Introduction

This article includes discussion of recurrent painful ophthalmoplegic neuropathy, ophthalmoplegic migraine, and RPON. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Recurrent painful ophthalmoplegic neuropathy, formerly termed “ophthalmoplegic migraine,” is a fascinating and controversial entity. The International Classification of Headache Disorders (ICHD-3 beta+) no longer considers the disorder a type of migraine but has reclassified it as a cranial neuralgia. Although many cases are typical of a cranial neuralgia, with enhancement of the involved cranial nerve on MRI and improvement using corticosteroids, other cases are more suggestive of a migraine variant. The third nerve is the nerve most frequently involved, and most cases appear in childhood or early adulthood. The episodes of ophthalmoplegia appear spontaneously and then resolve. As the etiology for recurrent painful ophthalmoplegic neuropathy is likely multifactorial and remains uncertain, the condition may more appropriately be considered a syndrome rather than a distinct diagnosis.

Key points

- The International Classification of Headache Disorders version 3-beta classifies recurrent painful ophthalmoplegic neuropathy as a cranial neuralgia.
- Although a clinical diagnosis, recurrent painful ophthalmoplegic neuropathy may show enhancement of the involved cranial nerve on post-gadolinium magnetic resonance imaging.
- The third cranial nerve is the most frequently involved nerve in recurrent painful ophthalmoplegic neuropathy.
- Most of the cases start in childhood or early adulthood.
- Episodes of recurrent painful ophthalmoplegic neuropathy appear spontaneously and then resolve without treatment.
- Ocular motor nerve schwannomas may produce identical symptoms and resolve spontaneously.
- The etiology for recurrent painful ophthalmoplegic neuropathy is controversial and likely multifactorial, and although a number of treatments have been proposed (eg, steroids, anti-migraine agents), none have proven to be a consistently effective therapy.

Historical note and terminology

Recurrent ocular motor palsies associated with a headache have been referred to as ophthalmoplegic migraine. The oculomotor (third) nerve is the one most commonly affected, but troclear (fourth) or abducens (sixth) nerve palsies may occur. The original 1860 report was by Gubler (Gubler 1860; Charcot 1890), but the term "ophthalmoplegic migraine" was first used by Charcot in 1890. Gubler's patient subsequently died, and autopsy showed a fibrous mass in which the third nerve was embedded. The patient had no history of migraine, but had been afflicted with syphilis 10 years earlier. Gowers believed that diplopia was a rare symptom of migraine, and Liveing only briefly alluded to diplopia in his monograph (Liveing 1873; Gowers 1888). Prior to Charcot's use of the expression "ophthalmoplegic migraine," other synonymous terms included "recurring ocular palsy," "periodic oculomotor paresis," and "recurring third nerve palsy." The advent of newer neuroimaging studies (eg, CT, MRI, and angiography) has made the diagnosis more secure, and the term "ophthalmoplegic migraine" has been replaced by "recurring painful ophthalmoplegic neuropathy," a definable, albeit rare, clinical condition.
Clinical manifestations

Presentation and course

The terms “ophthalmic migraine,” or “ocular migraine,” which may be erroneously used to describe migraine with visual aura or isolated visual aura without headache, should not be confused with “ophthalmoplegic migraine” or recurrent painful ophthalmoplegic neuropathy. However, adding to the confusion in terminology, the term “ophthalmoplegic migraine” is still pervasive, commonly used colloquially, and was applied to this condition until recently. Ophthalmoplegic migraine will be used in this chapter when referring to citations up to 2002, when Carlow described the MRI findings and questioned the migrainous etiology of the syndrome (Carlow 2002), as these older reports may represent a more heterogeneous group of patients.

