CASE REPORTS

A Case of Recurrent Painful Ophthalmoplegic Neuropathy with Associated Oculomotor Nerve Tumour

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ABSTRACT

Recurrent painful ophthalmoplegic neuropathy (RPON) replaced the term 'ophthalmoplegic migraine' as the condition behaves more like an inflammatory cranial neuropathy than a primary headache disorder. RPON may be associated with cranial nerve thickening on MR imaging and persistent oculomotor paresis. Oculomotor tumours have rarely been described in cases of relapsing painful ophthalmoplegia with and without persistent paresis. Here, we present a case of relapsing painful left ophthalmoplegia that gradually became persistent. MR imaging after 14 years of symptoms revealed an enhancing tumour of the left oculomotor nerve. It is unclear whether the tumour was the cause of the attacks or whether repeated cycles could lead to tumour development. MR imaging is indicated in patients with RPON who develop persistent deficits to screen for associated oculomotor tumour.

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Introduction

Recurrent painful ophthalmoplegic neuropathy (RPON) replaced 'ophthalmoplegic migraine' in the third edition of the International Classification of Headache Disorders.¹ RPON is characterised by repeated attacks of headache and ipsilateral ophthalmoplegia (most commonly oculomotor nerve paresis). It usually presents in children and can persist into adulthood.² The oculomotor nerve is typically involved but trochlear or abducens paresis is infrequently observed.²

The reclassification occurred as it was agreed that the condition behaves more like a cranial neuropathy than a primary migraine disorder.³ The interval between headache and ophthalmoplegia (up to 14 days), the focal oculomotor nerve enhancement and thickening observed on MRI during attacks and the beneficial effect of corticosteroids observed in some patients are all features more consistent with an inflammatory cranial neuropathy.^{2,3}

Symptoms usually last for 2–3 weeks with complete recovery between attacks.² Persistent oculomotor paresis develops in 54% of patients, typically after many years of relapsing disease.² During acute

attacks, MR imaging reveals oculomotor nerve thickening in 76% of cases and gadolinium enhancement in 75% of cases.² During quiescent periods, the enhancement typically resolves, whereas the nerve thickening may last for weeks to months or, in rare cases, persist permanently.⁴

Persistent ophthalmoplegia after an initial relapsing–remitting disease trajectory is rarely associated with oculomotor nerve tumours.^{5–9} Interictal oculomotor nerve contrast enhancement on MR imaging is not consistent with RPON. In cases of histologically proven oculomotor nerve schwannoma, the lesions demonstrate intense gadolinium enhancement and appear isointense to brain parenchyma on T1-weighted images and hypointense on T2-weighted images.^{7,10}

We describe an unusual case of relapsing painful ophthalmoplegia that became persistent after 14 years of symptoms and discuss its implications.

Case presentation

A 15-year-old Caucasian male presented with recurrent stereotyped episodes of left supraorbital pain followed by left oculomotor paresis. He had

no significant past medical history and there was no family history of neurological diseases, including migraine.

The first episode occurred when he was 10 months of age. His mother remembered that he woke that morning with a swollen and closed left upper eyelid. The left pupil was dilated and the left eye was deviated down and out. He had further attacks, 1 year and 3 years after the initial episode. Thereafter, he had approximately three episodes per year. Each attack began with severe stinging pain above the left eye that lasted for between 5 and 7 days. Two or 3 days into an episode, the left eyelid drooped and the left eye was displaced outwards. The oculomotor paresis lasted for between 2 and 3 weeks.

A diagnosis of possible RPON was made following the first three attacks. Oral (prednisolone 30 mg daily for 1 week) and intravenous (methylprednisolone 1000 mg daily for 5 days) corticosteroids were the only treatments that helped during episodes. Sumatriptan, Propranolol and Topiramate were ineffective. Initially, a complete recovery was achieved between attacks. However, more recent attacks appeared less steroid-responsive and a mild left oculomotor paresis and mydriasis has persisted. There were no other cranial neuropathies on examination. Visual acuity was normal.

Cranial non-contrast CT and MR scans were performed in childhood, but these images were not available for review by the authors. Radiologists working at the National Children's Hospital reported that the imaging was unremarkable. Mild residual left oculomotor paresis between attacks prompted the request of up-to-date imaging. An MR scan of brain showed a 0.4×0.5 cm enhancing nodular segment of the left oculomotor nerve (Figure 1). T2 constructive interference in steady state (CISS) sequences, which are useful in the assessment of cranial nerves, were ordered to further characterise the lesion (Figure 1D).

