Ophthalmoplegic migraine: A critical analysis and a new proposal

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Abstract

The nosology, classification and pathophysiology of ophthalmoplegic migraine (OM) remains complex and debatable. A recently proposed classification of OM leaves several caveats. A critical analysis of all reported cases of OM (1993–2010) has been made incorporating the authors' own experience to arrive at a simple, unambiguous and easy to use diagnostic criteria and classification of OM. Between 2005 and 2010, 18 adult cases of OM had been seen whose clinical details are summarized. Most had sixth nerve palsies associated with migraine-like headaches lasting more than 4 days. Other possibilities were carefully excluded. All subjects responded to corticosteroids favorably. We prefer using the term ophthalmoplegia with migraine-like headache (OMLH) rather than OM. We classify OMLH as a migraine subtype (1.7) and into two groups—childhood-onset type (where third nerve palsies and nerve enhancement are common) and adult-onset type (where sixth nerve palsies are more common and nerve enhancement unusual). This clinico–radiological classification does not in any way hint at any difference in pathophysiology between the two groups.

As we stand today at the doorstep to a new classification of headache disorders by the International Headache Society (IHS), debates continue for the nosological entity and diagnostic criteria of several headache disorders, prominent among which is ophthalmoplegic migraine (OM). We feel that future classification systems need to be simple, pragmatic, unambiguous and easy to be used by clinicians both for research purpose and routine patient assessment and care. It is in the backdrop of this that new classification, nomenclature and diagnostic criteria for OM (an uncommon entity known for over 150 years) need to be discussed.

The currently prevailing International Classification of Headache Disorders 2004 (ICHD-2),[1] classifies OM not as a subtype of migraine but as a cranial neuralgia. This probably had been made in view of a suggestion by Daroff[2] in an editorial published in connection with a publication by Lance and Zagami[3] in 2001, describing a single patient (one out of five cases) where thickening and contrast enhancement

could be seen at the exit zone of the third cranial nerve on contrast-enhanced magnetic resonance (MR) imaging and another who developed ophthalmoplegia with headache following an injection of triple vaccine. This was interpreted as an inflammatory demyelinating neuropathy and the migraine–like headache being generated through activation of the trigemino-vascular pathway stimulated by noxious stimuli carried by proprioceptive fibers of the ophthalmic division from the trunk of the third cranial nerve. Of course, there had been at least 11 similar reports (describing 18 patients) prior to Lance and Zagami's[3] article.

However, only 1 year later, Carlow[4] reported similar findings in six children with OM and offered an excellent hypothesis encompassing the then-known migraine pathophysiology that would be convincing enough to consider OM a migraine variant. Thus, where do we stand? The concept of OM remains debatable even today as we have no histologic/immunologic evidence about the exact pathology. However, ICHD is primarily a clinical classification system based on clinical characteristics and radiological findings. And, to call a headache disorder "secondary" or nonprimary may be problematic when the cause–effect relationship is not clear and purely hypothetical.

Ravishankar[5] made an excellent summary of all cases of OM reported between 1993 (that is after availability of MR imaging) and 2007 (including three patients of their own) and pleaded for a new classification system and diagnostic criteria. Lance and Davies[6] described only two patients of OM but with diverse

clinical details pointing out the heterogeneous nature of OM and also pleaded for an all-encompassing new classification. In an editorial following this and another report, Friedman[7] has proposed a new classification of OM in 2009. However, this new system is also not unambiguous and, although the editorial mentions of a large series of OM patients (mostly adults) from India by Lal *et al.*,[8] an essential feature highlighted in this study, is not reflected in the proposed classification. And, this is the difference in clinical and radiological features between childhood-onset and adult-onset patients with OM. We are also not at ease with introduction of the term "probable" in a condition with a positive clinical sign where use of such adjectives would only increase the preexisting confusion rather than clarifying it.

In this communication, we would first present our own observations on OM seen over 5 years and would then proceed to describe a more simple classification and diagnostic criteria for this vexing disorder.

