

A RELAPSE OF “RECURRENT PAINFUL OPHTHALMOPLEGIC NEUROPATHY” AFTER COVID-19 VACCINATION, CASE REPORT AND REVIEW OF THE LITERATURE.

Maria Lima, Vaios Samaras, Dimitrios Parisis, Nikolaos Grigoriadis, Panagiotis Ioannidis.

B' Department of Neurology, Aristotle University of Thessaloniki, AHEPA University General Hospital of Thessaloniki

ABSTRACT

The purpose of this paper is to describe the first case report of a relapse of “Recurrent Painful Ophthalmoplegic Neuropathy” (RPON), formerly known as “Ophthalmoplegic Migraine”, after COVID-19 immunization. RPON is a rare form of neuropathy characterized by repeated attacks of paresis of one or more ocular cranial nerves with ipsilateral headache. While headache and ocular cranial nerve palsies alone have been described after vaccination, especially after COVID-19 immunization, there are only minimal reports of RPON in *children*, or painful ocular cranial nerve palsies in the *adult* population. We hereby present the first case report of a patient with RPON, who had a recurrence after the 3rd dose of the BNT162b2 mRNA vaccine against SARS-Cov-2. In addition, as far we know, this case is also the first case report of a relapse of known RPON after immunization in the *adult* population. The rarity of these cases may be explained by the fact, that since recently adult vaccination was not so common, and RPON is also a rare entity. In our opinion, this article will add important insights not only to the field of COVID-19 vaccination, but also to the field investigating the pathogenesis of RPON. This paper comes to strengthen the current opinion, that RPON is actually a neuropathy, while headache could be a secondary event that takes place in some individuals whose anatomy and physiology endeavour the earlier triggering of an ipsilateral headache.

KEY-WORDS: COVID-19, vaccination, headache, ophthalmoplegic migraine, cranial neuropathy.

ΥΠΟΤΡΟΠΗ «ΕΠΑΝΑΛΑΜΒΑΝΟΜΕΝΗΣ ΕΠΩΔΥΝΗΣ ΟΦΘΑΛΜΟΠΛΗΓΙΚΗΣ ΝΕΥΡΟΠΑΘΕΙΑΣ» ΕΠΕΙΤΑ ΑΠΟ COVID-19 ΕΜΒΟΛΙΑΣΜΟ, ΑΝΑΦΟΡΑ ΠΕΡΙΠΤΩΣΕΩΣ ΚΑΙ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΒΙΒΛΙΟΓΡΑΦΙΑΣ.

Μαρία Λίμα, Βάιος Σαμαράς, Δημήτριος Παρίσις, Νικόλαος Γρηγοριάδης, Παναγιώτης Ιωαννίδης.

B' Νευρολογική Κλινική, Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης

ΠΕΡΙΛΗΨΗ

Ο σκοπός αυτού του άρθρου είναι η περιγραφή της πρώτης περίπτωσης εμφάνισης υποτροπής «Επαναλαμβανόμενης Επώδυνης Οφθαλμοπληγικής Νευροπάθειας» (ΕΕΟΝ), πρωτίτερα γνωστή ως «Οφθαλμοπληγική Ημικρανία», έπειτα από COVID-19 εμβολιασμό. Η ΕΕΟΝ είναι μία σπάνια μορφή νευροπάθειας που χαρακτηρίζεται από επαναλαμβανόμενες προσβολές πάρεσης ενός ή περισσότερων κρανιακών νεύρων με σύστοιχη κεφαλαλγία. Παρότι έχουν αναφερθεί περιστατικά κεφαλαλγίας ή πάρεσης κρανιακών νεύρων ξεχωριστά έπειτα από εμβολιασμό, ειδικά έπειτα από COVID-19 εμβολιασμό, υπάρχουν μόνο ελάχιστες αναφορές εμφάνισης ΕΕΟΝ *σε παιδιά*, ή «επώδυνης οφθαλμοπάρεσης» *σε ενήλικες*. Στο παρόν άρθρο περιγράφουμε το πρώτο γνωστό περιστατικό ασθενούς με ιστορικό ΕΕΟΝ, ο οποίος εμφάνισε υποτροπή έπειτα από την 3η δόση εμβολιασμού με το BNT162b2 mRNA εμβόλιο έναντι του κωρονοϊού (SARS-CoV-2). Επιπλέον, εξ όσων γνωρίζουμε, αυτή η περίπτωση είναι επίσης η πρώτη αναφορά υποτροπής γνωστής ΕΕΟΝ έπειτα από εμβολιασμό *σε ενήλικο* πληθυσμό. Η σπανιότητα αυτών των αναφορών εξηγείται από το γεγονός ότι μέχρι πρόσφατα ο εμβολιασμός ενηλικών δεν ήταν συνήθης, και η ΕΕΟΝ είναι επίσης μία σπάνια οντότητα. Κατά την γνώμη μας, το άρθρο αυτό θα προσθέσει σημαντική γνώση όχι μόνο στον τομέα μελέτης του

