


Ophthalmic complications of Lemierre syndrome

Robert Kreuzpointner,¹  Luca Valerio,² Gabriele Corsi,^{3,4} Federica Zane,⁵ Clara Sacco,⁶ Karin Holm,⁷ Christian Righini,⁸ Alessandro Pecci,⁹ Sandrine Zweifel^{10,11†} and Stefano Barco^{1,2†}

¹Clinic of Angiology, University Hospital Zurich, Zurich, Switzerland

²Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany

³Department of Clinical, Integrated and Experimental Medicine (DIMES), Alma Mater Studiorum University of Bologna, Bologna, Italy

⁴Department of Pneumology and Respiratory Intensive Therapy Unit, St Orsola University Hospital, Bologna, Italy

⁵Department of General Medicine, Hospital of Sondrio, Sondrio, Italy

⁶Thrombosis and Haemorrhagic Diseases Center, Humanitas Clinical and Research Center-IRCCS, Milan, Italy

⁷Department of Clinical Sciences, Division of Infection Medicine, Skåne University Hospital, Lund University, Lund, Sweden

⁸Department of ENT, Head and Neck Surgery, University Hospital of Grenoble, Grenoble, France

⁹Department of Internal Medicine, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy

¹⁰Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland

¹¹University of Zurich, Zurich, Switzerland

ABSTRACT.

Purpose: Lemierre syndrome is a life-threatening condition characterized by head/neck bacterial infection, local suppurative thrombophlebitis and septic embolic complications in a range of sites of distant organs. No prior study focused on the course and characteristics of ophthalmic complications of Lemierre syndrome.

Methods: We analysed data of 27 patients with ophthalmic complications from a large cohort of 712 cases with Lemierre syndrome reported globally between 2000 and 2017. We focused on initial manifestations, early (in-hospital) course and long-term ophthalmic deficits at the time of hospital discharge or during postdischarge follow-up. The study protocol was registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42016052572).

Results: Nine (33%) patients were women; the median age was 20 (Q1–Q3: 15–33) years. *Fusobacterium* spp. was involved in 56% of cases. The most prevalent initial manifestations were decreased vision (35%) and periocular oedema (38%), followed by impaired eye movements/nerve palsy (28%) and proptosis (28%). Venous involvement, notably cerebral vein thrombosis (70%) and ophthalmic vein thrombosis (55%), explained the symptomatology in most cases. Septic embolism (7%), orbital abscesses (2%) and carotid stenosis (14%) were also present. Ophthalmic sequelae were reported in 9 (33%) patients, often consisting of blindness or reduced visual acuity, and nerve paralysis/paresis.

Conclusion: Ophthalmic complications represent a severe manifestation of Lemierre syndrome, often reflecting an underlying cerebral vein thrombosis. Visual acuity loss and long-term severe complications are frequent. We call for an interdisciplinary approach to the management of patients with Lemierre syndrome and the routine involvement of ophthalmologists.

Key words: anticoagulation – bacterial infection – lemierre syndrome – mycotic aneurysm – ocular vein thrombosis – rare disorders

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Synopsis

Ophthalmic complications represent a severe manifestation of Lemierre syndrome, often reflecting an underlying cerebral vein thrombosis. Visual acuity loss and long-term severe complications are frequent, calling for an interdisciplinary management of patients with Lemierre syndrome.

Introduction

Lemierre syndrome is a life-threatening condition characterized by head/neck bacterial infection, local suppurative thrombophlebitis and septic embolic complications in a range of sites of distant organs, primarily the lungs. The disorder represents the most feared complications of bacterial tonsillitis and neck infections (Lemierre 1936; Sacco et al. 2019; Valerio et al., 2020a, 2020b). The bacterium most frequently involved is *Fusobacterium necrophorum*, a gram-negative anaerobe that is highly prevalent in the oropharynx of healthy subjects and can be isolated in patients with acute tonsillitis or peritonsillar abscess (Klug et al. 2011; Centor et al. 2015; Atkinson et al. 2018; Nygren & Holm 2019).

As in other thromboembolic conditions, such as infective endocarditis and

atrial fibrillation, the eyes represent a potential site of embolization. A recent study showed that up to 9% of patients with ischaemic monocular blindness had atrial fibrillation, which caused a transient or permanent occlusion of the central or branch retinal artery (Baddour et al. 2015; Zarkali et al. 2019). Data on the association between neck vein thrombosis or cerebral vein thrombosis and ophthalmic involvement are sparse, but indicates that ophthalmic complications are not uncommon (Wang et al. 2011; Yadegari et al. 2017). Lemierre syndrome may cause a wide range of ophthalmic complications and share some similarities with the aforementioned conditions. Its potential for local thromboembolic dissemination, the occurrence of both venous and arterial complications, and the presence of a strong bacterial trigger suggest that ophthalmic involvement in Lemierre syndrome may present peculiar features.

