COMMENTARY

Are some ophthalmoplegias migrainous in origin?

Vivek Lal, DM, and Louis Caplan, MD

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Correspondence
Dr. Lal
vivekl44@yahoo.com

Abstract

The 3rd edition of the International Classification of Headache Disorders replaced the term ophthalmoplegic migraine (OM) with Recurrent Painful Ophthalmoplegic Neuropathy (RPON) based on the presence of contrast enhancement of the involved cranial nerves on Gadolinium-enhanced magnetic resonance imaging. We review our experience and publications concerning ophthalmoplegia, migraine, and RPON. Majority of cases of acute ophthalmoplegia are associated with severe migrainous headaches. A positive history of migraine, increased severity of migraine headaches before the onset of ophthalmoplegia, and the close temporal association between migraine attacks and ophthalmoplegia all suggest an important role played by migraine in the causation of ophthalmoplegia. Enhancement of the involved cranial nerves may be due to the neuroinflammatory cascade associated with migraine. OM should be considered along with RPON in differential diagnoses of painful ophthalmoplegic syndromes.

The term "Ophthalmoplegic Migraine (OM)" was first coined by Charcot[1] in 1890 to describe a unique group of patients who developed ophthalmoplegia associated with migrainous headaches. The migrainous headaches associated with the ophthalmoplegic attack were often severe.[2–4] Ophthalmoplegia predominantly involved the 3rd nerve alone.[2,3] Rarely, the 6th or the 4th nerve were also involved in isolation.[4–8] Relevant investigations during the episode of ophthalmoplegia were normal in almost all patients. In view of the presence of severe migrainous headaches, a migrainous pathogenesis was postulated.[2–4] The first International Classification of Headache Disorders (ICHD)[9] classified OM as a variant of migraine. The presence of enhancement of the involved cranial nerves on Gadolinium-enhanced magnetic resonance imaging (GdMRI) has led to the reclassification of OM as "Recurrent Painful Ophthalmoplegic Neuropathy (RPON)" in ICHD-3.[10]

Origin of the controversy

In 1998, Mark et al.[11] described 6 patients of OM with enhancement of the cisternal segment of the 3rd cranial nerve on GdMRI. They posited OM a viral or post-viral demyelinating neuropathy. This hypothesis was endorsed by Lance and Zagami[12] based on the presence of strong enhancement of the involved cranial nerves in their own series. In an elegant editorial, Daroff[13] RB called OM a post-viral cranial neuralgia. The migrainous headaches were considered secondary to irritation of the sensory pain fibers of the 5th cranial nerve traversing the 3rd cranial nerve and thought to be inconsequential in the pathogenesis of the ophthalmoplegia.[12,13]

Department of Neurology (VL), Postgraduate Institute of Medical Education and Research, Chandigarh, India; Beth Israel Deaconess Medical Center (LC); and Department of Neurology (LC), Harvard University, Boston, MA.

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Majority of cases of acute ophthalmoplegia are associated with severe migrainous headaches.

Carlow[14] reported 6 children with migraine, recurrent ophthalmoplegia, and reversible enhancement of the 3rd cranial nerve. He explained that enhancement and thickening of 3rd cranial nerve were on the basis of the trigeminovascular hypothesis of migraine. Subsequently, Lane and Davies[15] described 2 patients of ophthalmoplegia associated with migraine and reversible enhancement of the 3rd cranial nerve. They concluded that the evidence for classification of OM as cranial neuralgia was far less compelling than the evidence suggesting a migrainous origin. Freidman[16] proposed a new classification for OM and recognized the importance of migraine in the causation of ophthalmoplegia. Ravishankar[17] reported that enhancement of the involved cranial nerve was not always present. He reviewed 34 and 20 OM patients with and without nerve enhancement respectively. Lal et al.,[18] in a prospective series of 62 OM patients, did not find nerve enhancement in any of their patients. They suggested that migraine was primarily responsible for ophthalmoplegia in OM.

Gelfand et al.[19] again suggested a demyelinating etiology for this entity based on the presence of reversible nerve enhancement. They put forward 2 points in favor of their hypothesis: (1) the absence of typical migraine in 1/3rd of their cases and (2) a long lag period (up to 2 weeks) between headache, and ophthalmoplegia in some cases. Chen and Wang[20] distanced themselves from the cranial neuralgia hypothesis citing that migraine always precedes the onset of ophthalmoplegia. Ambrosetto[21] and Förderreuther and Ruscheweyh[22] recognized the importance of migraine in causing this neuropathy.

