

Recurrent painful ophthalmoplegic neuropathy: a report of two new pediatric cases

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ABSTRACT

Background. Recurrent painful ophthalmologic neuropathy (RPON), formerly known as ophthalmoplegic migraine, is characterized by repeated attacks of one or more ocular cranial nerve palsies with an ipsilateral headache. While steroid therapy has been reported to be beneficial for attacks, no clear consensus on prophylactic treatments exists. We present two cases emphasizing the diagnostic significance of the loss of enhancement during the symptom-free period and valproate as a beneficial option in prophylaxis.

Case 1. A 4-year-old girl presented with a one-week right frontal headache, vomiting and photophobia. Neurological examination revealed ptosis, oculomotor nerve paresis, and delay in light reflex in the right eye. Brain magnetic resonance imaging (MRI) revealed a 5.5 mm nodular enhancement in the cisternal part of the 3rd cranial nerve in the right premenencephalic area. The enhancement regressed after a 6-month symptom-free period. While propranolol, topiramate and flunarizine were inefficacious in prophylaxis, the patient responded to valproate prophylaxis and benefited from the administration of steroids for one week during the attacks.

Case 2. A 7-year-old girl presented with a ten-day right-sided, throbbing headache in the frontal region, one-day eye deviation and double vision. Neurological examination revealed inward gaze restriction and ptosis in the ipsilateral eye to the headache. Brain MRI revealed a 4.5 mm, enhancing, nodular lesion in the 3rd cranial nerve lodge in the right perimesencephalic area. Her symptoms regressed in one week with dexamethasone and she received prophylactic propranolol. Neuroimaging findings disappeared after a 3-month symptom-free period. After valproate was added because of a relapse, she did not experience any further attacks.

Conclusions. RPON is an uncommon disease in childhood with unknown etiology. On brain MRI with contrast during the symptom-free period, regression of the enhancement or complete resolution of the lesion are guiding features in the diagnosis. Valproate may have beneficial effects on RPON treatment.

Key words: ophthalmoplegia, cranial nerves, neuropathy, headache, valproate.

Recurrent painful ophthalmoplegic neuropathy (RPON), previously known as ophthalmoplegic migraine, is a rare syndrome characterized by repeating attacks of one or more ocular cranial nerve palsies with an ipsilateral headache, in which secondary causes have been excluded.¹ The first contributions to the literature on this disease date back to the 19th century with Note in 1854 and Gubler in 1860, but Charcot named

it “migraine ophthalmology” for the first time in 1890. It was thought to be a migraine variant in the early years when the definition emerged as it is associated with one or more ocular cranial nerve palsies, most often the oculomotor nerve and a migrainous headache. The original International Classification of Headache Disorders (ICHD) classified this disorder as a migraine variant, but the ICHD 2 named this disorder “ophthalmoplegic migraine” and classified it as a cranial neuralgia in 2004. It was reclassified as a cranial neuropathy in the ICHD 3-beta by the International Headache Society in 2013, and the term “RPON” was established.² The exact prevalence of RPON, a

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disease in which pediatric patients account for the majority of reported cases, is unknown, but it is estimated to be 0.7 per million.³ Since RPON is a rare disease, there are few publications in the literature, and here we aimed to present two pediatric patients who were diagnosed with RPON according to the ICHD-3 criteria and emphasize the diagnostic significance of the loss of enhancement or lesion during the symptom free period and discuss valproate as a useful prophylactic alternative.

Case 1

A four-year-old girl presented with a one-week right-sided frontal throbbing headache, vomiting and photophobia which occurred every 1-2 months for the last year. Previous episodes of headache were unrelated to infections and had lasted for 2-3 days with vomiting 10-15 times a day. The patient's medical history apart from headache episodes was unremarkable. There was no family history of neurological disease except for a history of migraines in the patient's aunt. Neurological examination was normal. Brain magnetic resonance imaging (MRI) performed a year ago was normal. After 3 days, the patient presented with ptosis, ophthalmoparesis with impaired adduction and slowed pupillary light reflex in the right eye. Brain MRI revealed 5.5 mm contrast enhanced nodular lesion on the right at the level of the ambient cistern belonging to the cisternal part of the 3rd cranial nerve (Fig.1a). Magnetic resonance angiography (MRA) revealed reduced flow at P1 segment of the right posterior cerebral artery (PCA), moderate narrowing of the P1 segment posteriorly, compared to the left P1 segment, secondary to the lesion originating from the 3rd cranial nerve (Fig.1b). Two days later, the findings had spontaneous regression (normal light reflex, partial regression in the others). Propranolol prophylaxis was started and the patient was followed up with the prediagnoses of RPON and trigeminal nerve schwannoma. The patient had many further attacks and prophylaxis of propranolol, topiramate and flunarizine were

