Recurrent Painful Ophthalmoplegic Neuropathy: Migraine, Neuralgia, or Something Else?

Dejan Z. Aleksic, MD, PhD(c)
Svetlana Miletic Drakulic, MD, PhD
Department of Neurology
Faculty of Medical Sciences
University of Kragujevac,
Kragujevac, Serbia

Srdjan Ljubisavljevic, MD, PhD
Department of Neurology
Faculty of Medicine
University of Niš
Niš, Serbia

Correspondence to:
Dr Dejan Aleksic
Department of Neurology
Faculty of Medical Sciences
University of Kragujevac
Svetozara Markovica 69
34000 Kragujevac, Serbia
Fax: +38134370166
Email: drdeal1987@gmail.com

Submitted January 13, 2020; accepted June 20, 2020.
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Recurrent painful ophthalmoplegic neuropathy (RPON) is a very rare disease characterized by recurrent attacks (at least two) of unilateral headache associated with ipsilateral ophthalmoplegia due to paresis of one or more cranial motor nerves, not due to any orbital, parasellar, or posterior fossa lesions. The differential diagnoses for this condition are broad. In addition to disability during an acute attack, this disease could also cause a permanent neurologic deficit.

The understanding of RPON pathogenesis has changed over time, leading to a change in the classification of this disorder between editions of the International Classification of Headache Disorders, in which the condition was moved from the chapter on migraine to the chapter on cranial neuralgias and central causes of facial pain. There is no consensus on the pathogenesis of RPON. It is possible that multiple pathogenic mechanisms underlie various clinical forms of the disease. A depiction of pathologic analyses of patients with radiologically confirmed changes in the affected nerves during and outside of attacks would significantly contribute to knowledge of its pathogenesis. Brain imaging should be performed in each patient during an acute RPON attack and at a regular schedule between attacks. Further case reports and case series are required before further conclusions can be made regarding RPON pathogenesis and proposals for treatment options.

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Keywords: headache, migraine, neuropathy, ophthalmoplegia, painful ophthalmoplegic neuropathy, pathogenesis, RPON

Before the First Headache Classification (up to 1988)

In 1860, Gubler first described a patient who had recurrent episodes of oculomotor nerve paresis associated with a migraine-like headache. An autopsy of the patient showed a thickening of cranial nerve III as a consequence of neurosyphilis. Mòbius had called this disease “ocular periodic paralysis,” while Charcot used the term “migraine ophthalmoplegique” to describe a series of cases with this feature.

Initial assumptions about the pathogenesis of this disease were as follows: inflammation of cranial nerves III and VI occurs as the result of aneurysm compression; a transient pituitary edema forms with com-
pression of the cavernous sinus and cranial nerves; and vascular tone changes occur due to dilatation or aneurysm of a posterior communicating artery, causing compression on cranial nerve III.21

### Between the First and Second Headache Classifications (1988–2004)

In the ICHD-1 from 1988, RPON was called ophthalmoplegic migraine (OM) and classified as a subspecies of migraine headache. The definition of this disease was repeated attacks of headache associated with paresis of one or more ocular cranial nerves in the absence of a demonstrable intracranial lesion; however, whether OM has anything to do with migraine was questioned, since the headache often lasts for a week or more14 (Table 2). Brain MRI revealed thickening of the initial part of cranial nerve III in patients with clinical presentations suggestive of OM; among them, one was definitively diagnosed as having OM, while others were diagnosed with the following: lymphoma; leukemia; viral meningitis; neurofibromatosis; HIV polyneuropathy; Tolosa-Hunt syndrome; coccidioidomycosis; and diabetic neuropathy.22 The introduction of MRI into the diagnosis of this disease led to the development of two possible theories of OM pathogenesis.