Our experience

In a prospective study by Lal et al.,[18] OM (n = 62) was present in 0.89% of all migraine patients (n = 7,000) during the study period (1996–2005). Mean age was 36.4 ± 12.8 years. Thirty-three (53.2%) were women. Almost all (n = 59; 95.2%) patients developed ophthalmoplegia during a severe attack of migraine without aura. Fifty-one (82.3%) patients reported pronounced worsening in the severity of migraine for 2 or more weeks before the onset of ophthalmoplegia. The migraine headaches involved the side of ophthalmoplegia in all patients. These were hemicranial and ipsilateral to the side of ophthalmoplegia in 47 (75.8%) patients. Fifteen (24.2%) patients had bilateral headaches. Mean duration of migraine before the onset of ophthalmoplegia was 11.8 ± 8.1 years. Twenty-six (42%) patients had a positive family history of migraine. Forty-eight patients had single attack (probable OM) while 14 patients had 2 or more attacks of OM (definite OM). Isolated abducens, oculomotor, and trochlear nerve involvements were seen in 35 (56.5%), 21 (33.9%), and 5 (8.1%) patients, respectively. One (1.6%) patient had combined right abducens and oculomotor nerve palsy. Pupillary involvement was present in 4 out of 14 (28.6%) patients with complete 3rd nerve palsy. Fifty-two patients had MRI scans during the ophthalmoplegic episode, of which 45 were Gadolinium enhanced, majority of which were on a 1.5T unit. MRI was normal in all and did not show any thickening or enhancement of the involved cranial nerve. Dye contrast catheter angiography (n = 52) was normal in almost all patients. Fifty-four patients had cerebrospinal fluid (CSF) examination during the ophthalmoplegic episode. CSF opening pressure was normal in all patients. CSF was normal in 48 (88.9%) patients and showed nonspecific abnormalities in 6 (11.1%) patients.

During the 10 years follow-up of these 48 patients with probable OM, there were 9 patients who had a total of 14 more episodes involving the same (n = 8), different (n = 3) or unknown (n = 3) cranial nerves. No patient needed a revision of the diagnosis at follow-up.

During the same period, we also examined 6 patients with OM who were less than 15 years of age. All these patients had multiple attacks involving the 3rd cranial nerve (n = 5) and 6th cranial nerve (n = 1). Nerve enhancement was seen in 4 of these patients (3rd cranial nerve—3; 6th cranial nerve—1). One patient had aberrant regeneration of the 3rd cranial nerve.

Two illustrative cases of OM not previously published

Case vignette 1

A 38-year-old woman developed left abducens nerve palsy during an attack of severe migraine without aura. She had had either right or left temporal throbbing migrainous headaches for more than a decade. These headaches occurred once every "15–20" days and would last between "6–12" hours. These were associated with nausea, photophobia, and phonophobia. She never received antimigraine prophylaxis. Six months before presentation, her headaches increased in severity and frequency (twice a week) and started occurring almost exclusively in the left temporal region. Fifteen days before the onset of diplopia, she developed daily left temporal throbbing migrainous headaches with nausea, photophobia, and phonophobia. On examination, she had complete left 6th cranial nerve palsy. The remainder of her examination was normal. Detailed hematological and biochemical (including blood sugars, glycosylated hemoglobin, erythrocyte sedimentation rate, C reactive protein, renal, liver and thyroid function tests, vasculitic evaluation including antinuclear and anti-neutrophilic cytoplasmic antibodies, serum angiotensin converting enzyme levels) parameters were normal. Detailed CSF evaluation was also normal. GdMRI of 6th cranial nerve with magnetic resonance angiography and venography was normal. She recovered completely

(figure 1) in 10 weeks. She was given antimigraine prophylaxis in the form of nonsteroidal anti-inflammatory drugs and propranolol 40 mg twice daily. She was asymptomatic during the three-year period that she took propranolol.

Six years later, she again developed frequent left hemicranial migrainous headaches. Two months later, she developed partial left 6th cranial nerve palsy during an attack of left hemicranial migrainous headache which was less intense compared to the previous ophthalmoplegic attack. Repeat haematological, biochemical, CSF, and radiologic parameters were normal. She recovered completely and has had no further ophthalmoplegic episodes on propranolol 40 mg twice daily.

