Clinical Reasoning: Proptosis, headache, and fever in a healthy young woman

José Orquera, MD
Daniel Agustín Godoy,
MD
Réza Behrouz, DO
Alejandro Rabinstein,
MD
Mario Di Napoli, MD

Correspondence to
Dr. Behrouz:
behrouz@uthscsa.edu

SECTION 1

A 23-year-old healthy woman presented to the emergency department with a week-long history of intense, pulsatile, right-sided headache, accompanied by fever, diplopia, and right eye pain and decreased visual acuity. She reported partial relief with nonsteroidal anti-inflammatory drugs.

On admission, she was alert and cooperative. Body temperature was 37.7°C; other vitals were normal. She had right eye proptosis, bipalpebral edema, ocular congestion, and chemosis, causing global restriction in ocular motility. Pupillary reactions and fundi were normal. No afferent pupillary defect was noted. Her neurologic examination was otherwise normal. In the outer end of the right eyebrow, an indurated, erythematous

pustule was noted. The remainder of the physical examination was normal. Laboratory results were remarkable for leukocytosis with neutrophilia (leukocyte count 16,800/mm³, 8% immature forms) and elevated C-reactive protein (16.8 mg/L). Tests for pregnancy and HIV were negative. Chest and paranasal radiographs were normal. Acetaminophen and tobramycin ophthalmic drops were begun, and because the patient was allergic to penicillin, IV ceftriaxone 2 g/d plus clindamycin 1.8 g/d were initiated.

Questions for consideration:

1. What are the diagnoses to consider?
2. What studies need to be performed to confirm the diagnosis?

[GO TO SECTION 2](#)

From the Intensive Care Unit (J.O., D.A.G.), Hospital San Juan Bautista, Catamarca, Argentina; Department of Neurology (R.B.), School of Medicine, University of Texas Health Science Center, San Antonio; Neuroscience Critical Care Unit (A.R.), Mayo Clinic College of Medicine, Rochester, MN; Neurological Service (M.D.N.), San Camillo de' Lellis General Hospital, Rieti; and Neurological Section (M.D.N.), SMDN—Center for Cardiovascular Medicine and Cerebrovascular Disease Prevention, Sulmona, L'Aquila, Italy.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

According to the clinical picture described, the diagnoses to consider are as follows.

Orbital and periorbital cellulitis is an infection of the fatty tissue surrounding the eye.^{1,2} Periorbital cellulitis, also called “preseptal cellulitis,” is located anterior to the orbital septum, a fibrous tissue that acts as a barrier to the spreading of infection.^{1,2} Periorbital cellulitis typically occurs as a complication of cutaneous infections adjacent to the eye.^{1,2} It is clinically characterized by periorbital erythema and edema. Systemic manifestations are very rare.^{1,2} Orbital cellulitis, however, occurs as a complication of sinusitis or gingivodental, eye, and tear-duct infections. Clinical manifestations include eyelid edema, ocular pain, proptosis, ocular dysmotility, diplopia, and decreased visual acuity.^{1,2} Fever and systemic signs and symptoms are quite common. In both conditions, the most common causal agents are *Staphylococcus aureus* and *Streptococcus pyogenes*.^{1,2}

Cavernous sinus thrombophlebitis is an infection of the cavernous sinus secondary to dissemination of infection from contiguous or distant sites.^{3,4} Cavernous sinus thrombosis can also occur in the absence of infection, for instance as a postoperative complication or in patients with hypercoagulable states.^{3,4} To more elaborately define this condition, familiarity with the complex anatomy of the cavernous sinus is crucial. The cavernous sinuses are located on each side of sella turcica, extending from the superior orbital fissure to the petrous apex of the temporal bone.^{3,4} The paired structures are connected by the intercavernous sinus that expands over the pituitary gland. Cranial nerves III, IV, V1, and V2 run within the lateral wall of the cavernous sinus, while cranial nerve VI and the internal carotid artery pass directly through.^{3,4} Blood from each ophthalmic vein, superficial middle cerebral vein, inferior cerebral veins, sphenoparietal veins, and sphenoid sinuses all drain into the ipsilateral cavernous sinus.^{3,4}

