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Case Report

Case report recurrent painful ophthalmoplegic neuropathy

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Abstract

Recurrent painful ophthalmoplegic neuropathy is a rare condition, previously known as ophthalmoplegic migraine, it is characterized by headache ipsilateral to paresis of the III, IV or VI cranial nerve, usually affects children or young adults. This is a report of a case of recurrent painful ophthalmoplegic neuropathy in a 16-year-old woman treated at the Hospital do Servidor Público Estadual de São Paulo.

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Introduction

Recurrent painful ophthalmoplegic neuropathy (RPON) is a rare disorder that usually affects children or young adults and is described as recurrent bouts of unilateral headache associated to ipsilateral ocular cranial nerve paralysis.

Recurrent painful ophthalmoplegic neuropathy, previously known as migranea oftalmoplegica, was renamed in 2013 because the use of the term "migraine" could associate RPON with an inaccurate pathophysiology, which may lead to inappropriate treatment strategies.[1-3]

The pathophysiology of RPON remains controversial and a better understanding of its mechanisms is still necessary to establish the most appropriate treatment, but it may be considered an idiopathic inflammatory neuropathy and usually responds to corticosteroid treatment.[4,5]

Case Report

This case is a 16-year-old female patient with a history of polycystic ovary syndrome and migraine since the age of 14 years. She was admitted at the Hospital do Servidor Público Estadual de São Paulo (HSPE) in October 2018 with a complaint of diplopia and a different pattern of her usual headache, which was described as periorbital pain on the left, initiated the day before. Neurological examination revealed paresis of the left sixth cranial nerve.

Brain magnetic resonance (MRI) and magnetic resonance angiography were normal. The following laboratory tests were performed: rheumatoid factor, antiRo, antiLa, erythrocyte sedimentation rate, glucose, immunoglobulin A and immunoglobulin G, C-reactive protein, complement C3, alphaglycoprotein, renal, hepatic and thyroid functions, the results were all normal. Negative serologies for syphilis, HIV, hepatitis B and C. Serology for cytomegalovirus and varicella zoster with negative IgM and positive IgG. The cerebrospinal fluid (CSF) examination was normal

The patient was discharged with complete resolution of headache and persistence of the sixth cranial nerve paresis. The diagnostic hypothesis was idiopathic sixth cranial nerve palsy. About four months after discharge, the abduction of her left eye was just slightly impaired and the holocranial headache was less frequent and less intense.

In May 2021, the patient had a second episode of periorbital headache starting the day before and diplopia starting on the same day of evaluation. The ophthalmoparesis of the sixth cranial nerve on the left had worsened, Brain and orbits MRI were performed, no abnormalities were observed. This time, the hypothesis of RPON was considered and the patient received prednisone 30 mg/day for 20 days with recommendation to gradually reduce the dose after this period and increase the topiramate dose from 100 mg/day to 150 mg/day.

About one month later, the patient reported improvement in the diplopia and the paresis had already remitted up to the intensity that affected her before the second episode.

In October 2021 the patient maintained regular use of topiramate at a dose of 150 mg per day, even though, she reported that in the last three months she had twelve episodes of headache characterized as pulsatile, frontal or holocranial, intensity 8/10, without association with nausea and vomiting, with worsening pain on movement and associated with photophobia and phonophobia. The association of topiramate 150 mg/day with propranolol 40 mg/day was proposed for better control of migraine episodes.

Coments

The diagnostic criteria for RPON are:

A. At least two attacks fulfilling criterion B;

B. Both of the following: Unilateral headache AND ipsilateral paresis of one, two, or all three ocular motor nerves;

C. Orbital, parasellar, or posterior fossa lesions has been excluded by appropriate investigation;

D. It cannot be better explained by another diagnosis of The International Classification of Headache Disorders 3rd edition (ICHD-3).[3]

The patient had two episodes of headache with ophthalmoparesis, fulfilling criteria A and B. The neuroimaging exams performed excluded lesions, vascular alterations or neoplasia that could cause ophthalmoparesis, fulfilling criterion C.

