"What is wrong with my eye?"

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A 45-year-old African Canadian woman presented to the ED of the Saint John Regional Hospital complaining of subacute onset of severe bifrontal headache and the sensation of exophthalmos. Less then 24 hours later, she developed binocular diplopia. The right eye subsequently became swollen shut. She has had two similar presentations in the past, in 2003 and 2006.

Medical history

The patient has a history of pancreatitis, Type 2 diabetes, hypertension, colonic polyps, osteopenia and dental caries. Surgically, she has undergone appendectomy, cholecystectomy, tubal ligation and endoscopic retrograde cholangiopancreatography. She smokes 25 packs per year. She also has a history of pituitary apoplexy. The previous two presentations were similar to the current one and were diagnosed as cavernous sinus thrombosis, although magnetic resonance venogram failed to reveal evidence of a thrombosis. She is prescribed several medications to treat the maladies outlined above.

Physical examination

- Weight: 66.8 kg
- Height: 1.68 m
- BMI: 23.7 kg/m^2
- BP: 141 mmHg systolic, 89 mmHg diastolic
- Heart rate: 103 bpm
- Respiratory rate: 20 breaths per minute
- O_2 saturation: 99% on room air

Neurological examination revealed a right inferolateral ophthalmoplegia, indicative of a third nerve palsy. The patient also had a core ectopic non-reactive right pupil, right-sided ptosis and anisocoria (with the right pupil 2 mm larger in diameter compared to the left). Her left eye was normal on examination. The remainder of the neurological examination was non-contributory.

Clinical investigations

- Complete blood count:
  - Hemoglobin: low
  - White blood count: high
  - Platelets: high
- Electrolytes: normal
- Magnesium: normal
- Calcium: normal
- Random glucose: normal
- Hemoglobin A1C: normal
- Liver function:
  - Albumin, aspartate aminotransferase and alkaline phosphatase: all normal
  - Alanine aminotransferase and γ-glutamyl transferase: both high
- Renal function:
  - Blood urea nitrogen and creatinine: normal
- Prolactin: normal
- Lactate dehydrogenase: high
- C-reactive protein: normal
- Erythrocyte sedimentation rate: normal
- Haptoglobin: normal
- D-dimer: normal

- Fibrinogen: normal
- Parathyroid: normal
- INR: normal
- Activated partial thromboplastin time: normal
- Complement (C3 and C4): normal
- Antibody screen
  - Antinuclear cytoplasmic antibody: negative
  - Antinuclear antibody: negative
  - Anticardiolipin antibodies (IgG and IgM): negative
- Neuroimaging
  - MRI revealed a slightly enlarged right cavernous sinus lesion (Figure 1), estimated size about 2.1 cm by 1.5 cm when compared to prior imaging studies. The lesion extended medially into the sella, but did not involve the pituitary. The lesion also extended anteriorly and involved the right orbital apex (Figure 2). The intracavernous portion of the right carotid artery was encased by the lesion but remained patent and normal in caliber. The left cavernous sinus was unremarkable. Venogram showed no substantial venous flow through the right cavernous sinus. There was no superior ophthalmic venous distention. No other intracranial pathology was evident.
  - Plain axial CT depicted periorbital edema and exophthalmos of the right ocular globe (Figure 3)

What is your diagnosis?

a. Intracranial tumour
b. Tolosa-Hunt syndrome
c. Contiguous sinusitis
d. Trauma

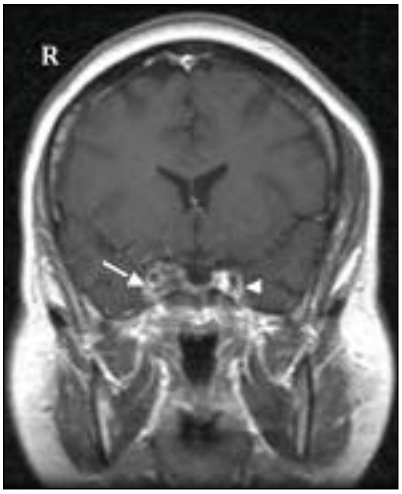

Figure 1. Coronal post-gadolinium T1-weighted MRI done several days after admission to hospital highlighting an inflammatory lesion in the right cavernous sinus (arrow), which encompasses the right carotid artery. The lumen of the right carotid artery is normal relative to the left. Note that the right lateral dural reflection of the cavernous sinus is convex, while that of the left cavernous sinus is concave (arrowhead).

