Ophthalmoplegic Migraine: Still a Diagnostic Dilemma?

K. Ravishankar, MD

Corresponding author
K. Ravishankar, MD
The Headache and Migraine Clinic, Jaslok Hospital and Research Centre, Lilavati Hospital and Research Centre; A-64, Kalpataru Residency, Sion, Mumbai – 400 022, India.
E-mail: dr.k.ravishankar@gmail.com

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The term ophthalmoplegic migraine (OM) was first coined by Charcot in 1890. This condition was included as a migraine variant in the first Headache Classification of the International Headache Society in 1988. Based on postcontrast enhancement seen on MRI in some patients who were diagnosed with OM, there was a suggestion that this could be an inflammatory/demyelinating disorder; therefore, it was moved out of the "migraine" group and repositioned as a "neuralgia" in the revised 2004 classification. However, there have been subsequent reports in the literature in which there was no enhancement on postcontrast MRI. Based on a survey of literature on OM in the post-imaging era, this article highlights the fact that enhancement on magnetic resonance is not a sine qua non for the diagnosis of OM. Some diagnostic dilemmas are discussed, and a protocol is included for documentation of clinical findings in future case reports on a prospective basis. Hopefully, this will help in modification of the criteria, better understanding the etiology, correct diagnosis, and determining appropriate treatment for OM.

Introduction

The term ophthalmoplegic migraine (OM) was first used by Charcot in 1890 to refer to the clinical presentation of headache with oculomotor nerve palsy in which other structural entities were excluded (with the investigational aids of the time) [1]. More than 100 years later, in spite of many case reports, better imaging facilities, two headache classifications, and significant progress in the headache field, confusion still prevails and controversies continue when referring to "ophthalmoplegic migraine" [2,3]. Because the clinical presentation is quite heterogeneous and the OM classification criteria are not ideal, survey of literature shows that authors who use this term do not describe a similar clinical phenotype. Based on review of literature from the post-imaging era, this article highlights the diagnostic dilemmas involving this rare entity. The epidemiology, clinical features, pathophysiology, and treatment options have been discussed in great detail by Levin and Ward [4] in an earlier article.

OM was included as a variant of migraine (1.3) in the 1988 Headache Classification of the International Headache Society (IHS) [2]. Based on subsequent MRI reports of postcontrast enhancement of the oculomotor nerve and atypical headache presentations, experts on the classification committee moved this entity to the group of "neuralgias" (13.17) in the revised 2004 classification [3]. It is important to mention that MRI, particularly following contrast, was not a well-established modality in 1988 (the time of the first headache classification).

In 1991, Mark et al. [5] first described 11 patients with postgadolinium enhancement of the third cranial nerve on MRI, but 10 of the cases had other underlying conditions to explain the third nerve involvement. In 1992, Mark et al. [6] reported a patient with OM in whom enhancement of the cisternal segment of the oculomotor nerve was seen during the acute phase on contrast-enhanced MRI. The enhancement resolved several weeks later as the patient's symptoms resolved. Subsequently, in 1993 Stommel et al. [7] reported a similar case of an 18-year-old male with a history of recurrent headaches and right-side ptosis in whom MRI revealed postcontrast enhancement of the oculomotor nerve. There was good clinical improvement 1 week after steroids were used, and MRI performed 5 weeks later showed resolution of the enhancement. These were some of the early reports on the use of MRI as correlative evidence for OM diagnosis.

In 1998, Mark et al. [8] reported the first large series of six patients clinically diagnosed with OM and in whom there was focal hypertrophy and enhancement on postcontrast MRI during the acute phase. There was resolution of the enhancement over several weeks as the symptoms resolved. Following this report, there have been many case reports of similar postcontrast enhancement on MRI of the intracisternal portion of

the third nerve at its point of origin in the brainstem. Based on a similar MRI finding in one of their patients and their personal experience, Lance and Zagami [9], in an excellent review, hypothesized that OM was most likely secondary to an inflammatory or demyelinating pathology. Based on all this evidence, experts on the classification committee of the revised 2004 classification decided to move this entity out of the migraine group and into the neuralgia group (it was no longer tenable and correct to retain OM as a migraine variant in the presence of imaging evidence to the contrary). The revised IHS classification lists the criteria for OM diagnosis as follows:

- A: At least two attacks fulfilling criterion B.
- B: Migraine-like headache accompanied or followed within 4 days of onset by paresis of one or more of the third, fourth, or sixth cranial nerves.
- C: Parasellar, orbital fissure, and posterior fossa lesions ruled out by appropriate investigations [3].