Case vignette 2

A 41-year-old man with a positive family history of migraine had been having bifrontal/hemicranial throbbing and non-throbbing migrainous headaches provoked by stress and reading since childhood. After an episode of severe bifrontal migrainous headache, he developed left sided lateral rectus palsy (figure 2A) that resolved in 8 weeks without steroids. He later developed pupil-sparing left partial 3rd cranial nerve palsy during a severe attack of migraine precipitated by a posting to a high altitude (figure 2B). He recovered completely in 3 weeks on antimigraine prophylaxis and oral steroids (figure 2C). All relevant investigations as mentioned for the first case were normal. He remains on beta blockers (propranolol 40 mg twice daily) and amitriptyline (25 mg daily), but continues to have occasional migrainous headaches without aura. There has been no recurrence of ophthalmoplegia during the 5 year follow-up.

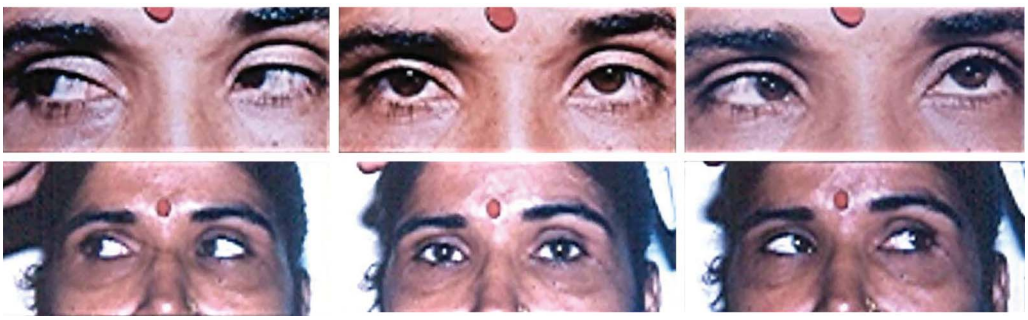
Review of the literature

We searched relevant literature (including PubMed and cross references from relevant articles) using the following terms "Ophthalmoplegic migraine," "Migraine with ophthalmoplegia," "Ophthalmoplegia in migraine," and "recurrent painful ophthalmoplegic neuropathy." The studies where there were doubts about the diagnosis, lack of details of clinical features, alternate diagnoses and/or inaccessibility were excluded. All the selected articles were reviewed in detail with special attention towards the pattern and characteristics of headaches, worsening or change of character of headaches during (or before) the ophthalmoplegic episode, cranial nerves involved, time from headache to ophthalmoplegia, duration of ophthalmoplegia, family and past history of headaches, neuroimaging, and CSF findings. Headache was considered "Migrainous" if either (1)the author(s) used the term "Migraine" to describe the headache, or (2) if the description of headache met ICHD-3 criteria for migraine, or (3) if the clinical description suggested migraine as the most likely cause of headache.

A total of 93 studies (228 patients) were included in the review process. One hundred forty-six (64%) patients had 3rd nerve involvement while 79 (34.6%) had sixth and 11 (4.8%) had fourth nerve involvement. Ten (4.5%) patients had involvement of 2 or more nerves during the index episode. Pupillary involvement was noted in 72/109 (66.1%) patients in whom details regarding pupillary involvement were provided. Past history of headaches was positive in 163/183 (89.1%) patients. Past headaches qualified as migrainous in 151/163 (92.6%) patients. Family history of migraine was positive in 84/159 (52.8%) patients.

The nature of headache during the index episode of ophthalmoplegia was available for 146 patients. Most patients (n = 134; 91.8%) described their migrainous headaches as severe using various terms such as "throbbing, sharp, pulsating, pounding, etc." Twelve (8.2%) patients did not have severe headaches before the index episode. History regarding worsening of headaches just before the ophthalmoplegic episode was available in 75 patients. It was positive in 60 (80%) patients. The mean duration of headache (available for 112 patients) before the onset of ophthalmoplegia was 2.63 ± 2.15 days (range 0–11 days).

Figure 1 Sixth cranial nerve palsy in ophthalmoplegic migraine



Sixth cranial nerve palsy in a 38 year old lady with ophthalmoplegic migraine. Note palsy of left lateral rectus (upper panel) during the attack and complete recovery (lower panel) after 10 weeks with antimigraine prophylaxis alone.