The patient had three further attacks of painful ophthalmoplegia over the next 12 months with stable persistent left oculomotor paresis between episodes. MR imaging performed 4 months after the last attack and 14 months after the previous scan showed an unchanged left oculomotor nerve lesion with persistent enhancement (Figure 2).

These radiological features are similar to those observed in pathologically confirmed cases of oculomotor schwannoma, one of which mimicked RPON.^{7,10}

Discussion

This patient presented with relapsing unilateral painful ophthalmoplegia with some initial response to corticosteroid. Over time, oculomotor paresis became persistent. His imaging after 14 years of symptoms showed an enhancing nodular lesion on the cisternal segment of the left oculomotor nerve (Figure 1). MR imaging 14 months later showed similar findings (Figure 2).

Uncertainty about the underlying pathophysiological mechanisms of RPON led to its reclassification in the International Classification of Headache Disorders.¹ It was originally considered a primary migraine disorder characterised by recurrent paroxysms of painful oculomotor paresis with complete recovery between attacks and normal neuroimaging.^{2,3} 'Ophthalmoplegic migraine' was replaced with RPON as gradually persistent oculomotor paresis and focal MRI findings were increasingly recognised.¹⁻⁴ A systematic review found oculomotor enhancement or thickening on MRI in more than three quarters of cases.² Typically, the swelling and enhancement resolve once the oculomotor palsy remits.⁴ Persistent deficits are noted in more than half of cases.²

We found eight reported cases of oculomotor tumour associated with relapsing painful ophthalmoplegia (Table 1).⁵⁻⁹ In all cases, MRI performed between attacks demonstrated persistent focal nodular enhancement of the oculomotor nerve with similar findings on follow-up imaging. One case revealed pathologically proven schwannoma following resection.⁷ Half the patients had their first attack of painful ophthalmoplegia in adulthood. In Gelfand and colleague's systematic review of RPON cases, the median age at the time of first attack was 8 years.²

The mean duration of relapsing painful ophthalmoplegia in cases of oculomotor tumour is just over 12 years.⁵⁻⁹ In patients with oculomotor tumours, attacks of ophthalmoplegia and ptosis typically last between 1 week and 6 months.

Figure 1. There is a 5 mm lesion arising from the left oculomotor nerve in its cisternal segment. Coronal T1-weighted sequence (A) shows that the lesion (black arrow) is isointense to grey matter. The coronal T1-weighted gadolinium enhanced sequence (B) shows homogeneous enhancement of the lesion post contrast. Coronal T2-weighted sequences (C) show that the lesion is hypointense to grey matter. These signal characteristics are consistent with, but not specific for, a schwannoma arising from the left oculomotor nerve. High-resolution imaging using constructive interference in steady state (CISS) sequence (D) depicts the abnormal oculomotor nerve (black arrow) on the left side and the normal appearance of the oculomotor nerve (white arrow) on the right side. High-resolution imaging also demonstrates the relationship of the oculomotor schwannoma to the left posterior cerebral artery (white arrowhead).

Similar findings were observed in Gelfand and colleagues's systematic review (2 weeks to 3 months).² All cases made a complete recovery after the first attack. Five patients developed persistent ophthalmoplegia, ptosis or mydriasis after a mean duration of 10.2 years. The remaining three patients made a full recovery after each attack.

There is insufficient follow-up data in the literature and in this case to comment on a possible cumulative effect of subsequent attacks once residual ophthalmoplegia is present. We approximated that those with oculomotor tumours had a mean of 16 attacks of painful ophthalmoplegia during follow-up. These findings suggest that

Figure 2. Repeat MR imaging 14 months after the initial scan and 4 months after the last attack revealed a stable 5 mm lesion arising from the left oculomotor nerve. Coronal Short T1 Inversion Recovery sequence (A) shows that the lesion (white arrow) is isointense to grey matter. The coronal T1-weighted gadolinium enhanced sequence (B) shows persistent homogeneous enhancement of the lesion post contrast.