Recently, we published the largest individual patient level analysis of Lemierre syndrome cases, amounting to a total of 712 patients which gave an overview of the course of the disease in the contemporary era (2000–2017) and contributed to define the clinical and epidemiological characteristics of the syndrome (Valerio et al., 2020a, 2020b). In the present analysis, we provided a comprehensive analysis of the prevalence, characteristics and course of ophthalmic complications in patients with Lemierre syndrome.

Patients and Methods

Data collection

We previously described the procedures of data collection, assessment of outcome variables, and analysis that were implemented for this study (Sacco et al. 2019). In brief, we searched all studies reporting cases or series of cases of Lemierre syndrome published in the biomedical or 'grey' literature in 2000–2017. The authors of these reports were contacted to retrieve individual level data or missing information. The study protocol is registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42016052572).

This study was conducted as an individual level analysis of patients diagnosed with Lemierre syndrome and aimed to describe the characteristics and course of those with ophthalmic

complications or symptoms. Cases were considered eligible for inclusion if the diagnosis of Lemierre syndrome was based on the following criteria (Valerio et al., 2020a, 2020b): the primary bacterial infection affected the head/neck, local thrombotic complications or septic embolism were objectively confirmed, and any ophthalmic involvement or eye-related symptom was described.

We focused on two main triggers of ophthalmic complications or symptoms present at baseline or detected during initial hospitalization: (i) objectively diagnosed acute venous thromboembolism or/and septic embolism, (ii) supra-aortic arterial stenosis/occlusion or mycotic aneurysms. We also collected data on in-hospital death and long-term ophthalmic complications after hospital discharge. Venous thromboembolism or/and septic embolism included cerebral vein thrombosis, neck vein thrombosis, ophthalmic vein thrombosis (OVT) and other venous thrombosis localized in the head/neck region which may have been involved in ophthalmic symptoms. Involvement of supra-aortic arteries included neck artery stenosis or occlusion of the carotid arteries, vertebral arteries or intracranial arteries. Thrombosis was only considered as such if it was objectively confirmed in a radiology report.

For each patient, we noted information on demographics, baseline characteristics, site of initial infection, characteristics of initial clinical presentation, use and type of antibiotics, use and type of anticoagulation, surgical procedures and clinical/ophthalmic outcome. The complete database and variable coding list are available upon request by directly contacting the authors.

Statistical analysis

We provided categorical variables as counts and percentages with corresponding 95% confidence intervals (CI) for the outcomes of interest and continuous variables as median and interquartile range (Q1–Q3) or as mean and standard deviation, according to their distribution. In this descriptive analysis, we refrained from performing explorative analyses on potential risk factors of ophthalmic complications due to the anticipated low number of events and lack of literature data to support the choice of the predictors. Data management was done in spss, version 25.0 (SPSS Inc. Chicago,

Illinois). Data analysis was conducted with R version 3.6.1 (The R Foundation for Statistical Computing, 2019).

Results

Of 712 patients with Lemierre syndrome included in the overall cohort, we found 27 (3.8%) who presented with or were described having ophthalmic complications or related symptoms (Benhayoun et al. 2003; Figueras Nadal et al. 2003; Ahad et al. 2004; Arat et al. 2004; Bentham et al. 2004; Peng et al. 2005; Olson & Mandava 2006; Westhout 2007; Kadiravan et al. 2008; Shiva-shankar et al. 2008; van Dijk et al. 2008; Jones & Arnold 2009; Aouad et al. 2010; Bababeygy et al. 2011; Kahn 2011; Miller et al. 2012; Rehman 2012; Akiyama et al. 2013; Gutzeit et al. 2013; Stauffer 2013; Creemers-Schild 2014; Golan et al. 2014; Garibova 2015; Holm et al. 2015; Nishida et al. 2015; Ballester et al. 2016; Hama et al. 2016). Nine (33%) patients were women and the median age was 20 (Q1–Q3 15–33) years. The most frequent site of initial bacterial infection was the oropharynx (44%) or the neck/head (33%). *Fusobacterium* spp. was involved in 56% of cases. All patients had neck vein thrombosis: internal jugular vein thrombosis was present in 21 (78%) cases and cerebral vein thrombosis was diagnosed in 19 (70%). Table 1 summarizes the key demographic and baseline characteristics of the study population.