The patient with recurrent painful ophthalmoplegic neuropathy typically presents with an otherwise usual, but particularly long-lived and severe headache, followed by a third or, much more rarely, sixth (De Renzi and Nichelli 1977; Lee et al 2002; Verhagen et al 2003; Celebisoy et al 2005; Manzouri et al 2007; Vasconcelos et al 2008) or fourth (Davidoff 1995; Huang et al 2017) nerve palsy. Although it may have its onset at any age, including adulthood (Mucchiut et al 2006), recurrent painful ophthalmoplegic neuropathy occurs most frequently in infants and children under 12 years of age (Weiss and Phillips 2004; Peck 2006). It may occur as a single event or, more commonly, as recurrent episodes of ophthalmoplegia. The headache is typically unilateral, severe, and ipsilateral to the side of the ophthalmoplegia. It is described as migrainous in 68% of cases (Gelfand et al 2012). The pain may precede the ophthalmoplegia by several days and is often in the recovery phase before the ophthalmoplegia ensues. Although the headache may alternate sides, bilateral, simultaneous ophthalmoplegia is exceedingly rare (Hutchinson and Donaldson 1989). In infants, the headache phase may be mistaken for “colic” or “fussiness” (Woody and Blaw 1986; Elser and Woody 1990), and only after the child grows older and is able to describe the symptoms is it apparent that this represents recurrent painful ophthalmoplegic neuropathy. The episodes, which tend to be recurrent and usually improve in the later teenage years, may occur as frequently as weekly (Cruciger and Mazow 1978) or much less frequently. Adult patients may also suffer from ophthalmoplegic migraine. The ophthalmoplegia is usually complete, but may be partial (superior or inferior branch) third nerve paresis (Katz and Rimmer 1989; Chabriat et al 1990; Hansen et al 1990). Persistent residual mydriasis has been reported (Sobreira et al 2013). Pupil involvement (mydriasis) is the rule, but on rare occasions the pupil is not involved (Vijayan 1980). Isolated recurrent ptosis has also been proposed as a form of ophthalmoplegic migraine in childhood (Stidham and Butler 2000).

Although the International Headache Society has considered ophthalmoplegic migraine a cranial neuralgia since 2004, some controversy remains about the origin and classification of the disorder (Crevits 2006; Giraud et al 2007). In the revised International Classification of Headache Disorders (ICHD-3 beta), recurrent painful ophthalmoplegic neuropathy (ophthalmoplegic migraine) is part of category 13, painful cranial neuralgias and other facial pains. The criteria are as follows (Headache Classification Committee of the International Headache Society 2013):

Recurrent Painful Ophthalmoplegic Neuropathy (13.9). Repeated attacks of paresis of one or more ocular cranial nerves (commonly the third) with ipsilateral headache.

Diagnostic criteria.

(A) At least 2 attacks fulfilling criterion B
(B) Unilateral headache accompanied by ipsilateral paresis of one, two, or all three ocular motor nerves.
(C) Orbital, parasellar, or posterior fossa lesion has been excluded by appropriate investigations.
(D) Not better accounted for by another ICHD-3 diagnosis.

Comment. The old and inappropriate term “ophthalmoplegic migraine” was rejected because this syndrome is not migrainous but rather a recurrent painful neuropathy. Data suggest that headache can develop up to 14 days prior to ocular motor paresis. Gadolinium enhancement or nerve thickening can be demonstrated using MRI. Treatment with corticosteroids is beneficial in some patients.

Some researchers also believe that a form of recurrent painful ophthalmoplegic neuropathy exists that consists simply
of isolated pupillary dilation associated with headache (Bailey et al 1984; Choi et al 2007); however, we, among others, consider benign episodic pupillary mydriasis to be separate from recurrent painful ophthalmoplegic neuropathy. In these cases, the pupil is large and reacts little, if at all, to light (Leone et al 1994; Jacobson 1995). This so-called "tadpole pupil" is broadly associated with headache, but it appears to be an abnormality of sector sympathetic innervation in some cases and possible parasympathetic tonic pupil dilation caused by sphincter paralysis in other cases (Thompson et al 1983). One should be careful to exclude episodes of unilateral glaucoma with pupillary block when considering the diagnosis of severe, unilateral headache associated with pupillary dilation and a red eye, particularly in a patient with migraine who is taking topiramate for prophylaxis (Alkhalil et al 2009; Cole et al 2012). Recurrent isolated ptosis has also been reported as a variant of presumed recurrent painful ophthalmoplegic neuropathy in childhood (Stidham 2000). Finally, recurrent painless oculomotor nerve palsy has been proposed as an acephalgic variety in children (Miller 1977; Durkan et al 1981).

**Prognosis and complications**

Following early attacks, recovery is the rule and usually occurs in 1 to 6 weeks. Later attacks may have the same recovery rate, but the completeness of recovery is commonly less than satisfactory. Partial ptosis, anisocoria (Iannetti et al 2009) and greater or lesser degrees of permanent disturbance of ocular motility may occur. Rarely, aberrant regeneration occurs. Presumably, preventing repeated episodes by the use of prophylactic drugs prevents permanent sequelae.