COVID-19 εμβολιασμού, αλλά ιδίως στον τομέα μελέτης της παθογένεσης της ΕΕΟΝ. Το άρθρο αυτό έρχεται να ισχυροποιήσει την τρέχουσα αντίληψη, ότι η ΕΕΟΝ είναι όντως νευροπάθεια, ενώ η κεφαλαλγία που την συνοδεύει θα μπορούσε να είναι ένα δευτερογενές γεγονός που λαμβάνει χώρα σε ορισμένα άτομα των οποίων η ανατομία και φυσιολογία ευνοούν την πρωθύστερη ενεργοποίηση μιας σύστοιχης κεφαλαλγίας.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: COVID-19, εμβολιασμός, κεφαλαλγία, οφθαλμοπληγική ημικρανία, κраниκή νευροπάθεια.

INTRODUCTION

According to the International Classification of Headache Disorders 3rd edition 2018 (ICHD3) (code 13.10), “Recurrent Painful Ophthalmoplegic Neuropathy” (RPON), formerly known as “Ophthalmoplegic Migraine” (OM), is characterized as: “Repeated attacks of paresis of one or more ocular cranial nerves (CN), commonly the third (IIIrd) CN, with ipsilateral headache”.^[1] The exact pathogenesis of the syndrome remains unclarified, while it may also not be the same in all cases. The only radiological finding that can be demonstrated using MRI, is thickening or enhancement of the IIIrd CN at its exit from the midbrain.^[1] Moreover, taking into consideration the

“relapsing-remitting” pattern of the syndrome and good response to corticosteroids, the disorder is in accordance with the current view that it is an inflammatory or demyelinating neuropathy.^[2] This process on the nerve could in turn affect trigeminal fibers and activate a trigeminovascular response, which causes ipsilateral headache.^[2,3]

Already since 1949, Rosen supported that ocular and neuro-ocular manifestations are not a rare post-vaccinal complication.^[4] There are many cases of post-vaccinal cranial neuropathies, ocular cranial nerve palsies (OCNP) included, some of them with a recurrent pattern. Many similar cases have also been described after COVID-19 immunization, where VIth

CN palsy is the most common among OCNP.^[5] Some of these cases are summarized in the table below (table 1).

Table 1. OCNP after immunization, especially after COVID-19 vaccination, and after COVID-19 infection.

1. Post-vaccinal OCNP	Rosen, 1948 (DOI:10.1016/S0002-9394(48)91808-X)	Ríos, Martín, & Mercadal, 2014 (DOI:10.1016/j.anpedi.2014.02.010)	Essrani, Essrani, Meherahahi, Lohana, & Sudhakaran, 2018 (DOI:10.7759/cureus.3759)	Kim et al., 2021 (DOI:10.1159/000511025)
2. Post-vaccinal OCNP with a recurrent pattern	Werner, Savino, & Schatz, 1983 (DOI:10.1001/archophth.1983.01040010607016)	McCormick, Dinkaran, Bhola, & Rennie, 2001 (DOI:10.1038/eye.2001.122)	Leiderman, Lessell, & Cestari, 2009 (DOI:10.1016/j.jaa-pos.2008.12.137)	
3. Post-vaccinal OCNP after COVID-19 immunization	Kubota, Hasegawa, Ikeda, & Aoki, 2021 (DOI:10.12688/f1000research.74299.2)	Reyes-Capo, Stevens, & Cavuoto, 2021 (DOI:10.1016/j.jaa-pos.2021.05.003)	Cicalese et al., 2022 (DOI:10.1136/bcr-2021-246485)	Kerbage, Haddad, & Haddad, 2022 (DOI:10.1177/2050313x221074454)
	Khalili, Khorrami, & Jahanbani-Ardakani, 2022 (DOI:10.1016/j.jfo.2022.03.001)	Veisi, Najafi, Has-sanpour, & Bagheri, 2022 (DOI:10.1080/01658107.2022.2032204)	Lotan, Lydston, & Levy, 2022 (DOI:10.1097/wno.0000000000001537)	Dutta et al., 2022 (DOI:10.7759/cure-us.21376)
4. OCNP after COVID-19 infection	Faucher, Rey, Agudisch, & Degos, 2020 (DOI:10.1007/s00415-020-09987-x)	Pascual-Goñi et al., 2020 (DOI:10.1212/nxi.0000000000000823)	Wei, Yin, Huang, & Guo, 2020 (DOI:10.1007/s00415-020-09773-9)	(adverse effects reports in VigiBase) Fitzpatrick et al., 2021 (DOI:10.1097/wno.0000000000001160)