Cavernous sinus thrombosis is typically characterized by headache, meningismus, chemosis, periorbital edema, and proptosis.^{3,4} Fever and systemic symptoms are often present. Papilledema and/or dilated retinal veins can be visualized via funduscopy.^{3,4} Hyper- or hypoesthesia of areas innervated by the trigeminal nerve is present in 25% of cases.^{3,4} Restriction in eye movements often occurs as a late complication, mostly because of cranial nerve VI dysfunction.^{3,4} Decreased

visual acuity is unusual because the course of the optic nerve lies outside the cavernous sinus. *S aureus* and *S pyogenes* are also the most common pathogens involved in infectious cavernous sinus thrombosis.^{3,4}

Carotid-cavernous fistula is an abnormal communication between the internal carotid artery and the cavernous sinus.⁵ It can occur spontaneously or subsequent to trauma, intracranial surgery, pregnancy, chronic sinusitis, or arterial hypertension. There are 2 main types: high-flow and low-flow.⁵ Proptosis, chemosis, episcleral congestion, ocular throbbing, decreased visual acuity, and increased intraocular pressure comprise the characteristics of this condition.⁵ The patient, however, did not describe pulsatility as part of her ocular symptoms and we also could not delineate this pattern objectively.

Dysthyroid ophthalmopathy is an autoimmune ocular disease caused by hyperthyroidism, hypothyroidism, or Hashimoto thyroiditis.⁶ Symptoms include conjunctival inflammation, exposure keratitis, eyelid retraction, proptosis, impaired ocular motility, decreased visual acuity, impaired color vision, increased intraocular pressure, and optic neuropathy.⁶ However, the patient's presentation suggested an acute inflammatory process, such as an infection. Moreover, she had no history of and never presented with constitutional symptoms of thyroid disease.

Neuroimaging is of tremendous importance in the diagnosis of these conditions. High-resolution CT scan and MRI have comparable sensitivity and specificity for the diagnosis of most of these conditions, but MRI can more accurately delineate cavernous sinus thrombosis by detecting the presence of thrombus and flow obstruction within the sinus. Conventional or CT angiography is also helpful in identifying flow abnormalities. Finally, it is important to assess thyroid function and thyroid antibodies.⁶

In the case described above, high-resolution CT scan with contrast showed evidence of retro-orbital cellulitis without a space-occupying lesion. CT angiography was normal in both arterial and venous phases. Thyroid hormones and ultrasound were normal and anti-thyroid antibodies were negative.

Questions for consideration:

1. What are the neurologic complications of retro-orbital cellulitis?
2. What studies need to be performed during follow-up?

GO TO SECTION 3

SECTION 3

Three days after admission, the patient's neurologic status grossly deteriorated. She was found obtunded and was transferred to the intensive care unit and placed on mechanical ventilation. On evaluation, she had a Glasgow Coma Scale score of 8 (eyes = 1, verbal = 1, motor = 6) and her vital signs were as follows: blood pressure, 127/68 mm Hg; temperature, 38.7°C; respiratory rate, 22 breaths per minute; and heart rate, 117 beats per minute. Her pupils were equal, medium-sized, and reactive to light. No meningeal signs were noted. Head CT scan was unchanged and her EEG showed no electrographic seizures. On lumbar puncture, opening pressure was 18 cm H₂O. CSF analysis showed 1,355 leukocytes/mm³, glucose of 22 mg/dL, and protein level at 160 mg/dL. Antibiotics were changed to IV vancomycin and meropenem, and dexamethasone was started. CSF culture was positive for *S aureus*. Blood cultures were negative and transesophageal echocardiography was normal. On the 10th day of admission, sedation was stopped and the patient was weaned off mechanical ventilation. After extubation, she was found alert, with no neurologic deficit. She was transferred to the general

ward. Follow-up head CT showed mild hydrocephalus with no evidence of blood.