### Migraine Pathogenesis: Primary Pathogenesis of Migraine with Secondary Neuropathy

Patients with thickening of the initial part of cranial nerve VI in the dorsal part of the brainstem on brain MRI have been reported. In this part of the brainstem is the raphe nucleus system, which produces serotonin, a neurotransmitter crucial for migraine pathogenesis.23 An analysis of 23 cases with thickening of cranial nerve III showed that trigeminovascular system activation during a migraine attack and release of neuropeptides in the bloodstream caused recurrent inflammatory processes, such as demyelination and remyelination, which are responsible for the thickening of the cranial nerve noted on the brain MRI.24

### Neuropathic Pathogenesis: Inflammatory and Demyelination Processes

There are results of six patients with thickening of the initial part of cranial nerve III during the acute phase of OM. After the spontaneous clinical resolution, no changes in the control brain imaging were detected. It was assumed that a benign viral infection leads to inflammatory changes in cranial nerve III, clinical findings, and the changes visible in the MRI brain scans. The migraine symptoms and signs were explained as a consequence of changes in vasomotion caused by

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**Table 1 Differential Diagnoses of RPON**

<table>
<thead>
<tr>
<th>Differential Diagnoses of RPON²⁻¹²</th>
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<tbody>
<tr>
<td>Tolosa-Hunt syndrome</td>
<td>Infections; eg, meningitis, Lyme disease, sarcoidosis, sympathetic, fungal, tuberculosis, HIV</td>
</tr>
<tr>
<td>Orbital myositis</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Neoplastic diseases; eg, pituitary adenoma, meningioma, craniopharyngioma, sarcoma, neurofibroma, epidermoid, chordoma, giant cell tumor, metastasis, nasopharyngeal cancer/carcinoma, squamous cell carcinoma, lymphoma, multiple myeloma, oculomotor nerve schwannoma</td>
<td>Miller Fisher syndrome</td>
</tr>
<tr>
<td>Vascular diseases; eg, aneurysm, thrombosis, carotid-cavernous fistula</td>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td>Brainstem ischemia</td>
<td>Idiopathic intracranial hypertension or hypotension</td>
</tr>
<tr>
<td>Mass lesions</td>
<td>Thyroid opthalmopathy</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Vincristine therapy</td>
</tr>
<tr>
<td>Microvascular cranial nerve palsy</td>
<td>Narrow-angle glaucoma</td>
</tr>
<tr>
<td>Traumatic nerve palsy</td>
<td>Granulomatosis with polyangiitis</td>
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</table>

**Table 2 Evolution of Diagnostic Criteria for RPON**

<table>
<thead>
<tr>
<th>ICHD-1, 1988¹⁴</th>
<th>ICHD-2, 2004¹⁵</th>
<th>ICHD-3, 2018¹⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. At least two attacks fulfilling criterion B</td>
<td>A. At least two attacks fulfilling criterion B</td>
<td>A. At least two attacks fulfilling criterion B</td>
</tr>
<tr>
<td>B. Headache overlapping with paresis of cranial nerves III, IV, and/or VI</td>
<td>B. Migraine-like headache accompanied by (within 4 days of onset) paresis of cranial nerves III, IV, and/or VI</td>
<td>B. Both of the following: 1. Unilateral headache 2. Ipsilateral paresis of cranial nerves III, IV, and/or VI</td>
</tr>
<tr>
<td>C. Parasellar lesion ruled out by appropriate investigation</td>
<td>C. Parasellar, orbital fissure, and posterior fossa lesions ruled out by appropriate investigation</td>
<td>C. Orbital, parasellar, and posterior fossa lesions ruled out by appropriate investigation</td>
</tr>
<tr>
<td>D. Not better accounted for by another ICHD-3 diagnosis</td>
<td></td>
<td></td>
</tr>
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inflammatory processes of cranial nerve III. Some results suggested that OM is more probably caused by demyelinating and/or inflammatory neuropathy. Demyelination of the initial part of cranial nerve III has been considered a consequence of intraneural edema, which was also confirmed in experimental and clinical demyelinating neuropathy. The headache appearance in that inflammatory condition is a consequence of the inflammatory process affecting the ophthalmic branch and activating the trigeminovascular system. Even then, there were suggestions that OM could be classified as cranial neuropathy in future classifications. Some authors confirmed an inflammatory pathogenesis based on an elevated immunoglobulin index in cerebrospinal fluid (CSF) seen during OM attacks. Again, all presumed inflammatory processes were recognized as the “triggers” for migraine attacks.