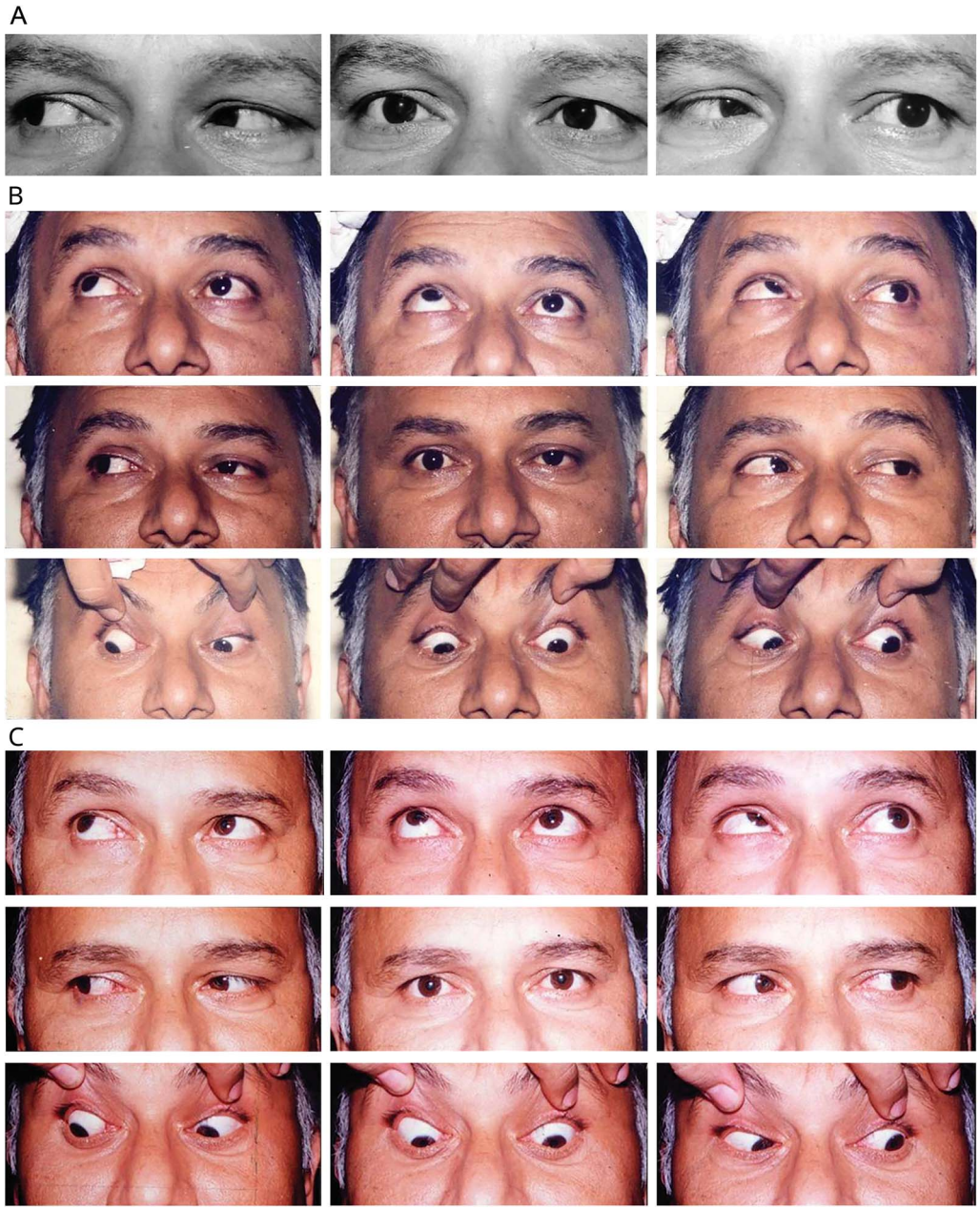
Nerve thickening with or without enhancement was reported in 53/123 (43.1%) patients. Angiography (n = 129) revealed nonspecific abnormalities in 13 (10.1%) patients.

Discussion

For nearly a century after its first description by Charcot,[1] OM was considered a variant of migraine. Recently, in ICHD-3,[10] the term "OM" was replaced by "RPON" citing that "OM" was a misnomer and migraine was not the cause of ophthalmoplegia in "RPON." The evidence both for nonmigrainous and migrainous pathogenesis of ophthalmoplegia in "OM" as well as our final proposal is being presented below.

A strong temporal correlation exists between migrainous attacks and ophthalmoplegia in OM.