However, somewhat paradoxically, despite repositioning of the same phenotypic presentation into the group of neuralgias in the revised classification, the old terminology is still in use. The use of the word migraine in the term ophthalmoplegic migraine only confuses the generalist and does not portray the current positioning of the entity. Keeping in mind the precept of the IHS classification that uniform language be used to convey the same meaning across different sections of the scientific world, the term OM is therefore a misnomer [3].

Table 1 lists initial reports of postcontrast enhancement on MRI in the cisternal portion of the third nerve at its point of exit in the brainstem in patients who were diagnosed with OM.

However, there have been subsequent reports in the literature of no enhancement of the involved cranial nerve in patients diagnosed with OM; these are listed in Table 2. Based on review of literature from the post-MRI era, enhancement on contrast imaging is not seen in all patients diagnosed with OM and therefore is not a sine qua non for OM. It is a heterogeneous disorder in which there is still no consensus on many issues.

Discussion

OM is a rare entity in which no author can claim the experience of having seen many patients, and even headache experts make a tentative diagnosis of exclusion. Some landmark articles have included personal experiences and reviewed findings in case reports from literature [8–11,12•,13•]. In the following text, salient observations from these studies are analyzed and followed by a discussion of the dilemmas confronting the clinician who must diagnose OM.

Review of literature

Mark et al. [8] included noncontrast and contrast-enhanced axial coronal T_1-weighted images in their OM MRI study. Focal thickening of the nerve was seen on the noncontrast studies, and further thickening was present on the contrast-enhanced images in the area of the exit zone of the nerve in the interpeduncular cistern. On follow-up study, 7 to 9 weeks after the first study when the symptoms had resolved in all patients, MRI demonstrated almost complete resolution of the enhancement. Minimal faint residual enhancement was seen in all patients at the point of exit of the oculomotor nerve from the cerebral peduncle.

Discussing the pathophysiology, Mark et al. [8] state that a benign viral infection affecting the oculomotor nerve could explain the clinical and imaging findings and spontaneous resolution over a couple of weeks. Based on their imaging experience in diabetic cranial nerve palsy, they think that ischemia is an unlikely cause of OM. In their opinion, other diseases such as vascular malformation, granulomatous infections, sarcoidosis, pituitary apoplexy, and chronic inflammatory, demyelinating polyneuropathies may have similar clinical presentation and can be excluded based on MRI and laboratory findings. Therefore, they state that contrast-enhanced MRI and magnetic resonance angiography (MRA) should be the investigations of first choice for the diagnosis of OM, followed by a careful clinical examination and spinal tap. If no obvious lesion of the third nerve is seen and MRA is negative, conventional angiogram may still be necessary to completely exclude an aneurysm [8].

In a detailed review, Lance and Zagami [9] comment on the etiologic possibilities and state that the magnetic resonance appearances favor demyelination or inflammation of the involved cranial nerve rather than an ischemic lesion. They think that the most striking feature on MRI is a globoid appearance of the first part of the oculomotor nerve on emerging from the midbrain, consistent with intraneural edema as reported in some experimental demyelinating neuropathies and in chronic demyelinating polyneuropathy.

Their explanation for the headache in OM is based on the fact that sensory fibers from the ophthalmic division of the trigeminal nerve enter the oculomotor nerve, pass through it into the brainstem, and terminate in the spinal trigeminal nucleus. Inflammatory processes affecting the oculomotor nerve could irritate these trigeminal sensory fibers and subsequently activate the trigeminovascular system in people who are already migraineurs, thereby triggering the associated migrainous headaches [9].

In an editorial published in the same issue, Daroff [10] concludes that OM almost always begins in childhood, the headache lasts several days, and the third nerve palsy recovers over weeks. He further states that postcontrast enhancement on MRI is an absolute requirement for