Five days later, she suddenly developed severe headache followed by generalized tonic-clonic seizures, rapidly progressing to coma and extensor posturing. Emergent head CT scan showed diffuse subarachnoid hemorrhage with central herniation and hydrocephalus (figure, B and C). Her CT angiography showed a 7-mm aneurysm involving the middle third of basilar artery and fusiform dilation of the proximal basilar artery (figure, D). A repeat transesophageal echocardiography showed no valvular abnormalities or vegetations. She passed away 3 days later of herniation and brainstem compression; no autopsy was done.

DISCUSSION Approximately 2% of orbital cellulitis cases are complicated by meningoencephalitis.^{1,2} *S aureus* is the predominant organism in these cases.^{1,2} Subarachnoid hemorrhage as a complication of meningoencephalitis is rare and associated with the development of infectious or mycotic aneurysms.⁷⁻⁹ These aneurysms are formed as a result of bacterial colonization of vasa vasorum and formation of

Figure Serial brain parenchymal and arterial imaging during the patient's hospitalization

(A) Initial 3-dimensional CT angiogram of the brain showing a normal vertebrobasilar system. (B and C) Head CT on admission day 15 showing diffuse subarachnoid hemorrhage and hydrocephalus. (D) CT angiography of the brain on admission day 15 showing a 7-mm aneurysm involving the middle third of the basilar artery (arrow 1) and fusiform dilation of the basilar artery origin (arrow 2). (E) Three-dimensional CT angiogram showing the basilar artery aneurysm (arrow 3) and the proximal dolichoectasia (arrow 4).

Table	Proposed criteria for diagnosis of IAs
Mandatory criterion	
Aneurysm demonstrated by imaging	
Supporting criteria	
Predisposing infection	
1. Infective endocarditis	
2. Meningitis	
3. Cavernous sinus thrombophlebitis	
4. Orbital cellulitis	
Angiographic features	
1. Multiplicity	
2. Distal location	
3. Fusiform shape	
4. Change in size of aneurysm/appearance of new aneurysm on follow-up angiogram	
Other features	
1. Younger age, <45 y	
2. History of recent lumbar puncture	
3. Fever at presentation	
4. ICH or SAH in CT/MRI	
Clinically definite diagnosis of IA	
Mandatory criteria + 3 supportive criteria	
Clinically probable IA	
Mandatory criteria + 2 supportive criteria	
Clinically possible IA	
Mandatory criteria + 1 supporting criteria	

Abbreviations: IA = infectious aneurysm; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage. Adapted with permission, courtesy of the BMJ Publishing Group Ltd.¹⁰

micro-abscesses within the arterial wall.⁷⁻⁹ Preexisting aneurysms can become secondarily infected, but aneurysmal formation due to degeneration of the arterial wall can also be a result of infection caused by bacteremia or septic emboli.^{7,8} The term “mycotic” aneurysm was coined by Osler in 1885 to describe the aneurysms associated with bacterial endocarditis.^{7,8} These were noted to have the appearance of “fresh fungal vegetations.”^{7,8} Therefore, “mycotic” does not imply a fungal etiology, but describes the shape.

Infectious aneurysms are usually asymptomatic, but their rupture can lead to life-threatening subarachnoid hemorrhage or intraparenchymal hemorrhage.⁷⁻⁹ They occur in the context of intravascular infection, including endocarditis. Intravascular infection with *S aureus* is most commonly associated with infectious aneurysms.^{7,8} The infectious particles reach the target by hematogenous (intravascular) dissemination, contiguous (extravascular) extension, or both.⁷⁻⁹ In our case, an aneurysm developed from

contiguous extension of meningitis. Because these aneurysms can be very small and located in distal branches, the sensitivity of noninvasive angiography (CT or magnetic resonance angiography) is lower.^{7,8} Catheter cerebral angiography can detect these aneurysms with high sensitivity.^{7,8}