Between the Second and Third Headache Classifications (2004–2018)

In the ICHD-2 from 2004, RPON was moved from the chapter on migraine to the chapter on cranial neuralgias and central causes of facial pain. The definition was recurrent attacks of headache with migraineous characteristics associated with paresis of one or more ocular cranial nerves (commonly the third nerve) in the absence of any demonstrable intracranial lesion, other than MRI changes, within the affected nerve. In some cases, MRI showed a gadolinium uptake in the cisternal part of the affected cranial nerve, which suggests that the condition may be a recurrent demyelinating neuropathy, as was the comment at that time.

Migraine Pathogenesis

The absence of any infection in almost all patients with OM and normal biochemical and cytologic findings in CSF speak against the hypothesis of trigeminovascular system activation via an inflammatory process. Also, this hypothesis cannot explain the pain associated with paresis of cranial nerves IV and VI. Some authors have pointed out that OM might be a clinical complication of severe migraine attacks and found that a majority of OM patients have previous chronic migraine, with clinical worsening of migraine during OM attacks. Since OM has been believed to be a trigger of migraine, its pathogenesis has been considered to be vascular. These authors suggested, therefore, that OM should remain classified as a migraine. In line with these notions, transient ischemia of the thalamus on the same side as the transient headaches and paresis of cranial nerve VI has been confirmed. It has been recommended to split OM into two clinical phenotypes: one at a juvenile age, including thickening of cranial nerve III visible on brain MRI; and one in adulthood, with more frequent involvement of cranial nerve VI and rare thickening of this nerve on brain MRI. There is a report showing neurovascular contact between the beginning of cranial nerve VI and the basilar artery, as well as the anterior inferior cerebellar artery, in a patient with OM and involvement of cranial nerve VI. This pathogenesis was explained by the vasodilation of blood vessels during the migraine attack followed by compression of the cranial nerve VI root. The reversible ischemic interruption of the blood-brain barrier due to changes in vasomotion during a migraine attack has been also proposed as a possible theory of OM pathogenesis. This neurovascular hypothesis led to the new name for OM, ophthalmoplegia migraine-like headache (OMLH). This proposed classification included OMLH starting prior to and starting after 15 years of age. Different pathogeneses have been suggested depending on the time of OMLH onset and whether OMLH was a result of the thickening of a nerve due to demyelination or migraine aggravation. While a majority of patients have severe attacks of migraine-like headache followed by ophthalmoplegia, if the neuropathy is a cause of OMLH, it would be reasonable to expect a much larger number of patients with ophthalmoplegia preceding the headache.

Neuropathic Pathogenesis

There was insufficient evidence of a structural lesion, a systemic inflammatory response, an intrathecal inflammatory response, a viral infection, or a tumor (schwannoma) in OM. The demyelination and remyelination could explain the thickening of the affected cranial nerve on brain MRI during OM attacks. It was concluded that this condition would be more appropriate classified as recurrent ophthalmoplegic cranial neuropathy. There is a report of a series of cases showing changes in CSF and affected cranial nerve IV, so the question is whether the rarest form of OM, including cranial nerve IV, is etiologically different from classic OM.

Two different forms of OM and two possible pathogenesis mechanisms. Based on the results that negative findings on brain MRI do not exclude the diagnosis of OM, two categories of OM have been suggested: with changes in brain MRI (inflammatory and/or demyelinating), and without changes in brain MRI (noninflammatory). It remains unclear whether OM migraine is a demyelinating or inflammatory process.

Tumor pathogenesis. A report of patients who had OM for more than 45 years and thickening of cranial nerve III on brain MRI during the acute phase of the disease was published. In the sixth decade of life, a patient experienced progression of the disease, and after that, a biopsy of the affected nerve showed neuromuscular hamartoma. The pathogenesis as suggested includes the following: the release of chemical...
substances from the tumor, activation of the trigeminovascular system, vasodilation of the blood vessels that supply cranial nerve III, contraction of neuromuscular hamartoma, and paralysis of the affected nerve.38

The Latest Headache Classification (2018–Present)

In the ICHD-3 from 2018, the term OM was replaced by RPON. According to the latest definition, RPON is characterized by repeated attacks of paresis of one or more ocular cranial nerves (commonly III) with ipsilateral headache. RPON replaced the term OM based on the fact that gadolinium enhancement, or nerve thickening, can be demonstrated on brain MRI. Treatment with corticosteroids is beneficial in some patients.36 Diagnostic criteria for RPON are at least two attacks of unilateral headache accompanied by ipsilateral paresis of one, two, or all three ocular motor nerves (III, IV, or VI). Orbital, parasellar, or posterior fossa lesions can be ruled out with appropriate investigation16 (Table 2).