Summary of case studies of OM: Our experience (2005–2010)

Between June 2005 and May 2010, we encountered 18 new cases of OM in our general neurology clinic, which mostly caters to adult patients. All cases fulfilled the ICHD2 diagnostic criteria of OM except that all had single attacks initially (but had past history of having had several attacks of migraine without aura [MAO]). The total number of headache patients seen during this period would be approximately 4000, yielding an approximate clinic incidence of OM to be 0.45%. The age of the subjects at presentation varied from 27 to 51 years (mean – 37 years) and there were 13 female and five male patients. No patient had past history of ophthalmoplegia, but all suffered from MAO in the past for 6–14 years. However, none ever had been on any migraine prophylaxis on a regular basis. None reported any systemic symptoms. Diabetic painful carnial neuropathy, ophthalmoplegia from tubercular basal meningitis, Tolosa-Hunt syndrome, orbital myositis, sarocoidosis, unruptured infraclinoid aneurysm of internal carotid artery and parasellar tumors were carefully excluded by detailed clinical examination and appropriate investigations like hematology, routine blood biochemistry, cerebrospinal fluid (CSF) studies in some, contrast MR imaging of brain and orbits and MR angiography.

Investigations

All 18 cases underwent detailed hematological (including coagulation profile), biochemical (including lipid profile and glucose tolerance test) and vasculitis screening tests (ESR, C-reactive protein, rheumatoid factor, ANA, DS-DNA, P-ANCA and C-ANCA) and chest radiographs. All these yielded normal results. All underwent contrast-enhanced MR scan of brain and orbit using 3 mm slices with a 1.5T scanner and the region of the basal cisterns and cavernous sinuses were carefully examined. All yielded normal results. MR angiographies were performed in the same sitting and were normal in all cases. CSF studies were performed in seven cases, and yielded normal results.

Pain

Pain was ipsilateral to the ophthalmoplegia in all, involving the orbit, periorbital, frontal and temporal regions. In eight patients, pain spread to the occipital region but none reported holocranial pain. Pain was pulsatile (like their previous migraine headaches) in most (12 cases) and aching/boring in nature in six. It was variable during the day from moderate to severe and, in all cases, was associated with nausea and photo and/or phonophobia but with vomiting in a minority (three cases). None reported any increase in frequency or severity in their migraine attacks preceding the pain onset that led to ophthalmoparesis.

Duration

Time from onset of pain to ophthalmoplegia varied from 4 to 7 days (mean 5.5 days). Pain persisted all along till presentation to clinic (2–6 days) and continued till institution of therapy. In no case did pain subside with onset of ophthalmoplegia.

Ophthalmoplegia

Of the 18 cases, 14 had sixth nerve palsies and the remaining four had palsies of the third cranial nerve. No case had more than one ocular motor nerve involvement. None had any sensory loss in the distribution of the ophthalmic division of trigeminal nerve. Detailed clinical examination did not reveal any other abnormal neurological signs.

Therapy

Based on our previous experience with a few similar cases, after full investigations, all cases were started on prednisolone 40–60 mg/day and continued for 5 days, after which the dosage of corticosteroids was gradually reduced and finally stopped in 2 weeks.

Follow-up

Pain subsided in all in 4–7 (mean 5.8) days time after institution of therapy, but ophthalmoparesis took 9–16 (mean 11) days to recover fully in all cases as assessed by disappearance of diplopia and return of full ocular movements. Orbital myositis, which is also steroid responsive, had been earlier excluded by contrast-enhanced MR imaging of brain and orbits.

All cases were followed-up for at least 6 months. In two patients, symptoms recurred within 4 and 7 weeks of withdrawal of corticosteroids. One developed pain with recurrence of ophthalmoplegia and one developed similar pain only but with vomiting. Both were restarted on steroids. Both became asymptomatic in 7–10 days time. Both had repeat neuroimaging (with contrast), which yielded normal results. These two cases apart, five more cases developed mild to moderate ipsilateral pulsatile headaches after about 3 months of therapy withdrawal and were started on Flunarazine (a Ca-channel blocker) to which they responded.