used, respectively, at the maximum effective doses. Although headache was observed in all of these attacks, ophthalmoparesis accompanied only the first one. This was attributed to starting steroid therapy as soon as the headache occurred, without waiting for the development of ophthalmoparesis. After a 5 month attack-free period -under flunarizine, the patient presented with a similar attack. Valproate was added to flunarizine. After 6 months without attacks under dual therapy, the valproate dose was gradually decreased. In the 41st month, when the last attack was 6 months ago, the patient was asymptomatic, the size of the lesion was 4 mm and there was no contrast enhancement on brain MRI (Fig.1c). Repeated MR angiography was normal (Fig.1d). However, the patient had a relapse at the 42nd month, and the dose of valproate was increased again. The fact that the lesion did not show progression made the diagnosis of trigeminal nerve schwannoma unlikely and loss of enhancement in the symptom free period was thought to be in favor of the diagnosis of RPON. Headache and ophthalmoplegia episodes regressed with methylprednisolone therapy used for 5-10 days without any sequelae. The only time the patient was not given steroids was on the last attack because she presented after the attack was over. The patient is currently in the 54th month of the follow-up and has been symptom free for 12months.

Case 2

A previously healthy seven-year-old girl presented with a right-sided frontal headache persisting for the last 10 days, with the addition of limited inward ocular movement and double vision for the last day. The patient described previous similar headache episodes that occurred almost every day for 3-4 months, lasting for 1-4 hours. The attacks restricting daily activity, became more pronounced with physical activity, benefited from analgesics, and were not accompanied by photophobia, phonophobia, nausea, vomiting and ocular symptoms. The patient presented with a similar