**Clinical vignette**

A 39-year-old man had recurrent painful ophthalmoplegic neuropathy episodes at 13 years of age, at which time he had a normal cerebral angiogram. Recurrent painful ophthalmoplegic neuropathy recurred at 35 years of age, with multiple attacks leaving him with a permanent pupil-involving third nerve palsy. MR scan during the acute event showed enhancement of the intracisternal portion of the third nerve.

**Biological basis**

**Etiology and pathogenesis**

Recurrent painful ophthalmoplegic neuropathy may represent an ischemic lesion, inflammation, a compressive lesion, or a combination of etiologies. It is possible that it represents a congenital anomaly whereby the third nerve or, less commonly, the sixth nerve is perforated by an arteriole at the base of the brain (Imes et al 1984) or, perhaps, harbors an occult cavernous hemangioma or other occult vascular malformation. Walsh and O'Doherty cited 200 cases from the literature and postulated that edema of the wall of the carotid within the confines of the cavernous sinus causes pressure on the third nerve, thereby producing an oculomotor nerve palsy involving the pupil (Walsh and O'Doherty 1960; O'Day et al 1980). In addition to the cavernous sinus, the other potential location for vascular compression is the locus where the third nerve passes between the posterior cerebral and superior cerebellar arteries (Ehlers 1928; Morimoto et al 1985).

Mark and colleagues reported 6 patients with ophthalmic migraine and cisternal enhancement of the oculomotor nerve on MR scans. No patient had enhancement of the cavernous sinus or adjacent dura (Mark et al 1998). A case of an adult with recurrent, self-limiting episodes of bilateral abducens palsies showed bilateral cisternal enhancement of the abducens nerves (Tripathi et al 2016). Shin and colleagues performed SPECT during an attack of ophthalmoplegic migraine. A significantly decreased regional cerebral blood flow in the ipsilateral thalamus reverted to normal. These authors postulate that reversible ischemia in the perforators of the posterior cerebral arteries may be a contributing feature (Shin et al 2002).

Vijayan reviewed the literature in 1980, and found only 17 cases meeting clear criteria for ophthalmic migraine. Pupil involvement was complete in 33% of these cases, suggesting a noncompressive mechanism (Vijayan 1980). Other possibilities include compression of the third nerve by a swollen hypothalamus and uncal herniation.

Lance and Zagami proposed recurrent demyelinating neuropathy as a mechanism (Lance and Zagami 2001). Vieira and colleagues reported a 7-year-old boy with an infundibular dilation of a perforating branch of the posterior cerebral artery with presumed compression on the symptomatic third nerve, and these authors speculate that this might be another mechanism for trigeminovascular system activation (Vieira et al 2008). Other authors have also offered the neurovascular compression theory (Linn et al 2008). Ischemic reversible breakdown of the blood-nerve barrier has also
been postulated (Ambrosetto et al 2014).

The genetics of recurrent painful ophthalmoplegic neuropathy are unknown, but family clusters have not been recorded. There has been no pathology of this condition because it is not fatal, although 1 case revealed an atrophic nerve at the level of the posterior cerebral artery at autopsy (Morimoto et al 1985). Cases of aneurysm and tumor coming to autopsy make it clear why this diagnosis has made clinicians wary over the years and why recurrent painful ophthalmoplegic neuropathy should be considered a diagnosis of exclusion.

Carlow reported 6 cases with thickening and enhancement of the involved third nerve. He postulated that the pathophysiology might be related to a trigeminovascular migraine epiphenomenon dependent on the anatomy of the third nerve, a porous blood-brain barrier, and demyelination (Carlow 2002). Although the possibility of an underlying structural lesion (eg, cavernous malformation) within the oculomotor nerve has been raised, there is little clinical or pathological evidence to support this theory (Lee 2003). Akimoto and colleagues reported a case of biopsy-confirmed neuromuscular hamartoma at the root exit zone, and proposed that trigeminovascular stimulation could lead to dilation of the blood vessels that supply the oculomotor nerve. The vascular dilation could induce muscle contraction of the neuromuscular hamartoma, leading to possible strangulation of the oculomotor nerve and ophthalmoplegia (Akimoto et al 2012).

Many patients with recurrent painful ophthalmoplegic neuropathy are empirically treated with corticosteroids, particularly if enhancement of the affected cranial nerve is present on MRI. Corticosteroid treatment complicates the diagnosis during the initial presentation, as secondary causes such as tumors, lymphoma, and demyelination may improve with corticosteroid treatment. Therefore, 1 proposed classification scheme endorses a primary migrainous etiology as well as a secondary cause, with the distinction based on the MRI scan and natural history without corticosteroid treatment in at least 1 event (Friedman 2010). Others have proposed classification schema that distinguish childhood from adult onset, with or without thickening/enhancement of the affective cranial nerve (Chakravarty and Mukherjee 2012).