Table 1. Clinical features in patients with oculomotor nerve tumours associated with recurrent painful oculomotor neuropathy.

n	Author	Age at onset	Gender	Involved nerve	Duration of illness	Approx. no. of attacks	Duration of ocular paresis	Persistent deficits	Interictal nodular enhancement	Histology	Response to steroids
1	Moloney et al. 2018	1	M	Left third	14 years	40	2–3 weeks	Yes	Yes	None	Initial positive response
2	Kim et al. 2015	42	M	Right third	10 years	5	1 week	Yes	Yes	None	Initial positive response
3	Kim et al. 2015	26	F	Right third	5 years	10	1 week	Yes	Yes	None	No clear benefit
4	Shin et al. 2015	41	F	Left third	13 years	3	6 weeks	No	Yes	None	No clear benefit
5	Shin et al. 2015	7	F	Right third	23 years	7	1 week	No	Yes	None	Steroids not given
6	Shin et al. 2015	27	M	Left third	15 years	30	Not reported	Yes	Yes	None	Steroids not given
7	Murakami et al. 2005	6	F	Left third	5 years	30	Not reported	Yes	Yes	Schwannoma	Initial positive response
8	Kawaski 1999	7	F	Right third	16 years	6	1 week	Yes	Yes	None	Beneficial response
9	Bisdorff & Wildanger 2006	2	F	Right third	12 years	15	1–2 weeks	No	Yes	None	Beneficial response

oculomotor tumours may be associated with later onset, prolonged disease duration and frequent attacks of relapsing painful ophthalmoplegia. However, it is difficult to extrapolate associations given the rarity of this finding.

The co-occurrence of two rare conditions (RPON and oculomotor tumour) is unlikely to be due to mere coincidence. Various explanations have been proposed to explain how schwannomas or other oculomotor tumours might cause relapsing symptoms. Some authors

postulate that RPON is a recurrent demyelinating cranial neuropathy.³ The focal-enhancing nerve swellings observed in chronic inflammatory demyelinating polyradiculopathy are considered analogous to the MR findings observed in RPON. Repeated episodes of demyelination with subsequent remyelination may lead to defective myelin remodelling and potentially to schwannoma development.² Others have proposed that noxious chemical substances released from the tumour may cause paroxysmal

symptoms through stimulation of trigeminal receptors or through oculomotor nerve oedema.³

Lesion size remained stable in all reported cases of oculomotor tumour mimicking RPON,^{5–9} with a 10-year interval between MRI scans in one case.⁹ Resective surgery in the case of histologically confirmed schwannoma causing painful ophthalmoplegia led to complete oculomotor paresis.⁷ Over 60% of patients with oculomotor schwannoma treated by surgery develop more severe ophthalmoplegia postoperatively.¹¹ Stereotactic radiotherapy in a case of oculomotor schwannoma mimicking RPON led to symptomatic improvement and radiological stability over 18 months.¹² For symptomatic treatment, steroids appear to be helpful in some cases of painful ophthalmoplegia with associated oculomotor tumour (Table 1).^{5–9} Of those treated with steroids, two derived clear benefit with shortened duration of ophthalmoplegia,^{8,9} two had attacks initially responsive to steroids^{5,7} and two patients had no beneficial response to steroids.^{5,6} In RPON, 54% of patients perceive benefit from corticosteroid treatment.² Strabismus surgery was not performed in any of the cases with associated oculomotor tumours.^{5–9} We plan to adopt a ‘wait and scan’ strategy and repeat MR imaging at 5 and 10 years provided there is no significant clinical change. We would consider radiotherapy or surgery if the tumour increased in size or if relapses became more frequent or disabling.

Conclusion

RPON is rare and in many cases carries a favourable prognosis, with spontaneous remission and no permanent deficits. Persistent ophthalmoplegia is observed in over half RPON cases.² Incomplete recovery of ophthalmoplegia might indicate an underlying oculomotor lesion, although full recovery has also been seen in such cases. MR imaging with CISS sequences, if available, is indicated in cases of recurrent painful ophthalmoplegia where persistent deficits are noted after an initial relapsing–remitting trajectory. It is unclear whether repeated episodes of painful demyelinating oculomotor neuropathy give rise to the appearance of a tumour or whether the oculomotor tumour is the cause of the recurrent attacks. Nodular enhancement of the oculomotor nerve between

attacks has been associated with pathologically proven schwannoma in one previous case report.⁷

Key points

- Oculomotor tumours are rarely associated with relapsing painful oculomotor nerve palsy, but are more likely in cases where persistent deficits develop.
- MR imaging of brain is indicated in cases where the clinical trajectory changes or where persistent ophthalmoplegia develops.
- Interictal nodular enhancement of the oculomotor nerve has been associated with oculomotor schwannoma.

Patient consent

We confirm that the patient in this case report gave written consent to his inclusion in the paper and he acknowledges that he cannot be identified via the paper. We can provide evidence of this written consent if requested.

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