Figure 2 Recurrent cranial nerve palsies in ophthalmoplegic migraine



Recurrent cranial nerve palsies in ophthalmoplegic migraine. Top panel: note palsy of left lateral rectus (A) during 1st attack of ophthalmoplegic migraine. Middle panel: left partial 3rd nerve palsy (B) during 2nd attack of ophthalmoplegic migraine after 8 weeks of first attack. Bottom panel: complete resolution of 3rd cranial nerve palsy (C) after 3 weeks of treatment with prednisone.

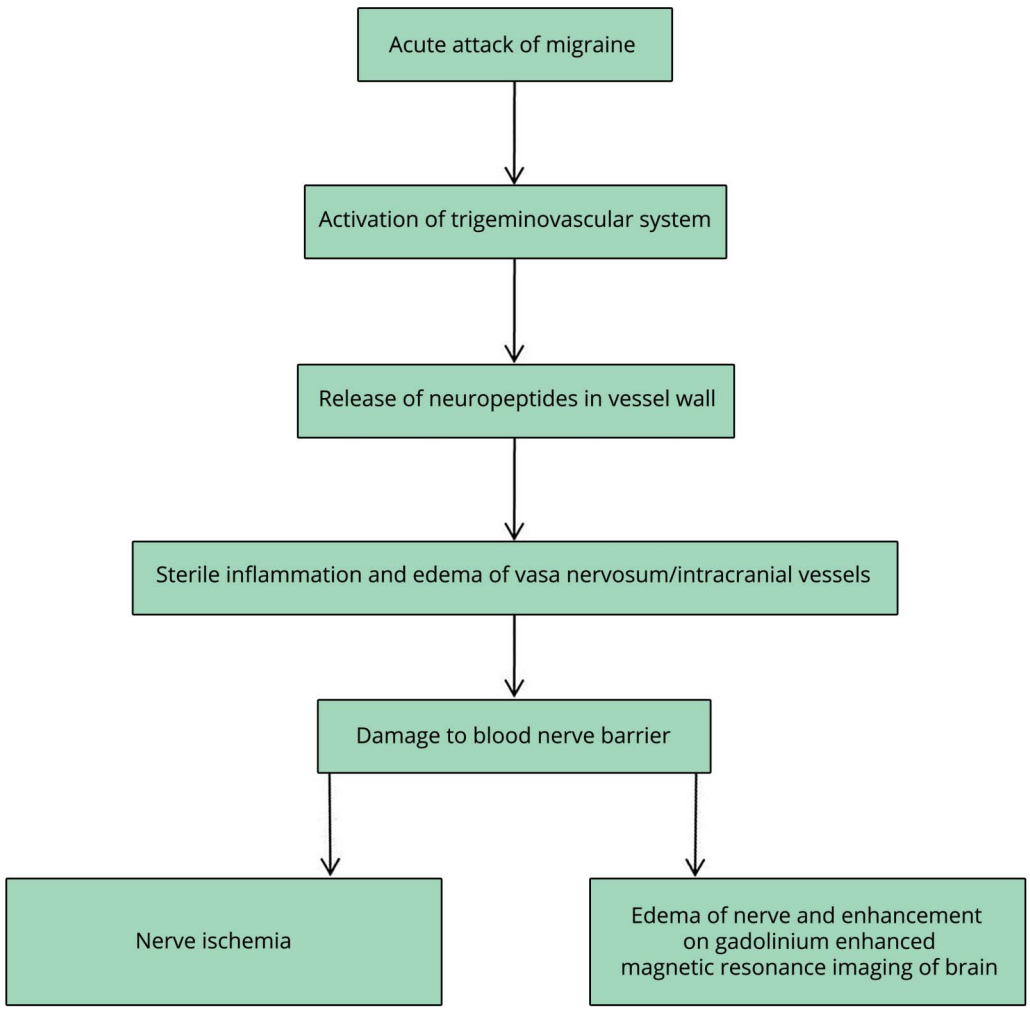
Following evidence supports a nonmigrainous pathogenesis of the ophthalmoplegia.

- Presence of reversible oculomotor nerve enhancement on GdMRI.[11–13] This enhancement is similar to that seen in chronic inflammatory demyelinating neuropathy. This is most pronounced during an attack and often resolves on follow-up. The migraine-like headaches present in these patients are secondary to irritation of afferent pain fibers of the 1st division of the 5th cranial nerve traversing the 3rd cranial nerve.[12,13,22]
- Unusually prolonged headache (>72 hours) during the attack of ophthalmoplegia. This is unusual for typical migraine.[19] Since migraine is very common and in no way protects from other etiologies, migraineurs often develop other conditions.
- A long lag period (up to 14 days) between the onset of headache and ophthalmoplegia in some reports.[22] Furthermore, there is no objective laboratory confirmatory test for migraine.
- Migraine may be absent in up to 1/3rd of the cases.[12,19,22] In few others, the headaches that accompany the ophthalmoplegia may be a response to inflammation.