Discussion

Ophthalmoplegic migraine or ophthalmoplegia with migraine-like headache (OMLH)?

There is no denying the fact that as many adult-onset cases of Ophthalmoplegic migraine described so far had past history of having had migraine headaches, commonly MOA. OM as it is generally perceived has some relationship to migraine. Unfortunately, long-term follow-up data of children presenting with ophthalmoplegia is not available. However, whether

migraine is related to the pathogenesis of the ophthalmoplegia or not may be debatable. In general, the headache preceding the development of cranial nerve palsy often lasts more than 4 days, often particularly severe and does not always disappear with the development of nerve palsy. Hence, it would be somewhat controversial to call the headache preceding nerve palsy as "migraine," ICHD2[1] and some authors have called the headache "migrainous" – literally meaning "migraine like" and some authors have used the term "migraine-like" as well. We therefore feel that perhaps a noncontroversial term such as OMLH would be more appropriate than simple OM.

Use of the term "probable"

Use of the term "probable" in disease nomenclature always increases confusion. Friedman[7] in her proposed classification of OM mentions of "probable" primary OM and "probable" secondary OM, based on ICHD2[1]-defined probable migraine headache. However, a close look at ICHD2[1] would reveal that the term "probable migraine" has been equated with a previously used term "migrainous disorders" – the term "migrainous" had been used by some authors in relation to OM. Also, ICHD-2 has linked the term "probable migraine" with "symptomatic migraine" under secondary headaches. Therefore, the use of the term probable primary OM is confusing if Friedman[7] believes the cases of OM without nerve enhancement to be "primary" cases. Similarly, use of the term "probable" in secondary OM (according to Friedman[7]) seems redundant as ICHD2 had already linked "probable migraine" with symptomatic migraine in relation to AVM and migraine-like headaches and medication overuse headaches (secondary headaches disorders).

Childhood-onset and adult-onset OM

Excluding Lal *et al.*'s[8] large series (62 patients – all adults), from 1993 to 2010, a total of 68 patients of OM have been described (children 38; adults 30). A further case of childhood-onset OM has been described more recently by Lyerly *et al.*[9] Ravishaknar[5] reviewed all cases published between 1993 and 2007. In children, all presented with third nerve palsies; in adults (*n*=30), there had been 17 with third nerve and 13 with sixth nerve palsies. This probably suggests that the incidence of sixth nerve palsy rises as presentation age advances. If Lal *et al.*'s[8] series is added, then we would have 92 adult-onset OM – 38 with third nerve and 48 with sixth nerve palsies. A few had more than one cranial nerve palsy and five had fourth nerve palsy (we are not sure whether cases with more than one nerve palsies should be called OM). Lane and Davies[6]'s case 2 is of interest that an adult patient had onset with a third nerve palsy but, several years later, developed an opposite-sided sixth nerve palsy with headache. Long follow-up of cases of OM therefore seems mandatory. Excluding Lal *et al.*'s series, in children, out of 39 third nerve palsies, 36 showed enhancement/thickening. But, in adults, out of 17 third nerve palsies, nine showed enhancement and out of 13 sixth nerve palsies, only two showed contrast enhancement – one in the intrapontine part[10] and one in the cisternal part of the nerve.[11] In none of the 62 adult patients of Lal *et al.*[8] could contrast enhancement be detected. The same had been our experience with a modest series of 18 patients as described earlier. Are we then looking at different pathologies in adults and children? Or, do the finer structure of the nerve trunk or the capillary walls of the microvasculature supplying the nerves change

with advancing age? We do not know the answers as we are still debating about the cause of the enhancement and debating which is the fire and which is the ash (nerve enhancement due to demyelination or migraine-like headache).

Which is the fire and which is the ash?