All patients received antibiotic therapy, which consisted of penicillins (41%), metronidazole (33%), clindamycin (9%), cephalosporins (56%) and carbapenems (33%) in most cases. Twenty (74%) patients underwent surgical procedures, such as abscess drainage (63%) and craniectomy or craniotomy (22%). Any-dosage anticoagulant use was recorded in the vast majority (85%) of patients.

Ophthalmic complications

The majority (63%) of complications were already present at the time of initial admission. Table 2 details the characteristics and outcome of ophthalmic complications on an individual patient level. As depicted in Table 3, the most prevalent signs and symptoms were decreased vision (35%) and periocular oedema or eye swelling (38%), followed by impaired eye movements/nerve palsy (28%) and

Table 1. Baseline characteristics of 27 patients with Lemierre syndrome and ophthalmic manifestations.

Variable	Number
Women, <i>n</i> (%)	9 (33)
Age (years), median (Q1–Q3, range)	20 (15–53; 3–65)
Initial site of infection, <i>n</i> (%)	
Oropharyngeal	12 (44)
Neck/head	9 (33)
Dental	7 (26)
Sinuses	6 (22)
Low-respiratory tract	5 (19)
Ear	3 (11)
Skin	1 (4)
Isolation of an anaerobe	20 (74)
Isolation of <i>Fusobacterium spp</i>	15 (56)
Arterial involvement (baseline)	5 (19)
Carotid arteries	4 (15)
Intracranial arteries	3 (11)
Venous thrombosis of the head-neck-arm district (baseline)	27 (100)
Jugular vein thrombosis	21 (78)
Peripheral embolism (baseline)	25 (93)
Lungs	18 (67)
Central nervous system	10 (37)
Surgical procedures	20 (74)
Abscess drainage (any)	17 (63)
Craniectomy/craniotomy/sinusoplasty	6 (22)
Tonsillar drainage	4 (15)
Epidural drainage	2 (7)
Jugular ligation	1 (4)
Anticoagulant used during hospitalization	17 (85)*

The key demographic and baseline characteristics of patients with ophthalmic complications in Lemierre syndrome, including the initial site of infection, the pathogenic organisms involved and the type of medical/surgical treatment performed.

* 7 patients had missing values.

proptosis (28%). The most frequent diagnoses explaining the ophthalmic complications were cerebral vein thrombosis (70%) and superior OVT (55%). Septic embolism (7%), orbital abscesses (2%) and carotid stenosis (14%) explained the symptoms in the remaining patients. Three patients had concomitant arterial and venous complications. Three patients (11%) had some type of intraocular bleeding, including (i) haemorrhages in the right eye fundus (off anticoagulant), (ii) vitreous haemorrhage in the right eye and preretinal bleeding in the left eye (off anticoagulant) and (iii) preretinal haemorrhage in fovea (on anticoagulant).

Two patients died during hospitalization due to sepsis and multiorgan failure. Long-term complications included blindness or reduced visual acuity in 7 (26%) patients and abnormal eye movements or cranial nerve palsies in 6 (21%) (Table 2).

Discussion

This study represents the largest analysis of ophthalmic complications of

Lemierre syndrome, a rare and potentially fatal thromboembolic complication of bacterial pharyngotonsillitis in otherwise healthy teenagers and young adults. We showed that venous complications, usually represented by neck vein thrombosis leading to cerebral vein thrombosis and OVT, dominate the clinical picture and explain ophthalmic manifestations in the vast majority of patients. Our data also indicate that long-term complications are potentially invalidating and may include reduced visual acuity, paralysis/paresis and cranial nerve palsies. Lemierre syndrome represents a severe condition with a broad spectrum of complications that go beyond early in-hospital death: the presence of ophthalmic involvement may represent a signal of cerebral vein involvement requiring rapid action.