Table 1. Ophthalmoplegic migraine with postcontrast enhancement on MRI

Study	Year	Cases, *n*	Gender/age	Cranial nerve involved
Straube et al. [24]	1993	1	M/23	III
Stommel et al. [7]	1993	1	M/18	III
Ostergaard et al. [35]	1996	1	F/1.5	III
Wong and Wong [25]	1997	1	M/6	III
Aers et al. [26]	1997	1	F/14	III
Hupp [27]	1998	1	F/5	III
Mark et al. [8]	1998	6	F/27	III
			F/8	III
			M/12	III
			F/5	III
			M/3	III
			F/23	III
Prats et al. [36]	1999	2	F/11	III
			M/3	III
Stidham and Butler [28]	2000	1	F/42	III
Ramelli et al. [30]	2000	1	F/8	III
O'Hara et al. [29]	2001	2	F/7	III
			M/3	
Lance and Zagami [9]	2001	1	F/16	III
Lee et al. [31]	2002	1	F/42	VI
Carlow [11]	2002	6	F/2	III
			M/3	III
			F/1.5	III
			F/1.5	III
			F/9	III
			F/5	III
Doran and Larner [32]	2004	1	F/36	III
Berbel-Garcia et al. [33]	2004	1	F/18	III
Zafeiriou and Vargiami [34]	2006	1	F/11	III
Crevits et al. [19]	2006	2	M/9	III
			F/41	VI
McMillan et al. [13•]	2007	3	M/1	III
			F/9	III
			F/16	III

F—female; M—male.

diagnosis of all cases of OM. Daroff [10] concurs with the view of Lance and Zagami [9] that OM is more likely a demyelination of probable viral origin rather than a migraine variant.

Carlow [11] studied the magnetic resonance scans in six patients diagnosed with OM and did a retrospective literature survey in 17 patients with OM, all of whom showed the presence of magnetic resonance signal abnormalities. Noncontrast T_1-weighted images documented thickened ipsilateral oculomotor nerves at the midbrain exit that were isodense with the brain. Contrast T_1-weighted magnetic resonance scans showed enhancement of the ipsilateral oculomotor nerves at the midbrain exit. A trapezoid configuration was typically seen, with the widest area adjacent to the midbrain. Magnetic resonance scans were also abnormal during the quiescent phase, with contrast scans demonstrating persistent third nerve enhancement that was less intense than during the acute phase.

Table 2. Ophthalmoplegic migraine with no postcontrast enhancement on MRI

Study	Year	Cases, *n*	Gender/age	Cranial nerve involved
Ostergaard et al. [35]	1996	1	F/1.5	III
Prats et al. [36]	1999	2	F/6	III
			M/4	III
Shin et al. [14]	2002	2	M/8	III
			F/11	III
Verhagen et al. [15]	2003	1	F/44	VI
Van der Dussen et al. [16]	2004	1	M/31	III
Celebisoy et al. [17]	2005	2	F/21	VI
			F/51	VI
De Silva and Siow [18]	2005	1	M/28	III
Crevits et al. [19]	2006	2	F/41	VI
			M/30	VI
O'Sullivan et al. [20]	2006	1	F/35	III
Mucchiut et al. [21]	2006	1	F/46	VI
Manzouri et al. [22]	2007	2	F/36	VI
			M/44	VI
Ravishankar and Karthik [23•]	2007	4	M/62	III
			M/37	III
			M/6	III
			M/27	III

F—female; M—male.

Based on his experience, Carlow [11] included the following as the general criteria for OM: 1) childhood onset; 2) headache preceding and ipsilateral to the third nerve paresis; 3) a commonly dilated pupil; 4) ophthalmoplegia that may be permanent and rarely accompanied by aberrant oculomotor regeneration; 5) a minimum of two episodes; and 6) no evidence for a structural lesion. In his opinion, the diagnostic criteria for OM should include an MRI contrast-enhanced thickened third nerve at the oculomotor midbrain exit during the acute phase, with less enhancement during the quiescent phase. If these MRI findings are not present, he thinks that other diagnostic etiologies must be excluded. Carlow [11] has also proposed a different hypothesis for the pathophysiology, based on the trigeminovascular theory of migraine, the unique oculomotor nerve anatomy at the brainstem exit, the blood–nerve barrier, and the pathology of demyelination.

Bharucha et al. [12•] included one case from personal experience and reviewed 52 case reports of OM patients in the literature. Their case report was a 16-year-old girl who did not exhibit MRI abnormalities of the oculomotor nerve until her eighth episode of OM. MRI findings were abnormal in 44 cases and normal in five cases. Most patients with OM and abnormal MRI findings exhibited enhancement of the third cranial nerve. Repeat MRI studies frequently showed improvement, with decreased intensity of enhancement of the third cranial nerve.