Current ICHD2[1] concept in classifying OM, based on the hypothesis of an inflammatory demyelinating process in the ocular motor nerves causing trigemino-vascular activation resulting in a migraine-like headache, was proposed by Lance and Zagami[3] and supported by Daroff,[2] Response of OM to corticosteroids may be a supportive evidence in favor of this hypothesis. However, the near-dramatic response to corticosteroids often seen in OM patients is not generally seen in other demyelinating neuropathies elsewhere in the body (like CIDP). In fact, some chronic demyelinating neuropathy may worsen with high-dose steroids, like multifocal motor neuropathy with conduction block (and even sometimes acute inflammatory demyelinating neuropathy). As already stated, the relationship of OM to migraine cannot be denied as adult-onset OM often occurs in migraine pain sufferers. This may not be apparent in children but long-term follow-up data on such children is not available to see how many of them would develop migraine with or without aura later in life. Carlow's[4] proposition of a neurovascular hypothesis seems more convincing. Carlow[4] noted that there is a uniquely intimate relationship between the third nerve root exit zone and the arteries of the circle of Willis (posterior cerebral and posterior communicating), which are highly innervated by the first division of trigeminal nerve, an integral part of the trigemino vascular reflex in migraine pathogenesis. Activation of this releases neuropeptides and other yet unidentified agents that would affect the adjacent nerve causing recurrent demyelination and remyelination with recurrent attacks of migraine. This would cause both nerve thickening and enhancement. Experimental studies[6] have shown that there is upregulation of a metalloproteinase (MMP) that would target components of the capillary junction, comprising the blood–brain (and likely the blood–nerve) barrier. Benefit of steroids in OM could be related to blocking the release of MMP. How would one account for the sixth nerve involvement, which is yet to be highlighted in the literature? A close look at the anatomical course of the sixth nerve shows that after its exit at the lower border of pons, it first comes close to the anterior inferior cerebellar artery and, finally, in the cavernous sinus, it lies almost on the wall of the internal carotid artery itself. Hence, the neurovascular hypothesis proposed by Carlow[4] can certainly be applied in the case of the sixth nerve as well. There is a solitary report of fourth cranial nerve enhancement.[12] The fourth nerve lies in close proximity to the superior cerebellar and posterior cerebral arteries, as it curves around the crus cerebri from the dorsal to the ventral aspect. While it is possible that heterogeneous pathological processes are involved in the pathogenesis of OM (which would not be settled till histopathological studies are available), in view of the arguments presented above, we feel that OM/OMLH need to be classified in conjunction with migraine in any forthcoming classification system.

We have intentionally avoided discussing the pathogenetic hypothesis relating to migraine vasodilatation and compression of cranial nerves as the vascular mechanism of migraine is a

controversial subject[13] and migraine-induced intracranial vasodilatation has not been conclusively demonstrated by angiographic studies.[14] Furthermore, the nerve ischemic hypothesis (highlighted in the articles by Lal *et al*.[8] and Lal[15]) is also perhaps not valid because of the near-dramatic response to steroids in many cases of OM. The latter would favor an inflammatory (neurovascular as applicable to migraine) rather than an ischemic pathology. Response of intractable migraine headaches to corticosteroids is well known. In view of the discussion made above, when we are not sure about the pathophysiology of OM, classifying these cases as primary and secondary[7] at the current state of our knowledge would be premature.

Proposed reclassification

There should be a good reason for proposing a new diagnostic criteria for a specific condition. One reason would be to clarify thinking about a condition and one would be to guide evaluation and treatment. The ICHD2 concept of OM is based on a hypothesis that has not yet been proved. Friedman's[7] classification is based on some apparently premature notion of primary and secondary OM and, again probable and perhaps definite OM, none of which can have a confirmed pathophysiologic basis. For the time, therefore, classification needs to be based on clinical history, physical findings and imaging features. The nomenclature and diagnostic criteria need to be simple and free of ambiguity as far as practicable. In view of the brief but critical review of the world literature of OM made above and taking into consideration Lal *et al*.[8]'s large series and our own observations mentioned in this article and the discussion made thereof, we propose the following classification of OMLH. We are a little hesitant about the nosology of cases described earlier, where prior history of having had ICHD2 defined migraine were lacking. For the time, such cases are being included within the rubric of OMLH, but it is expected that this might be changed in the future.
We classify OMLH as a migraine subtype.

