Children’s Hospital (Denver, CO) between January 2001 and January 2005 is unique in affording a preliminary understanding of VTE outcomes in this serious disorder. In our small series of pediatric LALLS (nevertheless one of the largest reported to date), anticoagulant therapy was administered in all but 1 case. After a median follow-up of 1 year, all children had survived, and no thrombus progression, recurrent VTE, or anticoagulant-associated major hemorrhage was observed.

In contrast to these favorable overall outcomes, we observed persistent JVT at 3 to 6 months in 44% of children. It is intriguing to note that these cases of persistent JVT were limited to patients in whom JVT was completely vaso-occlusive at diagnosis and to the patient who received no anticoagulation. Although additional investigation is necessary, these findings may suggest that therapeutic anticoagulation is an important component to the management of VTE in LALLS and that more aggressive approaches to antithrombotic therapy might be necessary to achieve optimal VTE outcomes in cases in which JVT is completely vaso-occlusive at diagnosis.

The persistence of thrombosis after 3 to 6 months of standard anticoagulation therapy raises concern for adverse long-term outcomes of thrombosis, given the former’s association with both recurrent VTE26 and venous valvular insufficiency.27 Valvular reflux after acute thrombosis often manifests in the post-thrombotic syndrome (PTS), a disorder of chronic venous insufficiency characterized by a spectrum of severity, including pain and swelling distal to the site of thrombosis, collateral venous formation, venous stasis dermatitis, and frank ulceration. Whether persistent thrombosis is also a precursor to recurrent VTE and the development of PTS in the context of LALLS in children remains a challenging question, which will require not only longer follow-up but also the adaptation of a validated scale for pediatric PTS assessment of deep vein thrombosis in the limbs28 to the setting of JVT. Present evidence suggests that PTS is a significant concern among the long-term outcomes of thrombosis in children.29

A few limitations of the present study should be noted. First, given that LALLS cases were identified from the database of a larger cohort study of pediatric thrombosis, the incidence of this disorder cannot be estimated from the present study. In addition, given that children with head and neck infections were not evaluated uniformly for anaerobic infection, cases of classic Lemierre’s syndrome are likely to have been missed. Finally, because radiologic evaluation for JVT was performed for diagnostic purposes (ie, in patients with signs and/or symptoms of JVT) rather than as a screening test, patients with LALLS are restricted mostly to those with symptomatic JVT. Although this could have led to a selection bias toward more severe cases, the excellent survival rate in these children suggests that selection of more severe cases was unlikely.

In summary, in our recent experience, LALLS seems to be an emerging pediatric concern with serious acute and chronic complications, including septic PE and persistent vascular occlusion, respectively. Septic JVT may not be limited in cause to anaerobes, and APLA and elevated FVIII levels are indicative of (and perhaps pathologic in) the prothrombotic inflammatory state. Early diagnosis and aggressive antimicrobial and antithrombotic therapies in LALLS may be necessary for optimal long-term outcomes.

**REFERENCES**


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