McMillan et al. [13•] reviewed three new and 37 reported pediatric OM cases. All of the patients showed enhancement of the oculomotor nerve on postcontrast MRI. In their opinion, headache was an inconsistent feature, with 25% of patients showing no evidence of pain at the initial OM episode. When present, headache typically preceded onset of ocular symptoms by several days. Associated migraine symptoms, such as nausea, vomiting, and photophobia, were present in only 12 patients in their survey. Patients demonstrated rapid improvement and shortened duration of illness with corticosteroid therapy, and investigation revealed transient, reversible MRI contrast enhancement of the affected cranial nerve in 21 of 40 patients. Symptom onset was abrupt, the oculomotor nerve was most commonly involved, and recurrent episodes always affected the same cranial nerve and occurred on the same side. They concluded that headache description and progression favor inflammation rather than migraine, and therefore OM is likely a recurrent inflammatory cranial neuropathy and headache is a secondary feature of this indication [13•].

MRI has become integral for the diagnosis of OM [10]. Based on their experience, Mark et al. [8], Lance

and Zagami [9], Daroff [10], Carlow [11], Bharucha et al. [12•], and McMillan et al. [13•] have concluded that postcontrast magnetic resonance enhancement should be included as an integral part of the OM diagnostic criteria. Review of the literature from the post-imaging era, particularly after 2002, shows that postcontrast MRI in patients who fulfilled the criteria for OM has not always revealed enhancement (Table 2). However, most of the reports that did not show enhancement were published during and after the revision of the headache classification.

Earlier reviews compiled case reports in children diagnosed with OM and noted the results of MRI [11,12•,13•]. These are probably the first reviews that included a compilation of evidence from OM literature of studies that have not shown an enhancement of the cranial nerve on magnetic resonance postcontrast imaging (Table 2). Based on imaging findings in OM, it is more appropriate to adopt an unbiased view and state that contrast enhancement on MRI is not a sine qua non for the diagnosis of OM. Depending on the presence or absence of enhancement after contrast on MRI, one can postulate that OM is of two types:

1. Inflammatory/demyelinating, in which there is postcontrast enhancement on MRI.
2. Noninflammatory, in which there is no enhancement on MRI.

Two different imaging findings in patients with similar phenotypic presentation confirm that OM is a heterogeneous disorder with different underlying mechanisms and consequently may need to be treated differently.

Dilemmas in diagnosis

When faced with a patient who complains of headache and has a third, fourth, or sixth cranial nerve palsy on examination, and other conditions that can cause a painful ophthalmoplegia are ruled out, some diagnostic issues must be sorted out before this clinical presentation can be labeled as OM. Some of these diagnostic dilemmas are listed in the following text:

1. The initial reports of OM have been in children, and because literature surveys also focus on comparative findings in children, subsequent reports of a similar clinical presentation in adults have gone unnoticed [11,12•,13•]. Eighteen adults with OM have been described. The patients in the reports of Strommel et al. [7] and Straube et al. [24] were 18 and 19 years of age. Two cases from the series by Mark et al. [8] were 23 and 27 years old. Most of the authors have looked at OM as a disorder that is seen only in children, but some have mentioned case reports in adults [4,9,11,12•,13•,17]. Thus, it is more appropriate to state that OM, although more common in children, can be seen in young adults too. Therefore, it need not be regarded as a childhood disorder [11].
2. The revised 2004 classification criteria for OM state that A) there should be at least two attacks fulfilling criteria for B; and B) migraine-like headache accompanied or followed within 4 days by onset of paresis of one or more of the third, fourth, or sixth cranial nerves. However, a critical analysis of literature on the subject shows that very few studies clearly mentioned that the headache of OM fulfilled the criteria for migraine without aura. The use of "migraine-like" in the classification criteria gives room for ambiguity and inclusion of any headache that throbs. Most reports have used the words "migrainous" or "throbbing" and have not detailed the headache profile. The headache profiles must be clearly defined in the criteria. Details of the family history and the history of recurrent headaches that fulfill the criteria for migraine without aura are also absent in many reports.
3. Only 12 reports in the literature have clearly mentioned the time gap between the headache and the cranial nerve palsy. When it has been stated, the gap between the onset of headache and the cranial nerve palsy has varied between 2 days and 10 weeks. Therefore, the arbitrary 4-day gap (as required by the criteria) must be revised.
4. The timing of MRI in relation to the acute event has also been variable across different reports. Only 18 studies mentioned the details of the MRI timing. Only a few studies have discussed resolution patterns on MRI. Only the series of Mark et al. [8] and Carlow [11] provide details of the MRI protocol used to investigate these patients.
5. The entity OM has been moved to the group of neuralgias, but the treatment modality that has been used has not been uniform, and the outcome does not clearly show ways to determine patients who will resolve spontaneously and those who will progress to have permanent damage. Most studies have not discussed treatment, but some have used steroids [13•]. A number of studies have used antimigraine prophylactics for treatment. This is paradoxical considering that the etiologic thinking no longer supports a migrainous etiology. Bharucha et al. [12•] state that various treatments have been described, including steroids acutely and flunarizine, acetazolamide, propranolol, cyproheptadine, or verapamil prophylactically. They think that prompt administration of steroid therapy at the time of attack might minimize permanent sequelae of OM, including residual weakness of the third cranial nerve and pupillary dysfunction.

