Third nerve palsies associated with headache can have a number of etiologies.

**CLINICAL HISTORY**

A 48-year-old woman presented with a 5-day history of right, retroorbital, dull aching or stabbing and throbbing pain occasionally felt in the right side of the nose. The headache started out mild and became severe over the first day. She was seen in an emergency department 3 days after headache onset. A computed tomography (CT) scan of the brain was negative. She was prescribed hydrocodone, which only dulled the pain. The day prior to consultation, she developed horizontal and vertical diplopia. On the morning of the visit, she noted drooping of her right eyelid. There was a past medical history of bronchial asthma and gastroesophageal reflux, but no history of hypertension, diabetes, ischemic heart or cerebrovascular disease. The blood pressure was 130/90 mm Hg. Neurologic examination was normal except for a pupil-sparing, partial, right third nerve palsy. The pupils were 3 mm, equal, and reactive to light. A magnetic resonance imaging (MRI) scan of the brain with intracranial magnetic resonance angiography (MRA) was normal. An erythrocyte sedimentation rate (ESR) was 10 mm/h. A lipid profile and glycosylated hemoglobin level were normal.

On follow-up 1 week later, she reported that she had not been able to open her right eye for several days and complained of the same persistent headache, rated in intensity as 7 to 8/10. Hydrocodone was of minimal benefit. The pain was worse with looking up and could awaken her from sleep. Examination revealed a pupil-sparing, complete, right third nerve palsy.

**Questions.**—What is the cause of the third nerve palsy? Is further testing such as a cerebral arteriogram, lumbar puncture, or additional blood work indicated? What are the features of headache associated with ischemic third nerve palsies? What medications might be helpful for the headache? What is her prognosis for recovery of third nerve function?

**EXPERT COMMENTARY**

This 48-year-old woman had the relatively sudden onset of a painful, pupil-sparing, third nerve palsy. Although ischemic (hypertensive, diabetic) third nerve palsies are typically painful and are usually pupillary sparing, this individual had no such risk factors. There was no history of trauma. Therefore, other diagnoses such as Tolosa-Hunt syndrome, posterior communicating aneurysm, vasculitis, and ophthalmoplegic migraine must be considered.

Third nerve palsies caused by subarachnoid lesions, such as posterior communicating artery aneurysms, may be extremely painful. Even so, patients with aneurysmal third nerve palsies almost always exhibit pupillary involvement within 1 week of onset, and this did not occur in the case presented here. Given this, and particularly since the MR angiogram

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was negative, I would not proceed to selective cerebral arteriography.

Third nerve palsies related to processes in the cavernous sinus or superior orbital fissure also may be painful, but lesions in these areas are characterized by co-involvement of fourth, fifth, and sixth nerves, as well as a Horner syndrome. Nonspecific inflammation within the cavernous sinus causing painful oculomotor palsies is often termed Tolosa-Hunt syndrome, but this patient exhibited no other signs of intracavernous disease. Carotid cavernous fistulas also may present with painful third nerve palsy, but this patient had no antecedent history of ocular trauma, no pulsating exophthalmos, and no MRI/MRA evidence of such pathology. Ischemic third nerve palsies associated with hypertension or diabetes are often preceded by orbital pain. Characterized by pupillary sparing, such palsies may be due to infarction of the nerve in its intracavernous or subarachnoid portions or within the mesencephalon. Most patients with ischemic third nerve palsies recover spontaneously within 8 to 12 weeks. The pain typically lasts only a few days and may respond to acetaminophen or ibuprofen; pain suppression with tricyclic antidepressants or other medications sometimes is required.

Ophthalmoplegic migraine also may cause painful third nerve palsy, lasting for days or weeks and then spontaneously resolving. The first episode of ophthalmoplegic migraine almost always occurs before aged 10, however, and this patient provided no such history.

Nuclear and fascicular third nerve palsies are typically painless and accompanied by other neurologic signs or symptoms. For instance, lesions of the midbrain tegmentum can affect the oculomotor nerve fascicles as they travel ventrally, often with “crossed” neurologic signs. A lesion of the cerebral peduncle results in ipsilateral third nerve palsy and contralateral hemiparesis (Weber syndrome). The usual cause of a nuclear or fascicular oculomotor palsy is infarction in the territory of a mesencephalic paramedian penetrating vessel arising from the proximal posterior cerebral artery, but other etiologies include metastatic tumors and abscesses.

In this patient, I would perform a lumbar puncture with cytology to exclude infectious or carcinomatous meningitis. I also would screen for vasculitis with an antinuclear antibody titer (ANA), an ESR, and a rheumatoid factor (RF). I would recheck the blood pressure to make sure there was no hypertension. If these were negative, I would prescribe a course of oral steroids (starting at 60 to 80 mg per day) for a presumptive diagnosis of Tolosa-Hunt syndrome.

Without a clear diagnosis, her prognosis for resolution of the third nerve palsy is uncertain, but I suspect she will improve.

**FOLLOW-UP**

The patient underwent extensive additional diagnostic testing. An anti-acetylcholine receptor antibody, ANA titer, RF, and human immunodeficiency virus (HIV)-1 antibody screen were negative. A lumbar puncture produced an opening pressure of 19.0 cm of H$_2$O. Cerebrospinal fluid examination demonstrated 2 white blood cells, 0 red blood cells, a glucose of 50 mg/dL, and protein of 59 mg/dL. Cryptococcal antigen and cytology were negative. Because of the mild protein elevation, a serum protein electrophoresis and thyroid stimulating hormone level were obtained and were normal. An MRI scan of the skull base with and without contrast showed no lesions or abnormal enhancement in the region of the cavernous sinus or the orbital apex.

A cerebral arteriogram revealed fusiform dilation of the right internal carotid artery near the take-off of the posterior communicating artery and similar fusiform dilation of the left posterior cerebral artery just after its take-off from the basilar apex. A meningeal biopsy was negative. The cause and clinical significance of the arteriographic findings were considered uncertain, but etiologies were felt to include residual from prior arterial dissections, isolated central nervous system angiitis (unlikely given the negative meningeal biopsy), and congenital dolichotesia. The films were reviewed by three neuroradiologists, a neurologist and neurosurgeon both subspecializing in cerebrovascular disease, and a neuroophthalmologist.

She was empirically placed on prednisone 60 mg daily for a few days and then 40 mg daily for treatment of possible Tolosa-Hunt syndrome. Two weeks later, there was no improvement in the complete ptosis or oculomotor palsy. In addition, for the first
time the right pupil was noted to be 0.5 mm larger than the left but reactive. The right retroorbital pain was still present on a daily intermittent basis and was relieved with gabapentin 300 mg three times a day as needed or tramadol 50 mg every 4 hours as needed. Following the negative meningeal biopsy, she was tapered off prednisone. Total duration of prednisone therapy was 6 weeks.

The ocular pain ceased 7 weeks after onset. Blood pressure remained normal. Five weeks following onset, there was mild improvement in the ptosis and ophthalmoparesis. Nine weeks following onset, the ptosis and extraocular muscle paresis had resolved. The right pupil remained slightly larger than the left but reactive. She was placed on clopidogrel bisulfate 75 mg and aspirin 81 mg daily. A repeat cerebral arteriogram after 6 months is anticipated.

**SUGGESTED READING**