The evidence that suggests migraine may be the underlying cause of the ophthalmoplegia in OM is as follows.

- The very frequent presence of typical migraine headaches before the onset of ophthalmoplegia.[19,22] *The headaches are very often (91.8% in this review) typical migraines during the ophthalmoplegic episode*. Although more intense, these headaches are otherwise similar to the patient's prior migraine attacks.[18,22]
- A strong temporal correlation exists between migrainous attacks and ophthalmoplegia in OM. Almost all cases develop ophthalmoplegia either during or within 24 hours of a severe attack of migraine.[15,17,18,22–27] In the series of Lal et al.,[18] all patients developed ophthalmoplegia during a severe attack of migraine. 82.3% of patients reported worsening of migrainous headaches

Figure 3 Pathogenesis of nerve damage in ophthalmoplegic migraine



Proposed mechanism for palsies and enhancement of ocular motor nerves on magnetic resonance imaging in ophthalmoplegic migraine (adapted and modified from Lal et al.[18]).

Table Proposed inclusion criteria for diagnosis of ophthalmoplegic migraine

1. History of established migraine before the first attack of ophthalmoplegic migraine
2. History of worsening of migraine severity before the ophthalmoplegic attack
3. Ophthalmoplegia developing during or within 24 h of a migraine attack
4. Normal Gadolinium enhanced MRI and angiography of brain (1.5 T machine) with or without enhancement of involved nerve.
5. No other likely cause of ophthalmoplegia e.g., diabetes, hypertension, ischemic heart disease, malignancy, vasculitis, active infection, active CNS disease, trauma, etc.

preceding the ophthalmoplegic attack. The migrainous headaches were always ipsilateral to ophthalmoplegia.[2–8,18,23–32]

- At times, a single prolonged migraine attack explains reports wherein headache was considered to precede ophthalmoplegia by up to 14 days.[15,16,32]
- Absence of a viral prodrome with normal CSF findings during the ophthalmoplegia militates against para/postinfectious demyelination.[3,18,20–22,33] Inflammatory demyelination involving the 6th and 4th nerve cannot explain headaches as these nerves lack pain-sensitive fibers.[15,18,20]
- It is possible that during migraine attacks, activation of trigeminovascular system stimulates proinflammatory neuropeptides' (substance P, cytokines, calcitonin gene related peptides, etc) entry into the vessel wall causing breaching of the blood nerve barrier (BNB). Nerve edema and ischemia develop with or without enhancement of involved cranial nerves on GdMRI (figure 3).[14,18] Enhancement of the involved nerve occurs commonly in pediatric patients related to relative immaturity of BNB in children and is uncommon or absent in adults.[2–8,18,22,33]

Based on the above discussion, the ophthalmoplegia may be due to migraine rather than demyelinating neuropathy. We accept the existence of cases which may in fact be painful ophthalmoplegic neuropathy due to other causes (including idiopathic) rather than OM. These cases should not be used to replace this classic entity of OM known for decades. We propose the criteria for diagnosis of pure "*OPHTHALMOPLEGIC MIGRAINE*" (table). Patients who meet all those criteria should be classified as "OM", while the term "RPON" should be reserved for patients who do not meet these criteria.

OM should be considered along with RPON in painful ophthalmoplegic syndromes.

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TAKE-HOME POINTS

- The term "Ophthalmoplegic Migraine (OM)" has been replaced by "Recurrent Painful Ophthalmoplegic Neuropathy (RPON)" in International Classification of Headache disorders (ICHD)-3.
- Migraine may be the cause of ophthalmoplegia in "OM" as suggested by (1) increased severity of migrainous headaches before ophthalmoplegia and (2) strong temporal association and side locking between migrainous attack and ophthalmoplegia
- OM should be considered along with RPON in painful ophthalmoplegic syndromes.

Disclosure

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Appendix Authors

Name	Location	Role	Contribution
Vivek Lal, DM	Professor and Head, Department of Neurology, PGIMER, Chandigarh, India	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Louis Caplan, MD	Neurologist Beth Israel Deaconess Medical Center Boston MA, USA; Professor Neurology, Harvard University	Author	Interpreted the data; revised the manuscript for intellectual content

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