Answer: Tolosa-Hunt syndrome (THS)

About THS

THS is quite rare, with an estimated annual incidence of one case per million. The clinical features of THS were described first by Tolosa and its treatment described a short time later by Hunt > 50 years ago. THS typically presents as a painful, unilateral ophthalmoplegia with diplopia secondary to paralysis of the third, fourth and/or sixth cranial nerves. Approximately 85% of reported cases affect primarily the third cranial nerve. Patients may also present with ptosis and anisocoria. With the exception of nausea and vomiting (which are likely secondary to pain), there appears to be no systemic involvement. The

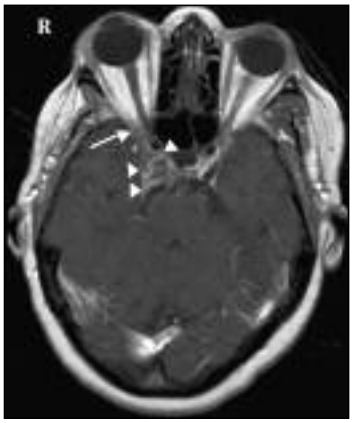

Figure 2. Axial post-gadolinium T1-weighted MRI done several days after admission to hospital highlighting an inflammatory lesion in the right cavernous sinus (arrowheads), which extends anteriorly and involves the right orbital apex (arrow).

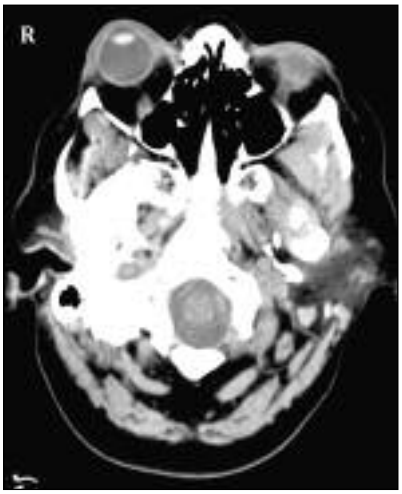

Figure 3. Plain axial CT done at time of admission to hospital depicting periorbital edema and exophthalmos of the right ocular globe. Note that the rostral pole of the right globe extends at least as anterior as that of the nasal tip.

etiology is still unknown; however, the pathophysiology is characterized by granulomatous inflammation of the cavernous sinus. Less commonly, the inflammatory process may affect the superior orbital fissure or the orbit itself. Symptom presentation is secondary to this inflammatory process.

Patients can present at any age, with no gender bias. Typical presentation sees patients developing a gnawing- or boring-type pain behind the eye several days to two weeks preceding onset of ophthalmoplegia. Importantly, most patients (> 75%) who present with these symptoms will have some other underlying pathology, with tumours being the most common (30% of cases). Thus, a full diagnostic work-up is essential.

Diagnosis

Diagnosis is largely clinical, augmented by laboratory and neuroimaging studies as well as the patient's response to glucocorticoid treatment. The International Headache Society recommends the following diagnostic criteria:

1. One or more episodes of unilateral orbital pain persisting for weeks if untreated
2. Paresis of one or more of the third, fourth and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy
3. Paresis coincides with the onset of pain or follows it within two weeks
4. Pain and paresis resolve within 72 hours when treated adequately with corticosteroids

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5. Other causes have been excluded by appropriate investigations

The syndrome typically presents as a painful, unilateral ophthalmoplegia with diplopia secondary to paralysis of the third, fourth and/or sixth cranial nerves.

Treatment

Left untreated, the natural history of THS is a relapsing and remitting one, with illness-free intervals anywhere from months to years. Administration of glucocorticoids serves both a diagnostic and therapeutic purpose. Patients often experience a resolution of the orbital pain in a matter of days. Resolution of the ophthalmoplegia and associated symptoms typically occurs over two to eight weeks, independent of glucocorticoid treatment. While no guidelines for treatment exist, a common glucocorticoid regimen employed is as follows:

1. prednisone 80 mg to 100 mg q.d. for three days and if pain resolves,
2. taper to 60 mg q.d., then 40 mg, then 20 mg, then 10 mg every two weeks, then discontinue treatment.

Again, given the rarity of the condition and the seriousness of missing another etiology, complete work-up and close follow-up is important. Recurrences are common, occurring in about 50% of patients. There is no evidence that glucocorticoid treatment alters this prognosis. With recurrence and in the absence of other pathology, reinstitution of glucocorticoid treatment is warranted. Dx

Resources
1. UpToDate: www.uptodate.com. (Shindler KP: Tolosa-Hunt Syndrome).
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