There are reports of patients with RPON who turned out to have schwannoma of cranial nerve III. RPON pathogenesis has been understood as the consequence of a release of chemical substances from the tumor resulting in activation of the trigeminovascular system. Inflammation, demyelination, and remyelination have been also confirmed. It has been concluded that in all patients with an MRI change in the affected nerve and incomplete recovery, a possible tumor etiology must be considered.9 Serial brain MRIs during acute exacerbations and between attacks are essential in the long-term follow-up of patients, as the negative findings of an MRI do not rule out the possibility of future evidence of the tumor.39

RPON has been defined as a syndrome that can be primary or secondary. Patients with clinical OM without cause and without changes in brain MRI experiencing a spontaneous passage of symptoms should be diagnosed as having primary RPON, which should be considered a form of migraine. Secondary RPON is associated with a change in brain MRI, likely recurrent inflammatory demyelination or cranial mononeuropathy.40 It has been shown that most patients have a history of previous migraine and no contrast enhancement of the nerve root on MRI.29 There is a report of a patient having recurrent painless steroid-sensitive cranial nerve paresis unaffected by migraine prophylactic therapy.41 Smith and Schuster suggested two clinical phenotypes of RPON, which could explain the absence of a unifying theory of pathogenesis that would satisfy all cases of this disease.42 Interestingly, there are suggestions that OM should not be forgotten and should be considered together with RPON in differential diagnoses of headache associated with ophthalmoplegia.43

The present authors have shown two patients with RPON (a patient from a Romani population and an 82-year-old patient) who can contribute to the future consideration of the pathogenesis of this disease. These are cases without MRI findings that may be grouped using the previous suggestion of a primary-type presentation.45,43 There are also larger series of patients with ophthalmoplegia and migraine.29 Symptoms began in the adult period in these patients, and no patients showed any changes in MRI. The unique genetic heritage of Roma people has been known to be prone to certain neuromuscular diseases (especially neuropathies).44 RPON is considered a disease of childhood and younger age. An older age implies a weakening of the mechanisms of transduction, modulation, and nociception (all parameters of the pain matrix documented by neuroimaging studies), and there is evidence of a decrease in neurohumoral pain mediators45; however, there are also patients who experience first onset of the disease in old age. The present authors studied a case in an 82-year-old previously healthy man with two episodes of nerve palsy (IV), who is the oldest RPON patient to date.46

Conclusions

There is no consensus on the pathogenesis of RPON, as it a very heterogenous disease. It is possible that multiple pathogenic mechanisms underlie various clinical forms of the disease. A depiction of pathologic analyses of patients with MRI-confirmed changes in the affected nerves during and outside of the disease attack would significantly contribute to knowledge of the RPON pathogenesis. Brain MRI should be performed in each patient during acute attack of RPON and at a regular schedule between attacks. Further case reports and case series are required before further conclusions can be made regarding its pathogenesis and proposals for treatment options.

Highlights

- RPON is a rare disorder with repeated episodes of ocular cranial nerve neuropathy associated with ipsilateral headache. Orbital, parasellar, or posterior fossa lesions can be excluded by appropriate investigation.
- Multiple pathogenic mechanisms underlie various clinical forms of the disease. Migraine pathogenesis, neuropathy pathogenesis, and tumor pathogenesis are the most investigated pathogenetic mechanisms.
- Future investigation and better understanding of pathogenesis are needed to clarify diagnosis and treatment of RPON.
Acknowledgments

The authors report no conflicts of interest. Author contributions: D.A.: wrote paper; S.M.D.: analyzed data, wrote paper; S.L.: designed and performed research/study, collected and analyzed data, wrote paper.

References