In a systematic review of 84 patients diagnosed with RPON, the clinical features observed were: most patients affected were female, the interval between the onset of headache

and the observation of ophthalmoparesis had a median of 1.6 days, the headache remained for less time than ophthalmoparesis, and the headache that appears during the RPON outbreak is usually unilateral, on the same side of the ophthalmoparesis and has the maximum intensity in the peri- or retro-orbital region. The patient reported presented a difference of one day between the onset of the headache and the ophthalmoparesis, the headache of the RPON attack was periorbital and on the same side as the ophthalmoparesis and ceased before the VI cranial nerve paresis.[6,7]

The patient had some atypical features such as: the affected cranial nerve was the VI, usually, it is affected in only 20% of all cases, it is known that the third cranial nerve is the most frequently affected, in addition, she maintained the neurological deficit of the first episode for years, which occurs in only 30% of cases.[8]

The contrast-enhanced MRI scan of the brain did not show any remarkable features, a review of published cases of RPON demonstrates that cranial MRI performed in the acute phase may demonstrate increased enhancement and enlargement of the affected nerves with frequencies ranging from 25% to 81% between studies, a very variable prevalence. Recurrent painful ophthalmoplegic neuropathy is not associated with any specific changes in blood or CSF, and the patient had no changes in laboratory tests.[4,7,9]

The change in the classification of the syndrome, which was no longer treated as a variant of migraine and now is considered a recurrent neuropathy, seems to have been adequate because the previous classification could lead to diagnostic errors and treatments aimed only at migraine prevention. However, patients affected with RPON often present a previous clinical features compatible with migraine, which was observed in this reported case, showing that there is a close relationship between RPON and migraine, this was observed in a review with more than 84 patients diagnosed with RPON, it was observed that 83% of the patients had a history of headache on occasions not related to the ophthalmoparesis episodes, associated symptoms were reported in half of the cases, with nausea and vomiting being the most common symptoms, followed by photophobia and phonophobia.[6,7]

The pathophysiology of RPON remains quite controversial, histopathological analyzes led to consider the hypotheses of ischemia, infectious neuritis or recurrent demyelination and remyelination processes. Before the common use of computed tomography and angiography, the vascular etiology gained strength, however, the images obtained by MRI did not support the hypothesis of ischemia, in addition, the presence of aneurysms compressing the cranial nerves is unlikely, considering that most affected patients were children or young adults, a population where the occurrence of aneurysms is rare.[4-6]

In 1988 Mark et al. published a series of six cases of what was then called ophthalmoplegic migraine (OM), these patients underwent cranial MRI performed in the acute phase of the disease and an increase in the enhancement of oculomotor nerve, at the cisternal segment, was observed, which persisted for a few weeks after the episodes of painful ophthalmoparesis. The authors considered that such enhancement could be observed in infectious neuritis but normal results of CSF and serum serology ruled out this etiology. The fact that there is complete remission, is transient and responds to treatment with corticosteroids could lead to the conclusion that OM would be an idiopathic inflammatory neuropathy, other authors have proposed that there could be the release of a cascade of neuropeptides that promote the breakdown of the blood-brain barrier and lead to the process of demyelination observed on MRI.[4,5] Therefore, the pathophysiology of RPON has not yet been fully clarified and this understanding could contribute to determining what would be the best therapeutic approach.

Regarding treatment, oral steroids remain the most prescribed medication, it seems to minimize the occurrence of permanent ophthalmoparesis and accelerate recovery. In a systematic review of the literature conducted by Liu et al.[1], 78 patients received corticosteroids after diagnosis of RPON, and 34 patients received only anti-migraine treatments such as beta-blockers and calcium channel blockers, comparatively, those who received corticosteroids had their recovery accelerated in relation to those who received only anti-migraines.

The patient reported received only topiramate for the treatment of migraine in the first episode and did not receive corticosteroids, as result, the ophthalmoparesis improved only after 4 months, without complete recovery. In the second episode, the diagnosis of RPON was considered, leading to the prescription of corticosteroids, this time the patient showed improvement in the paresis in approximately one month.

In conclusion, RPON is a rare syndrome, this makes difficult to conduct experimental studies to determine the real effectiveness of the treatments used, and there is still much to be clarified about the pathophysiology of the disease, making researchers rely on the analysis of observational studies and reports of case like the one presented.

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