Infectious aneurysms have peculiar characteristics, often being multiple, fusiform, and located distal to the circle of Willis.^{7,8} The proposed diagnostic criteria are listed in the table; our patient met 8 of these criteria.¹⁰ Infectious basilar aneurysms are very uncommon. In a recent literature review of 287 cases from 27 clinical series, the total number of basilar aneurysms was 8.^{7,8} The true natural history of infectious aneurysms is unknown.^{7,8} Although many cases remain asymptomatic, the majority of persons with symptomatic aneurysms present with symptoms related to rupture of the aneurysm and to its etiology.^{7,8} The developing time for an infectious aneurysm is also uncertain. While not conclusive, some literature have described the development of secondary mycotic aneurysms in a period of 3 to 4 weeks or more (subacute), while infectious aneurysms as a complication of meningoencephalitis may have a more accelerated development (acute).^{7,8}

There is no standard treatment for infectious aneurysms other than antibiotics. Surgical clipping and endovascular embolization are therapeutic options in case of rupture or if the size of the aneurysm poses a high risk of rupture. In these situations, the ideal treatment needs to be ascertained on a case-by-case basis.⁷⁻⁹

AUTHOR CONTRIBUTIONS

José Orquera, MD: drafting of the manuscript, literature search. Daniel Agustín Godoy, MD: supervising the project, drafting of the manuscript, literature search. Réza Behrouz, DO: manuscript editing for appropriate grammar and syntax, editing of the manuscript for appropriate intellectual content. Alejandro Rabinstein, MD: editing of the manuscript for appropriate intellectual content. Mario Di Napoli, MD: editing of the manuscript for appropriate intellectual content.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

- Howe L, Jones NS. Guidelines for the management of periorbital cellulitis/abscess. *Clin Otolaryngol* 2004;29:725-728.
- Durand ML. Periocular infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Elsevier Churchill Livingstone; 2014:1432-1438.
- Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. *Lancet Neurol* 2007;6:162-170.

4. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005;352:1791–1798.
5. Keltner J, Satterfield D, Dublin A, Lee B. Dural and carotid cavernous fistulas: diagnosis, management and complications. *Ophthalmology* 1987;94:1585–1599.
6. Bahn R. Graves ophthalmopathy. *N Engl J Med* 2010;362:726–738.
7. Kanno S, Thomas SV. Intracranial microbial aneurysm (infectious aneurysm): current options for diagnosis and management. *Neurocrit Care* 2009;11:120–129.
8. Ducruet AF, Hickman ZL, Zacharia BE, et al. Intracranial infectious aneurysms: a comprehensive review. *Neurosurg Rev* 2010;33:37–46.
9. Ramos-Estebanez C, Yavagal D. Meningitis complicated by mycotic aneurysms. *Oxf Med Case Rep* 2014;2014:40–42.
10. Kanno S, Thomas SV, Nair S, Sarma PS. Proposed diagnostic criteria for intracranial infectious aneurysms. *J Neurol Neurosurg Psychiatry* 2008;79:943–946.

Neurology®

Clinical Reasoning: Proptosis, headache, and fever in a healthy young woman

José Orquera, Daniel Agustín Godoy, Réza Behrouz, et al.

Neurology 2016;86:e168-e172

DOI 10.1212/WNL.0000000000002591

This information is current as of April 18, 2016

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/86/16/e168.full
References	This article cites 9 articles, 1 of which you can access for free at: http://n.neurology.org/content/86/16/e168.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Cerebrovascular disease/Stroke http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke All Infections http://n.neurology.org/cgi/collection/all_infections Bacterial infections http://n.neurology.org/cgi/collection/bacterial_infections Subarachnoid hemorrhage http://n.neurology.org/cgi/collection/subarachnoid_hemorrhage
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.