CASE REPORT
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Recurrent painful ophthalmoplegic neuropathy: A report on the patient from the Romani population and 82-year-old patient

Rekurentna bolna oftalmoplagička neuropatija – prikaz bolesnika iz romske populacije i 82-godišnjeg bolesnika

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Abstract

Introduction. The current diagnostic criteria for recurrent painful ophthalmoplegic neuropathy (RPON) are at least two attacks of unilateral headache, associated with ipsilateral paresis of one, two or all three cranial nerves (III, IV or VI). There is no case report about RPON in the Romany population. The oldest patient with RPON, published in the literature, was 74 years old. **Case report.** The first patient was a 31-year-old man from the Romani population who was treated during three episodes of RPON, with III nerve palsy during one episode and with alternating VI nerve palsy during two episodes. All examination were normal except serum lipid levels and Cytomegalovirus immunoglobulin G (CMV IgG), *Toxoplasma gondii* IgG, Epstein–Barr virus (EVB) IgG and Varicella zoster IgG which were elevated. The second patient was a 82-year-old male patient with two RPON episodes with alternating VI nerve palsy. All examinations were normal, except Herpes simplex type 1 virus IgG, CMV IgG, *Toxoplasma gondii* IgG, EBV IgG and Varicella zoster IgG which were elevated, and his brain magnetic resonance imaging (MRI) showed lacunar ischemic lesions. Both patients were started on corticosteroid. Recovery was completed after all five episodes of RPON. **Conclusion.** There are no data on the frequency of RPON among the Romani population. The presentation of RPON in the oldest age is rare. RPON should be considered as a diagnostic option in these minorities. New case reports or systematic review articles about RPON are necessary to create a new insight into the nature of the disease.

Key words:
ophtalmologic migraine; adult; aged, 80 and over; diagnosis; drug therapy; roma; treatment outcome.

Apstrakt

Uvod. Aktuelni dijagnostički kriterijumi za rekurentnu bolnu oftalmoplegičnu neuropatiju (RPON) su najmanje dva ataka jednostrane glavobolje, udružene sa ipsilateralnom parezom jednog, dva ili sva tri kranijalna nerva (III, IV ili VI). Do sada nije prikazan slučaj RPON u populaciji Roma. Najstariji bolesnik sa RPON, prikazan u literaturi, imao je 74 godine. **Prikaz bolesnika.** Prvi bolesnik je bio 31-godišnji muškarac romske nacionalnosti koji je lečen tokom tri epizode RPON, sa parezom III kranijalnog nerva u tokom jedne epizode i VI kranijalnog nerva na različitim stranama, u toku druge dve epizode. Sva ispitivanja su bila uredna, osim povišenih vrednosti lipida u serumu i imunoglobulina G (IgG) na citomegalovirus (CMV IgG), IgG na toksoplazmu gondi, IgG na Epstein–Barr virus (EVB) i IgG na Varicela zoster virus. Drugi bolesnik je bio 82-godišnji muškarac sa dve epizode RPON i zahvećenim VI kranijalnim nervom na različitim stranama. Sva ispitivanja su bila uredna, osim povišenih vrednosti IgG na Herpes simplex virus tip 1, CMV IgG, IgG na toksoplazmu gondi, EBV IgG i IgG na Varicela zoster virus i lakunarnih ishemijskih lezija koje je imao na snimku magnetne rezonance (MR) mozga. Oba bolesnika su lečena kortikosteroidnom terapijom. Oporavak je bio kompletan nakon svih pet epizoda RPON. **Zaključak.** Ne postoje podaci o učestalosti RPON među pripadnicima romske nacionanosti. Pojava RPON u najstarijem životnom dobu je veoma retka. RPON bi trebalo imati u vidu kao jednu od dijagnostičkih opcija kod ovih grupa bolesnika. Novi prikazi bolesnika ili revijalni radovi o RPON su neophodni da bi se razjasnila priroda same bolesti.

Ključne reči:
migrena, oftalmoplegična; odrasle osobe; stare osobe, 80 i više godina; dijagnoza; lečenje lekovima; romi; lečenje, ishod.