Epidemiology

The estimated incidence in childhood is 0.7 per million (Hansen et al 1990). A study from India identified 18 new adult cases of recurrent painful ophthalmoplegic neuropathy among approximately 4000 headache patients over a 5-year period; most patients had sixth nerve palsies, which is not typical of the general reported experience favoring third nerve palsies (Chakravarty and Mukherjee 2012). Only 1 case was identified in a study of 111 migraine patients in a pediatric practice (Pacheva 2013). No matter what the venue, it is a rare condition. There appears to be a male preponderance as opposed to the female preponderance seen with migraine with and without aura.

Prevention

It was previously recommended that ophthalmoplegic migraine be treated with preventive medications as in other types of migraine, with a preference for calcium channel blockers. However, given that recurrent painful ophthalmoplegic neuropathy is no longer felt to be of migrainous origin, standard migraine prevention is likely ineffective.

Differential diagnosis

Other conditions that can produce unilateral head pain and ophthalmoplegia should be considered in the differential diagnosis of recurrent painful ophthalmoplegic neuropathy (De Silva and Siow 2005). Intracranial aneurysm must be excluded, particularly with third nerve involvement. Microvascular ocular motor cranial nerve palsies may be associated with ipsilateral pain and are a likely cause of misdiagnosed cases of recurrent painful ophthalmoplegic neuropathy in the literature. The Tolosa-Hunt syndrome is a painful ophthalmoplegia syndrome with pain that persists long after the ocular motility defect appears and is associated with multiple cranial nerve involvement, proptosis, and a red eye (Kandt 1986; Stommel et al 1993b; Straube et al 1993; del Toro et al 2001). The ICHD-3 criteria allow for the presence of simultaneous, ipsilateral third, fourth, and sixth nerve palsies with recurrent painful ophthalmoplegic neuropathy; however, the diagnosis should be made with extreme caution in such cases. Recurrent painful ophthalmoplegic neuropathy generally affects only one ocular motor nerve. Reliance on MRI to distinguish Tolosa-Hunt syndrome from recurrent painful ophthalmoplegic neuropathy is unreliable as the MRI is normal in up to half of the cases of Tolosa-Hunt syndrome (Abdelghany et al 2015). Sphenoid sinus mucoceles, cavernous sinus (Berbel-Garcia et
al 2004), sellar and parasellar tumors (eg, pituitary apoplexy), and sinus infections (eg, fungal) (Silvestrini et al 1994) should be considered.

At least 1 patient with ophthalmoplegic migraine has been shown to have an internal carotid artery dissection with a tapered occlusion but no hemiparesis or other evidence of ischemia (Corbett 1983). Diabetic neuropathies and neuropathies associated with collagen vascular disease, Wegener granulomatosis, and idiopathic orbital inflammation (inflammatory orbital pseudotumor) may produce the same constellation of unilateral head pain with oculomotor and orbital symptoms (Ing et al 1992). The major differential clue is that patients with RPON have a headache, which is usually excruciating, a day or more before the onset of ophthalmoplegia, which usually appears as the pain is abating. A painless variant may exist, and this needs to be considered (Durkan et al 1981). A previous history of similar spells, a personal or family history of migraine, and relative youth at onset of symptoms should point to the correct diagnosis, but we consider recurrent painful ophthalmoplegic neuropathy to be a diagnosis of exclusion.

Schwannoma of the third cranial nerve can produce a similar MR appearance and mimic the clinical presentation of recurrent painful ophthalmoplegic neuropathy (Murakami et al 2005; Bisdorff and Wildanger 2006). Shin and colleagues reported 10 cases of patients with ocular motor nerve schwannomas, 4 of which involved the third nerve, 4 affected the fourth nerve, 1 involved the sixth nerve, and 1 affected the third and sixth nerves in Meckel cave (Shin et al 2015). Of the 3 patients with headache, all had third nerve palsies, and 2 had a history of migraine.