OMLH

Definition

This syndrome would include cases of ocular motor nerve palsies involving one ocular motor nerve preceded by ipsilateral migraine-like headache where other conditions of painful ophthalmoplegias have been carefully excluded by appropriate investigations. Such conditions include diabetic cranial neuropathy, Tolosa Hunt syndrome, polyneuritis cranialis of undetermined etiology, orbital myositis, infraclinoid aneurysm, vasculitic diseases, basal meningitis, other granulomatous diseases like sarcoidosis, parasellar tumors, cranial nerve schwannomas and others. Diagnosis can be made on the basis of a single attack only provided the patient had had at least five attacks of HIS-defined migraine with or without aura in the past.

Classification

- OMLH with onset in childhood (15 years or below)
  - With nerve thickening and/or enhancement in Gd-contrast enhanced MR brain scan (commonly third cranial nerve palsy occurs)
  - Without nerve thickening or enhancement in Gd-contrast enhanced MR brain scan (any ocular motor nerve may be involved)
- OMLH with onset in adult life (above 15 years age) (commonly sixth cranial nerve involved)
  - Without nerve thickening or enhancement (common)
  - With nerve thickening and/or enhancement (uncommon)

Diagnostic criteria for all types and subtypes

- Unilateral headache involving orbit, periorbital and frontal areas (may involve ipsilateral temporal or occipital area) preceding onset of ophthalmoplegia by 1–7 days.
- Migraine-like features include headache with at least two of the following features including either of 1 and 2.
  - Pulsatile quality
  - Severe aching or boring
  - Nausea and/or vomiting accompanying headache
  - Photophobia and/or phonophobia
- Ophthalmoplegia should involve only one ocular motor nerve and never the ophthalmic division of trigeminal nerve. Rare cases of isolated pupillary autonomic involvement may be included.
- Not attributed to any other disorder.

Note

- Diagnostic criteria A to D must be fulfilled. Adult patients with OMLH often have past history of having had 1.1 or 1.2 migraine headache. However, in children, OMLH may be the first manifestation of migraine. Long-term follow-up data in such subjects is not available.
- Contrast MR imaging of brain and orbits including MR angiography is a must for diagnosis of OMLH. Gd-enhanced studies to be done with 3 mm slices using 1.5T MR scanners only. Detailed laboratory investigations including hematology, coagulation profile, vasculitic markers and chest radiographs are essential.
- Tolosa–Hunt syndrome to be excluded using diagnostic criteria proposed by Colnaghi *et al*.[16]
- Steroids generally hasten relief of pain and ophthalmoplegia, but should be used only after exclusion of all conditions mentioned in the definition. Indomethacin may be useful in steroid-unresponsive cases.[17] Lack of or inadequate response to steroids should not exclude diagnosis of OMLH if other conditions are fulfilled.
- Recurrences with pain and ophthalmoplegia or only periorbital pain may occur, and usually responds to steroids with or without migraine prophylactic agents.

Concluding Remarks

We have classified OM as a migraine subtype and feel that the ocular palsy pathogenesis is intimately related to the migraine process. We however feel that some neurologists, while subscribing to our view that OM is essentially a migraine-related phenomenon, might feel happier to classify OM as a complication of migraine (1.5). This would simply be a matter of semantics without having any pathophysiological significance.

The classification system proposed above does not in any way hint at any essential pathophysiological difference between

childhood-onset and adult-onset cases. This is entirely based on so far described phenomenology of the syndrome and imaging features. We feel the proposed classification system addresses the two fundamental requirements of any new diagnostic criteria as mentioned earlier in this article.

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