6. Whether OM is a self-limiting condition that resolves spontaneously or the deficit progresses to become permanent has not been specified in most of the studies. McMillan et al. [13•] analyzed the final outcome. Whether the accompanying cranial nerve deficit resolves spontaneously or can be long lasting and permanent is also debated [4,8]. We still do not have definite parameters by which we can predict the future course in these patients, except to state that use of steroids is more likely to hasten recovery.

Given the rarity of this condition, a preset protocol for reporting findings on a prospective basis in patients with OM will help resolve some of these dilemmas. A set protocol that records findings from patients who fit the diagnostic label of OM will give us important clues regarding etiology, modification of the criteria, treatment, and prognostication of the final outcome.

The following lists our suggestions as to what should be included in an ideal future protocol questionnaire for patients diagnosed with OM:

1. Age at onset.
2. Number of previous similar or near-similar episodes.
3. Cranial nerve(s) involved.
4. Details of the headache profile—migraine or probable migraine.
5. Whether there is more than one headache type.
6. Whether the present headache and the past episodes fulfill the criteria for migraine.
7. The time gap between the onset of the headache and the onset of the cranial nerve palsy.
8. The pupillary details when there is a third nerve palsy.
9. The time to resolve and recover for the headache and the cranial nerve.
10. Magnetic resonance findings before and after contrast, and the MRI protocol.
11. Timing of the MRI and clinical status at the time of the MRI.
12. Clinical phase in which MRI is done—acute or quiescent phase.
13. Timing of the MRI after the acute attack and the clinical parameters.
14. MRI findings in subsequent attacks.
15. Details of imaging technology used and quantity of contrast.
16. Family history of headaches, migraine or otherwise.
17. Investigations done to exclude other conditions (eg, blood tests, cerebrospinal fluid examination).
18. Exclusion of Tolosa-Hunt syndrome and other causes of painful ophthalmoplegia.
19. Treatment administered, response to treatment, and final outcome.
20. Recovery—spontaneous or with specific treatment.
21. Final outcome.

The underlying etiology is still debated, and the controversy as to whether OM is migrainous, inflammatory, or demyelinating is unresolved. Until more cases are reported using a standard protocol, it seems premature to place OM in the group of neuralgias. At present, it might be better to position OM in the appendix of the classification. With greater focus on imaging to increase the diagnostic yield and as more patients are treated with antimigraine prophylactics, the future evidence may show that OM is a heterogeneous disorder that is still a migraine variant and was prematurely repositioned.

Conclusions

Routine MRI, MRA, and imaging with gadolinium contrast have clearly helped to rule out other causes of painful ophthalmoplegia and Tolosa-Hunt syndrome that are closely linked to OM. Postcontrast magnetic resonance enhancement has also helped to rule out OM but has caused controversy regarding the possible etiology. Based on the clinical presentation, OM was included as a migraine variant in the first IHS classification (1988). Subsequent reports that showed an enhancement of the third nerve on postcontrast MRI forced the classification committee to review the nosology of this entity and reposition the entity as neuralgia on grounds that the underlying cause was either inflammatory or demyelinating. Subsequent reports that have shown no enhancement on MRI confirm that OM is a heterogeneous disorder that needs careful scrutiny, periodic magnetic resonance monitoring, and clinical correlation before we can conclude, classify, and draw definite management guidelines. We hope that future classification committees will address the issues raised in this article when proposing a revision to this entity. Only time, better imaging strategies, and meticulous clinical observations will give us the final answer to the elusive etiology of this enigmatic entity.

Disclosure

No potential conflict of interest relevant to this article was reported.

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