**Diagnostic workup**

A sedated MRI with contrast and MRA should suffice for an infant or young child. When a patient over 12 years of age has a third nerve palsy, it is imperative to rule out internal carotid-posterior communicating aneurysms with MR angiography, CT angiography, or digital subtraction angiography as the risk of the procedure is low and the benefit, if an aneurysm is found, is great. During an attack, MRA and MR scans focusing on the locations in which nerves III, IV, or VI can be involved, may help to delineate the condition. Several cases have demonstrated gadolinium enhancement of the third nerve on MR, and some authors have suggested that enhancement of this type may obviate the need for cerebral angiography in these patients (Mark et al 1998). This gadolinium enhancement is usually in the interpeduncular space and cisternal segment on MR scans (Mark et al 1998; Mark et al 1992; Straube et al 1993; Wang and Wang 1997; Ramelli et al 2000; O'Hara et al 2001; Fujita et al 2003; Bharucha et al 2007; Choi et al 2007). The enhancement and thickening of the oculomotor nerve in recurrent painful ophthalmoplegic neuropathy is usually transient and almost completely resolved by 7 to 9 weeks (Mark et al 1998; O'Hara et al 2001). Some patients have shown no pathologic enhancement on the MRI, however (Ravishankar 2008). Detailed MR imaging of the cavernous sinuses with gadolinium is needed, especially when Tolosa-Hunt syndrome is suspected.

Lumbar puncture and clinical evaluation for infiltrative (eg, lymphoma and leukemia) and infectious etiologies may be necessary, however. The parasellar regions, cavernous sinuses, pituitary fossa, suprasellar space, interpeduncular spaces, clivus (in the case of the sixth nerve), and the tentorial edge (in the case of the fourth nerve) should be scrutinized.

**Management**

As recurrent painful ophthalmoplegic neuropathy is so rare, and the cases reported in the literature so heterogeneous, there is little evidence to guide therapy. Symptomatic treatment with a course of corticosteroids may be employed (Durkan et al 1981; Hansen et al 1990; Wang and Wang 1997; Carlow 2002). Some cases resolve spontaneously although pain control is typically needed. Ishikawa and colleagues reported a remarkable case in which the frequency and symptoms of migraine were reduced by topical administration of 0.25% timolol maleate twice daily to both eyes (Ishikawa et al 2000). Pareja and colleagues reported response to indomethacin (Pareja et al 2010).

**References cited**


Friedman DI. The ophthalmoplegic migraines: a proposed classification. Cephalalgia 2010;30(6):646-7. PMID 19732067


Hutchinson DO, Donaldson IM. Ophthalmoplegic migraine with bilateral involvement. J Neurol Neurosurg Psychiatry 1989;52:807-8. PMID 2746282


Kandt S. Can we reliably differentiate Tolosa-Hunt syndrome from ophthalmoplegic migraine. Headache 1986;26:436-7. PMID 3771212


Lee TG, Choi WS, Chung KC. Ophthalmoplegic migraine with reversible enhancement of intraparenchymal abducens nerve on MRI. Headache 2002;42:140-1. PMID 12005290


Shin DJ, Kim JH, Kang SS. Ophthalmoplegic migraine with reversible thalamic ischemia shown by brain SPECT. Headache 2002;42(2):132-5. PMID 12005288


1994;34:484-6. PMID 7960735


Tripathi R, Tselis A, Berntsis E. Bilateral cisternal abducens nerve involvement with ophthalmoplegic migraines. Cephalalgia 2016. [Epub ahead of print]. PMID 27881687


**References especially recommended by the author or editor for general reading.

**Former authors

James Corbett MD (original author), Andrew G Lee MD, Paul W Brazis MD, and Priyanka Chaudhry MD

**ICD and OMIM codes

**ICD codes

ICD-9:
Ophthalmoplegic migraine: 346.8

ICD-10:
Ophthalmoplegic migraine: G43.8
Profile

Age range of presentation
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years

Sex preponderance
male>female, >1:1

Family history
none

Heredity
none

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none selectively affected

Differential diagnosis list
schwannoma of the third cranial nerve
microvascular ocular motor cranial nerve palsies
Tolosa-Hunt syndrome
sphenoid sinus mucoceles
cavernous sinus
sellar tumors
parasellar tumors
pituitary apoplexy
sinus infections (fungal)
diabetic neuropathies
neuropathies associated with collagen vascular disease
Wegener granulomatosis
orbital pseudotumor
cranial nerve schwannoma or other neoplasm

Associated disorders
Migraine with aura
Migraine without aura

Other topics to consider
Childhood migraine
Eye-related headache
Migraine
Pupillary abnormalities