Superior OVT may result from retrograde extension of cavernous sinus thrombosis (which, in turn, is involved via the inferior petrosal sinus from a primary thrombophlebitis of the jugular vein or the lateral sinus) or, in cases with paranasal sinusitis or odontogenic

infection as the primary focus, orbital inflammation and cellulitis (van der Poel et al. 2019). Less common mechanisms may include a systemically hypercoagulable state induced by sepsis (Valerio & Riva 2020) or haematogenous spread of bacteria from a distant focus with septic embolization (Hajar et al. 2019). Superior OVT impairs local venous drainage and leads to orbital congestion, which ultimately causes orbital manifestations including chemosis, proptosis, diplopia and pain (van der Poel et al. 2019). In this context, ocular pain is probably multifactorial. The most direct causes are local swelling and inflammation. Venous stasis can lead to increased pressure in the eye and the surrounding structures. Overall increased intracranial pressure could lead to headache that the patient may experience as retro-ocular pain. Last, orbital pain is common in sinusitis, one of the possible primary infections in Lemierre syndrome. The spectrum of clinical findings can extend to ocular signs and symptoms, including reduced visual acuity and relative afferent pupillary defect, if the optic nerve is affected by compression and an optic neuropathy is diagnosed (Lim et al. 2014). A key finding of our study is the description of cavernous sinus thrombosis in association with superior OVT, which was diagnosed in four patients and was bilateral in one case. Lateral rectus paralysis due to abducens nerve palsy is one of the most frequently observed symptoms in these patients. The presence of abducens nerve palsy is likely to be most often associated with cavernous sinus thrombosis, and more rarely inflammatory swelling of the rectus lateral muscle or orbital cellulitis. Of note, it must be recognized that no standard definition and validated diagnostic work-up of superior (septic) OVT and OV dilation are available to date: the same applies to other rare localizations of vein thrombosis, including splanchnic or ovarian vein thrombosis.

The prevalence of any cerebral vein thrombosis was remarkable (70%) in patients with ophthalmic complications of Lemierre syndrome and much higher than that (20%) described in the whole cohort of 712 patients with Lemierre syndrome (Valerio et al., 2020a,2020b). Our data suggest, therefore, that if (mild) ophthalmic manifestations are present, physicians should immediately exclude the presence of cerebral vein/

Table 2. Clinical outcomes and course

Age, sex	Anaerobe	Initial site of infection	Initial ophthalmic involvement and visual acuity	Diagnosis	Survival and long-term outcomes	References
53, M	Yes	Left internal jugular vein thrombosis	After 3 days hospitalization, right eye slightly injected. Instead of good recovery, decreased vision in the right eye	Anterior uveitis and few posterior synechiae. Big white fluffy mass in vitreous. Right endogenous endophthalmitis	Visual acuity 6/12 right eye (3 months follow-up)	Ahad et al. (2004)
55, W	Yes	Right cavernous sinus enlargement	Severe left orbital pain. Visual acuity (counting fingers, bilateral)	Bilateral proptosis with severe periocular oedema and erythema with conjunctival hyperaemia and chemosis	Bilateral blindness	Arat et al. (2004)
59, M	Yes	Abscess in the right pterygomaxillary region	Proptosis of the left eye	Thrombosis of the left ophthalmic vein with proptosis	Completely recovered	Ballester et al. (2016)
15, M	No	Anaerobic sinus infection	Left homonymous hemianopia. Right proptosis. Injection of the right sclera.	Direct posterior extension of infection to involve carotid sheath and cavernous sinus; cerebral artery territory infarction	Left homonymous hemianopia	Bentham et al. (2004)
39, M	Yes	Acute pharyngitis	Right orbital pain, bilateral eyelid swelling. Slightly impaired bilateral eye movements	Thrombosis in the left superior ophthalmic vein	Full recovery	Hama et al. (2016)
16, W	Yes	Sore throat	Right periorbital swelling. Minimal ipsilateral proptosis. Diplopia. Normal visual acuity.	Bilateral Jugular vein thrombosis	No functional limitations	Kadhiravan et al. (2008)
14, W	Yes	Left parapharyngeal abscess	Significant reduced visual acuity of light perception in both eyes	Septic emboli with dense vitreous haemorrhage and a subretinal mass in the right eye. Preretinal haemorrhage in the left eye	At the 2 month visit: Vision improved to 20/80 in the right and 20/25 in the left eye	Olson & Mandava (2006)
3, M	Yes	Bilateral otomastoiditis	Normal linear visual acuity. Left abducens nerve palsy	Left superior ophthalmic vein thrombosis secondary to left cavernous sinus thrombosis	Some improvement in the abducens nerve palsy	Bababegy et al. (2011)
22, W	Yes	Left side tonsillitis	Acute right abducens nerve paresis, partial right oculomotor nerve paresis. Reduced visual acuity in prism cover test	Right superior ophthalmic vein thrombosis secondary to bilateral cavernous sinus thrombosis, mycotic aneurism	After 3 months: discrete abducens nerve paralysis on both sides	Gutzeit et al. (2013)
32, M	No	Left face furuncle	Visual acuity left eye: 6/24. Chemosis and swelling of the left eye	Left internal jugular thrombus	No loss of vision in the left eye	Shivashankar et al. (2008)
65, M	NA	-	Right sided blindness, bilateral eye pain and eyelid oedema	Bilateral septic thrombosis of the superior ophthalmic veins	Right sided visual loss	Akiyama et al. (2013)
4, M	Yes	Right peritonsillar abscess	Oedema of his right lower lid	Multiple orbital abscesses secondary to regional abscess from the cavernous sinus	In hospital death (sepsis)	Aouad et al. (2010)
13, M	Yes	Empyema of the right frontal sinus	Periorbital headache	Left superior ophthalmic vein thrombosis	Full recovery	Benhayoun et al. (2003)
14, W	Yes	Right internal jugular vein thrombosis	Left ocular proptosis, left exophthalmos	Left superior ophthalmic vein elongation, right internal vein thrombosis, sigmoid sinus thrombosis	Discharged without any residual disability	Figueras Nadal et al. (2003)