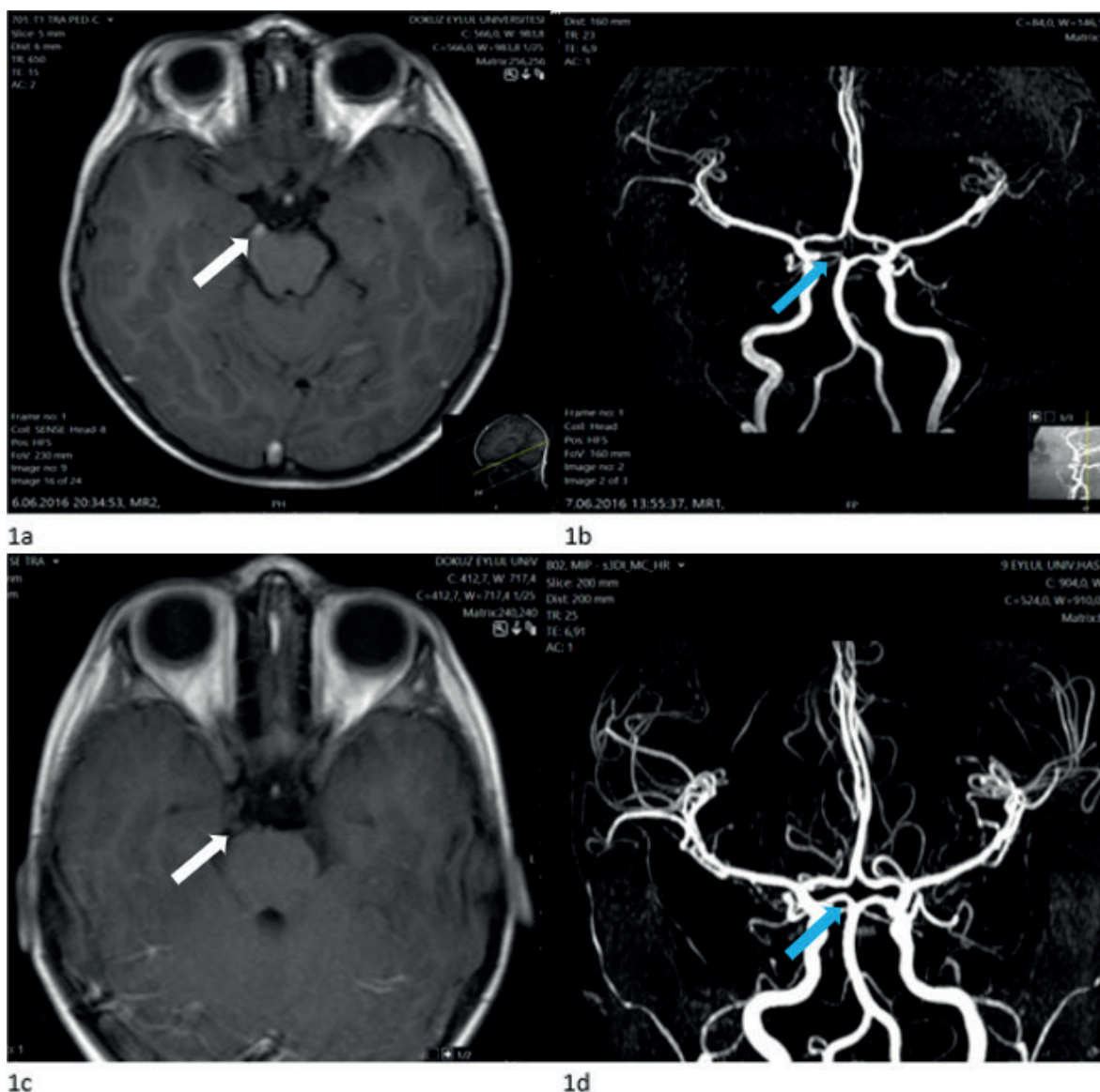
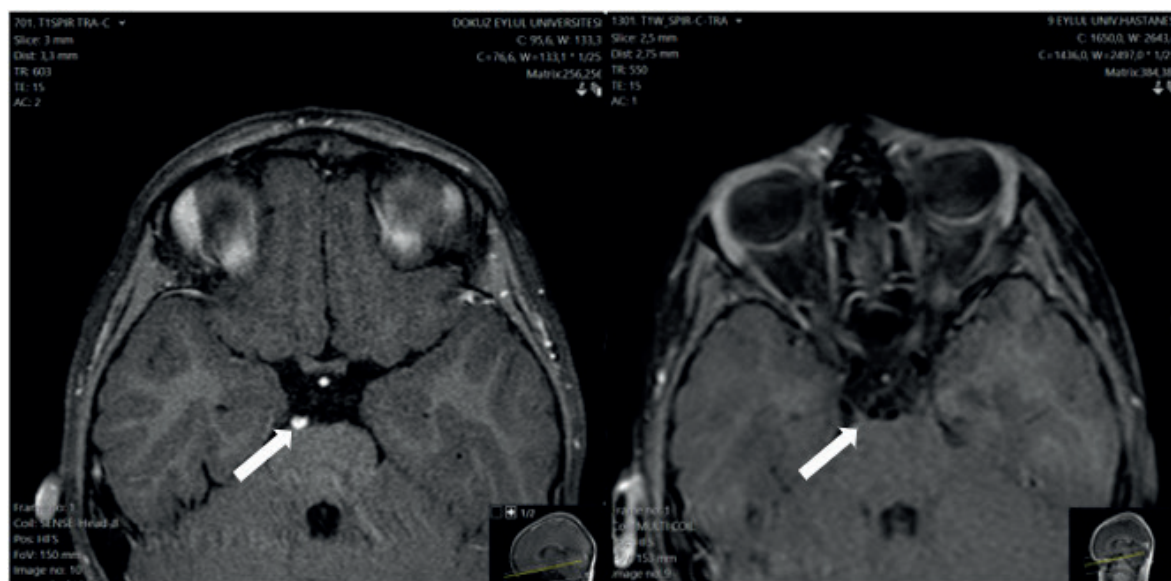


Fig. 1. (a) Axial postcontrast T1 images show thickening and increased enhancement 5.5 mm nodular lesion on the right at the cisternal portion of the 3rd cranial nerve. **(b)** Reduced flow at right P1 segment of posterior cerebral artery secondary to lesion. **(c)** After 6 months, the lesion size decreased to 4 mm and there was no enhancement on postcontrast T1 weighted image. **(d)** Repeated MR angiography study was normal.

headache persisting for the last 10 days, with the addition of impaired adduction and double vision within the last 24 hours. The patient had an unremarkable family history. Neurological examination was normal except for limited inward gaze and ptosis in the ipsilateral eye. Brain computed tomography (CT) was normal. Brain MRI revealed a 4.5 mm, enhancing, nodular lesion in the 3rd cranial nerve lodge in the right perimesencephalic area (Fig. 2a). Brain

CT angiography was performed to rule out vascular causes and was normal. Dexamethasone was initiated with pre-diagnoses of trigeminal nerve schwannoma and RPON. Headache regressed in 8 days and ophthalmoplegia in 6 days. Propranolol prophylaxis (1 mg/kg/day) was started. The patient had a second attack in the 9th month of the follow-up. Headache and ophthalmoplegia in this attack had the same characteristics as in the previous one.