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Introduction

Recurrent painful ophthalmoplegic neuropathy (RPON) is new concept from the 3rd edition of the International Classification of Headache Disorders (ICHD-3) and classified under the category of painful cranial neuropathies and other facial pains [1] which according to previous classification from 2004 marked as ophthalmoplegic migraine (OM) and classified under the category of cranial neuralgias [2].

The current diagnostic criteria for RPON are at least two attacks of unilateral headache, associated with ipsilateral paresis of one, two or all three cranial nerves (III, IV or VI). Orbital and parasellar and posterior fossa pathological lesions must be excluded by appropriate diagnostic techniques as well as other potential diagnoses according to the ICHD-3 criteria [1].

There is no case report about RPON in the Romani population. There is only one study about prevalence of migraine and risk factor for migraine in the Romani population from Spain. Prevalence of migraines is greater in the Romani living in Spain than in the general Spanish population [3].

The oldest patient with RPON, published in the literature so far, was 74 years old [4].

RPON is diagnosis of exclusion. Possible dilemma that should not be overlooked is Tolosa-Hunt syndrome. Diagnostic criteria for Tolosa-Hunt syndrome are granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by magnetic resonance imaging (MRI) or biopsy [5]. Other diagnostic dilemmas are orbital myositis, neoplastic disease, vascular disease, brain stem ischemia, mass or multiple sclerosis lesions, diabetic palsy, traumatic nerve palsy, infection, myasthenia gravis, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), idiopathic intracranial hypertension or hypotension, thyroid ophthalmopathy, orbital mass, narrow angle glaucoma, Wegener's granulomatosis, vincristine therapy [1, 6–11].

The RPON is rare entity whose pathophysiology is unknown and for which no therapeutic recommendations are available [11].

Case reports

Case 1

A 31-year-old man from the Romani population was admitted to the Clinic of Neurology, Faculty of Medical Sciences, University of Kragujevac, during the third RPON episode which began in 2014, as left side periorbital headache, 7/10 in intensity, pulsating in character, associated with nausea. A few hours after, the patient developed left sided VI cranial nerve palsy and diplopia. He was started on prednisolone 120 mg for 10 days, after that 80 mg for 10 days, followed by 60 mg for 10 days. The second day of the disease, headache intensity was reduced. At the discharge, the patient was without headache and with mild recovery of the mobility of the eyeball. After 3 months of the onset of symptoms, patients was completely recovered.

During hospitalization his general examination was normal. Nervous system examination showed left sided VI nerve palsy. All laboratory results were normal except serum lipid levels which were high. Blood glucose levela and hemoglobin A1c (HbA1c) levels were normal. Immunological analysis, thyroid hormones and antibodies to thyroid hormones were normal. Virological, bacteriological and parasitological analyses were normal. Brain MRI with contrast, MR angiography of the brain arteries, chest X-ray and visually evoked potentials (VEP), all were normal. We excluded neuromuscular junction disorders by prostigmin test. Cerebrospinal fluid (CSF) analysis was normal [cell counts, protein, glucose levels, imunoglobulin G (IgG) index].

The first episode occurred in 2010 with right-sided headache, 8/10 in intensity, nausea, vomiting, photophobia and diplopia. On neurological examination, the patient had isolated right VI nerve palsy. We applied corticosteroid therapy. The headache lasted 6 months, while the double vision were present 7 months after the onset of symptoms. All results were normal.

The second episode occurred in 2013, with right-sided occipital headache, 9/10 in intensity, nausea and vomiting. A few days later, the patient developed diplopia. On neurological examination, he had isolated right III nerve palsy. During hospitalization, the patient developed right ptosis. The reaction of the pupil to light and accommodation were normal, bilaterally. Headache was stopped within 3 days from administration of corticosteroid therapy while diplopia lasted for about 2 months. All results were normal.

Before the onset of RPON, the patient was healthy and had never suffered from headaches. The mother of the patient had a migraine in generative period of life.