Table 2 (Continued)

Age, sex	Anaerobe	Initial site of infection	Initial ophthalmic involvement and visual acuity	Diagnosis	Survival and long-term outcomes	References
17, W	No	NA	NA	Ophthalmic vein thrombosis	NA	Holm et al. (2015)
54, W	Yes	Left dental abscess	Right eye proptosis, reduced right visual acuity (right Snellen visual acuity 6/12)	Thrombosis in cavernous sinus, left retromandibular vein, bilateral internal jugular veins and right superior ophthalmic vein	Left middle cerebral artery infarct, homonymous hemianopia	Jones & Arnold (2009)
45, M	Yes	Sore throat	Bilateral eye swelling, pain, blurry vision, right eye visual acuity of 20/40	Bilateral superior ophthalmic vein thrombi, mycotic aneurism	In hospital death because of sepsis	Kahn (2011)
35, M	NA	Sore throat	Binocular diplopia, right eye proptosis, bilateral reduced visual acuity (20/30 right eye and 20/25 left eye)	Right transverse and sigmoid sinus thrombosis, right superior ophthalmic vein thrombosis	6 months later: 20/20 vision in both eyes	Miller et al. (2012)
54, W	Yes	Decayed tooth teeth	Pain and bilateral swelling of the orbital portion	Right cavernous sinus thrombosis, right ophthalmic vein thrombosis	NA	Nishida et al. (2015)
20, M	Yes	Sore throat, tonsillitis	Day 5 of hospitalization: Blurred vision in the right eye, preretinal haemorrhage in fovea	Left internal jugular vein thrombophlebitis	Full recovery	Peng et al. (2005)
61, W	No	Painful blister behind the right 3 rd molar	Prosis of the left eyelid	Left superior ophthalmic vein thrombosis	NA	Rehman (2012)
18, M	Yes	Retropharyngeal abscess	Progressive visual loss, left periorbital oedema, progressive bilateral eye swelling	Bilateral cavernous sinus thrombosis with potential extension into the ophthalmic veins. Narrowed right internal carotid artery	Binocular blindness	Stauffer (2013)
16, M	Yes	Right peritonsillar abscess	Prosis	Narrowing of the right internal carotid artery, right superior ophthalmic vein thrombosis	After 3 months: No neurological deficit	Westhout (2007)
20, W	Yes	Sore throat	Right proptosis, right abduccens nerve palsy	Right superior ophthalmic vein thrombosis	NA	Garibova (2015)
17, M	Yes	Pharyngitis	Left abduccens nerve palsy, diminished visual acuity of the left eye	Left internal carotid artery occlusion, subtotal right carotid artery stenosis	Within 3 months full recovery of visual acuity	van Dijk et al. (2008)
14, M	Yes	Abscess in the paranasal sinus	Left eye swelling	Thrombosis of the superior sagittal sinus and right sigmoid sinus	NA	Creemers-Schild (2014)
41, M	No	Right peritonsillar abscess	Right-sided ophthalmoplegia	Intraorbital abscess, occluded right internal jugular vein, fusiform aneurysm of the right internal carotid artery with stenosis	NA	Golan et al. (2014)

We reported individual patient level demographics and clinical characteristics of patients with ophthalmic complications of Lemierre syndrome, along with the original reference and information on the long-term course of the disease. M = man, NA = data not available or not reported, W = woman.