2a

2b

Fig. 2. (a) Nodular lesion in the right 3rd cranial nerve at the perimesencephalic area show prominent contrast enhancement. (b) 12th month follow up study shows no lesion and no abnormal enhancement of the right oculomotor nerve at postcontrast T1 image.

The patient received only analgesic treatment as the patient presented after the symptoms regressed. The propranolol dose was increased to 1.5 mg/kg/day. Brain MRI revealed similar lesion size and contrast enhancement. No lesions and enhancement in the cranial nerve lodge were observed in the brain MRI in the symptom-free period (12th month) (Fig.2b). At the 13th month of follow-up, the patient had an attack (headache without ophthalmoplegia) lasting 7 days but steroid treatment was not given owing to improvement of headache with symptomatic treatment. Valproate was added to the propranolol prophylaxis. The patient is currently in the 18th month of the follow-up (5-month symptom free). Table I shows the clinical findings and neuroimaging results of the cases. The parents gave their informed consent for this publication.

Discussion

In the literature, the age of onset of RPON ranges from 3 months to 74 years. Liu et al.³ showed that although the average age of onset for this disorder was 22.1years, 65.8% of the

cases were in the pediatric age group. The patients we reported were 4 and 7 years old. While cases with predominantly female gender were reported, some publications stated that the frequency of male cases was higher, and in some others no difference between the sexes was found.^{4,5} Liu et al.³ reported the female:male ratio as 1.4: 1 in their review in 2020. Our cases, which support this rate in the literature, were female. In the literature, a family history of migraine was reported as 34.5%.³ Case 1's aunt suffered from migraines, while the family history of the other members was unremarkable.

The differential diagnosis for cranial neuropathy is extensive, and all possibilities should be considered in the diagnosis of RPON. Exclusion of orbital, parasellar, or posterior fossa lesions is essential.¹ Apart from excluding these lesions, another advantage of brain MRI is to demonstrate the affected cranial nerves. Nerve thickening and/or gadolinium enhancement of the affected nerve can be seen using brain MRI during an attack of RPON, whereas negative findings are highly common during the symptom-free period.^{1,6-8} Although the most commonly involved nerve is the 3rd cranial nerve,

Table I. The clinical findings and neuroimaging results of the cases.

	Number of episodes with spontaneous regression	Duration of episodes (days)						MRI findings					
		Before steroid therapy		After steroid therapy		With spontaneous regression		During attacks		During symptom free periods		Mean duration of steroid therapy (days)	
	Number of episodes with ophthalmoplegia	Headache	Ophthalmoplegia	Headache	Ophthalmoplegia	Headache	Ophthalmoplegia	Number	Lesion	Contrast enhancement	Number	Lesion	Contrast enhancement
Case 1	16	3	8.6 (1-25)	1.5 (1-2)	3 (1-7)	1	1.7 (1-4)	12	6 (3-10)	6 (+)	1	6 (+)	1 (-)
Case 2	3	2	10	1	8	6	5.5 (4-7)	1	6	2 (+)	1	2 (+)	1 (-)

abducens and trochlear nerve involvement have been reported in the literature. Our patients also presented with 3rd cranial nerve involvement. Similar to our cases, cranial nerve involvements have been reported as contrast enhancing nodular lesions.^{8,9} Hashimoto's encephalopathy and myelin oligodendrocyte glycoprotein-associated disease, which may present with recurrent ophthalmoplegia, were not considered in our patients with long-term follow-up due to their clinical and radiological features. Imaging findings are more commonly seen in pediatric cases and the disappearance of lesion usually takes 12 weeks.¹⁰ Since Case 1 experienced frequent attacks, contrast regression on brain MRI occurred in the 41st month after the first attack (24th week after the last attack). In Case 2, the lesion completely regressed in the brain MRI and this regression was observed 12 months after the first attack (12 weeks after the last attack), similar to the literature. Although brain CT findings are generally normal, abnormalities in the involved nerve have been rarely reported in RPON patients.¹¹ Brain CT was performed in one of our cases and was normal. Also, angiographic evaluations revealed right-sided fetal-type PCA endorsing the compressive/ischemic hypothesis which remarks that edema of the wall of the internal carotid artery or PCA could block the arterial supply for cranial nerves or compress the cranial nerves in RPON.^{5,7,12} Concerning pathophysiological considerations, in favour of a migrainous, not neuropathic etiology, several mechanisms have been discussed to explain how migraine may induce ophthalmoplegia. Migraine-related intumescence of the vessel walls of the PCA has been proposed to cause occlusion of arterial branches supplying the cisternal portion of the oculomotor nerve. Ischemic havoc of the blood-nerve barrier would cause vasogenic edema, explaining ophthalmoplegia, thickening, and contrast enhancement of the nerves.¹³ Shin et al.¹⁴ have shown reversible, ipsilateral ischemia in the areas of perforating branches of the PCA by brain technetium Tc 99m ethyl cysteinate dimer single photon emission computed tomography