Case 2

A 82-year-old male patient was admitted in our Clinic during the second RPON episode which began in 2017 with a pain in the depth of the right eye and diplopia. Seven days later, the patient developed the right VI nerve paralysis, and other neurological findings were normal. Increased cholesterol levels were found in laboratory analyses. Blood glucose level and HbA1c level were normal. Immunological analysis, thyroid hormones and antibodies to thyroid hormones were normal. Virological, bacteriological and parasitological analyses were normal. The test for diplopia showed diplopia in the direction of left lateral rectus muscle. The ophthalmologic examination showed the initial cataract. Lacunar ischemic lesions in white matter of parieto-occipital region on the brain MRI were seen. MR angiography of the brain arteries, visually evoked potentials (VEP), echo tomography of the orbits, eye pressure, and Doppler ultrasonography of the blood vessels of the neck – all were normal. We excluded neuromuscular junction disorders by prostigmin test. We applied dexamethasone and acetylsalicylic acid for 7 days. Ophthalmological rehabilitation was conducted. Three

months later there was a complete recovery. A diagnosis of RPON was made.

The first episode of RPON occurred in 2015 due to left side orbital pain, 6/10 in intensity, nausea and diplopia. In the neurological examination, the patient had isolated left VI nerve palsy. The same therapy was administered. After 3 months of the onset of symptoms, patients was completely recovered.

Before the onset of RPON, the patient was healthy and had never suffered from headaches.

Discussion

RPON is a very rare disease, with an incidence of 0.7 per million [12]. The incidence of RPON is two times higher in female, according to some studies [4, 13, 14], whereas in one case series ratio of men to women is approximately 1: 1 [15].

The side of headache and nerve palsy is the same in the largest number of cases during different attacks of RPON [14], while the change of side is very rare (Gelfand et al. [4] found only two cases in their series of 84 patients). Alternating side of VI nerve palsy during different RPON episodes was described in a few cases [15, 16] like alternating side of III nerve palsy [15].

Only 1–6.5% of patients had symptoms on different side in two different attacks like our first patient [4, 15].

The most of patients (up to 94%) had normal CSF findings [4] and only few had nonspecific CSF abnormalities [15].

The brain MRI in 75% of patients with III nerve palsy shows an accumulation of gadolinium in the affected nerve area during the attack of the disease, but in remaining cases, the brain MRI is normal [4, 6–8, 14, 15, 17].

Our second patients had VI nerve palsy in two episodes of RPON, on different side, without changes on the brain MRI. The brain MRI [7, 15, 17] and brain single photon emission computed tomography (SPECT) [18] show no lesions in the most patients with VI nerve palsy, although there have been cases presented with the enhancement of intraparenchymal and cisternal part of VI nerve [9, 18]. In our patients, after three and two attacks of RPON, the symptoms resolved completely in a period of several weeks to several months, such as the recently published case of RPON [19].

Recently, a report on recurrent Tolosa-Hunt syndrome in patients with and without granulomatous changes in the brain MRI has been published [5]. Since, it is virtually impossible to distinguish patients with recurrent Tolosa-Hunt syndrome without a change in the brain MRI from patients with RPON, and at a time when biopsy is practically very rarely performed and in the era of modern high-quality neuroradiology diagnostics, the brain MRI remains a key factor for diagnosis of RPON and Tolosa-Hunt syndrome. It is extremely important to strictly follow the brain MRI criteria for diagnosis of Tolosa-Hunt syndrome (granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by the brain MRI or biopsy) and the brain MRI criteria for RPON (orbital and parasellar and posterior fossa pathological lesions must be excluded by appropriate diagnostic techniques). An excellent response to corticosteroid therapy for RPON and Tolosa-Hunt syndrome patients eliminates the therapeutic dilemma.

However, new case reports or systematic review articles about RPON are necessary to create a new insight into the nature of the disease.

Conclusion

Due to the excellent response to corticosteroid therapy in RPON and Tolosa-Hunt syndrome and due to the same differential diagnosis, we consider that the detailed examination should be conducted in all patients with suspicion on RPON/Tolosa-Hunt and corticosteroid therapy should be administered. Also, it is necessary to make a more detailed distinction between the definitions of clinical picture between these two diseases in new headache classification.

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