Table 3. Summary of clinical presentation and main diagnosis in patients with ophthalmic complications of Lemierre syndrome

Signs and symptoms	
Periocular oedema or eye swelling, <i>n</i> (%)	11 (38)
Decreased vision	10 (35)
Proptosis	8 (28)
Impaired eye movement or cranial nerve palsy	8 (28)
Pain	6 (21)
Eye injection	4 (14)
Diplopia	2 (7)
Hemianopia	2 (7)
Diagnoses	
Cerebral vein thrombosis, <i>n</i> (%)	19 (70)
Superior ophthalmic vein thrombosis	16 (55)
Complications involving the carotid arteries	5 (19)
Carotid stenosis	3 (11)
Mycotic aneurysm	3 (11)
Cavernous sinus thrombosis/enlargement	2 (7)
Vitreous haemorrhage	2 (7)
Orbital abscess	2 (7)
Septic embolism	2 (7)
In-hospital death	2 (7)
Endophthalmitis	2 (7)
Sinus infection	1 (3)
Preretinal haemorrhage	1 (3)
Anterior uveitis	1 (3)

A summary of the ocular clinical signs and symptoms in patients with Lemierre syndrome are presented together with the final cumulative diagnoses reported.

septic involvement to prevent potentially devastating early and late complications. Prior reports demonstrated that ophthalmic signs and symptoms may be the initial manifestation of cerebral vein thrombosis (Wang et al. 2011; Yadegari et al. 2017). Indeed, intracranial involvement emerged as a key prognostic factor associated with poorer prognosis in patients with Lemierre syndrome (Valerio et al., 2020a, 2020b). No specific treatment has an established role in treating and preventing further complications of (septic) cerebral vein thrombosis. The role of anticoagulant therapy in Lemierre syndrome has long been a matter of controversy. Its use is meant to prevent thrombus extension or recurrence, and is often recommended in the case of intracerebral extension, in analogy with observations in patients with lateral sinus thrombosis (Valerio & Riva 2020). However, the possibility of haemorrhagic transformation of peripheral septic lesions or the bleeding risk from sepsis-associated thrombocytopenia often deter clinicians from its use, despite no evidence of an intrinsically raised bleeding risk in Lemierre syndrome (Valerio et al., 2020a, 2020b). In patients with cerebral vein

thrombosis, the use of anticoagulant therapy appears reasonable based on current evidence (Dentali et al. 2012).

Endogenous endophthalmitis was described in two cases only. Due to the pathophysiological characteristics of Lemierre syndrome, it may be possible that the actual rate of septic emboli is higher. In case of ophthalmic artery involvement due to sepsis, endogenous endophthalmitis may occur and worsen the ocular symptoms (chemosis, Best Corrected Visual Acuity decrease): therefore, in the presence of worsening of the ocular symptoms, an endogenous endophthalmitis should be promptly ruled out. While this complication is rare, its possibility implies that the rate of ophthalmic complications in patients with Lemierre syndrome might be even higher if these patients underwent standard ophthalmologic assessment even in the absence of ophthalmic symptoms or visible ophthalmic findings like chemosis, swelling and proptosis.

Our study has limitations, including the relative small sample size, the lack of a predefined assessment of ophthalmic signs or symptoms, the high risk of reporting bias, and the lack of complete information of specific

diagnostic testing. Nonetheless, it represents the first, necessary step to highlight the importance of a correct multidisciplinary evaluation of patients with Lemierre syndrome, including distant organ and potentially silent manifestations of disease. This likely represents a group of patients with the most severe ophthalmic complications of Lemierre syndrome, suggesting that the number of those with milder manifestations could be much larger.

Despite the young age of these patients and the lack of severe comorbidities, ophthalmic complications manifested as a severe condition often characterized by visual acuity loss and substantial burden of symptoms. In-hospital death and major ophthalmic and neurologic sequelae affected approximately one-third of patients, supporting the need for an early identification and management of these potentially invalidating complications. We call for an interdisciplinary approach to the management of patients with Lemierre syndrome and the routine involvement of ophthalmologists.

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Correspondence:
Stefano Barco
Clinic of Angiology
University Hospital Zurich
Zurich
Switzerland
Email: stefano.barco@usz.ch
Luca Valerio
Center for Thrombosis and Hemostasis
University Medical Center Mainz
Langenbeckstraße 1
Building 403
Room 117
55131 Mainz
Germany
Tel: +49 6131 17 8251
Fax: +49 6131 17 8461
Email: luca.valerio@uni-mainz.de

†Equally contributed as senior authors.

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