(SPECT), in two patients with oculomotor nerve involvement. Reverting to normal levels of regional cerebral blood flow has been demonstrated on a follow-up SPECT during the symptom-free period suggesting reversible ischemia in the territories of the branches of the PCA may be a possible pathophysiological mechanism for this disease. In Case 1, the angiographic evaluation revealed reduced flow right PCA (P1 segment), moderate narrowing of the P1 segment posteriorly, secondary to the lesion originating from the 3rd cranial nerve. This image supported the ischemic hypothesis similar to those reported in the literature. In our study, the headaches were localized to the frontal region. While the location of headache in RPON patients was 48.3% orbital-related, frontal headaches were detected as 11.6% in the literature.³ The time interval between headache and ophthalmoplegia was reported ≤ 1 week in 95.7% of the patients.³ We found that this interval was 3-5 days (mean 4 days) in Case 1 and 3-9 days (mean 6 days) in Case 2, similar to the literature. Cranial nerve palsies may continue for a few days to weeks, but the headache resolves completely with or without any special treatment.^{3,15-17} Headaches in our patients regressed in an average of 9.2 days (1-32 days). The spontaneous regression rate of headache was 31.5%. Ophthalmoplegia in our patients regressed in an average of 5 days (1-12 days). The spontaneous regression rate of ophthalmoplegia was 40%. In attacks without spontaneous regression, the duration of symptom relief with treatment was between 1-8 days (mean 3.4 days) for headache and 1-6 days (mean 2.6 days) for ophthalmoplegia.

Since RPON is a very rare disease, no treatment trials or guidelines for RPON exist. Observational studies are the only publication that can make recommendations on effective treatments. In the review by Liu et al.³ in 2020, it was reported that 47.3% of the patients received corticosteroid treatment and 96.2% of them benefited from this treatment within 1 hour-8 weeks. In our study, while 3-10 days of steroid treatments in Case 1 regressed the headache between 1-7 days (mean

3 days), ophthalmoplegia regressed in 1 day. In Case 2, steroid treatment (6 days) was given in one of the attacks; where headache regressed in 8 days and ophthalmoplegia in 6 days. Indomethacin, intravenous immunoglobulin, nonsteroidal anti-inflammatory drugs, ergotamine and furosemide are other agents used in the treatment of attacks. Other prophylactic agents with variable efficacy are flunarizine, propranolol, verapamil, valproate, cyproheptadine, gabapentin, pizotifen, imipramine, and amitriptyline.¹⁶ In the literature, pregabalin was found to be useful in a patient whose headache and ocular paralysis regressed with steroid therapy but recurred with gradual dose reduction, and who was also unresponsive to prophylaxis with beta-blockers, calcium channel blockers, and topiramate.¹⁸ Wang et al.¹⁹ reported an adult patient who did not experience an attack with the combination of valproate and flunarizine. Margari et al.⁷ reported that valproate was used in a pediatric patient with a history of focal seizures and epileptic abnormalities on electroencephalography, and both electroencephalography findings and the attack frequency decreased. In our study, when Case 1 continued to have frequent attacks with propranolol, topiramate and flunarizine, valproate was initiated. While valproate decreased the attack frequency and enhancement in MRI, reduction of its dose caused a relapse. In Case 2, there was no attack with valproate, which was initiated after the attacks continued while using propranolol.

In conclusion, the changes in the naming and classification of RPON for nearly two decades indicate the ongoing debate around this rare disorder. A brain MRA during initial work-up and a brain MRI with contrast after a symptom-free period of at least 3 months may be helpful in both the differential diagnosis and diagnostic challenges of RPON. A combined treatment approach with acute attack and prophylactic treatments can manage acute symptoms as well as minimize recurrence for which valproate may be an effective prophylaxis option.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ÇG, PE, UY; data collection: ÇG, PE; analysis and interpretation of results: ÇG, EY, ASHK, UY; draft manuscript preparation: ÇG, PE, EY, ASHK, UY. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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