However, according to the research of the literature that we have conducted, there are only a few cases of post-vaccinal attack of RPON or painful OCNP. Chan et al. described a case of a 17-month-old, who developed an isolated IIIrd CN palsy two weeks after measles immunization^[6]. Later, the boy developed same episodes with headache, that were finally characterized as OM (RPON).^[7] Another very interesting case is the story of a 9-year-old boy, who developed three attacks of IIIrd CN palsy with headache, each of them 10 days after the injection of a

triple vaccine.^[3] As regards the adult population, there is a case of painful IIIrd CN palsy in a 79-year-old man after influenza vaccination,^[8] and a report of VIth CN palsy with throbbing occipital headache two days after the 2nd dose of COVID-19 vaccination, with the ChAdOx1/AD1222 vaccine, but in that case the patient was also febrile.^[9] However, we could not find any case of *relapse* of known RPON after vaccination in the *adult* population. The results are summarized in table 2.

Table 2. Post-vaccinal RPON or painful OCNP

Chan, Sogg et al. 1980 (DOI:10.1016/0002-9394(80)90019-7)	Hassin 1987 (DOI:10.1016/0002-9394(87)90020-1)	Lance and Zagami 2001 (DOI:10.1046/j.1468-2982.2001.00160.x)	de Almeida, Teodoro et al. 2011 (DOI:10.5402/2011/849757)	Basnet, Bhandari et al. 2022 (DOI:10.1016/j.amsu.2022.104434)
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CASE DESCRIPTION

Hereby, we present a case of a 65-year-old man, who had been diagnosed earlier in our clinic with RPON, and this time came with another attack, 10 days after the 3rd dose of the BNT162b2 COVID-19 mRNA vaccine.

The patient suffered from migraine type headaches since childhood, usually right periorbital throbbing headache, with nausea, photophobia and echophobia. Later on his life the episodes were accompanied by diplopia, due to oculomotor nerve palsy, and for these episodes he had been investigated in our department. Paraclinical investigation with laboratory, immunological, imaging examination (including brain MRI and chest CT), antibodies for myasthenia, electromyography, and lumbar puncture (cytochemistry, oligoclonal bands in serum and cerebrospinal fluid), did not reveal any underlying structural, vascular, ischemic, inflammatory or demyelinating pathology. The patient is under medication for hypertension, which is well-controlled, without any other vascular risk factors. From his family history, his mother was also suffering from headaches. According to the International Classification of Headache Disorders 3rd edition 2018 (ICHD3) (code 13.10) the patient fulfills the criteria of RPON (1).

This time, the patient had another relapse of RPON, only 10 days after a booster dose of COVID-19 mRNA immunization. He presented to our clinic with right periorbital throbbing headache, as well as corresponding blepharoptosis and diplopia 2 days later. The neurological examination revealed a right IIIrd CN palsy, with blepharoptosis, eye in abduction and downward turn, pupils with mild right supremacy, with preservation of the photomotor reflex, and diplopia, without other neurological symptoms or signs. We performed another thorough investigation, with laboratory, immunological, imaging examination

(Brain CT, CT-Angiography, CT-Venography, Brain MRI) and lumbar puncture (cytochemistry, oligoclonal bands in serum and cerebrospinal fluid), which again did not reveal any underlying structural, vascular, ischemic, inflammatory or demyelinating pathology. The patient was treated with corticosteroids in the acute and subacute phase and oculomotor palsy gradually resolved within three months.

DISCUSSION

According to the algorithm of World Health Organization (WHO) for the assessment of the causality of Adverse Events Following Immunization (AEFI),^[10] we could classify our case in the category of "*consistent causal association to immunization*". First of all, a possible causal association of OCNP and RPON with vaccination has been described and can be explained, accepting the current view, that RPON is more of neuropathy (inflammatory or demyelinating in nature) rather than migraine. Moreover as regards SARS-CoV-2, it is known that it can enter the Central Nervous System (CNS) and cause neurological manifestations,^[11] while in addition it may have a strong link with demyelination in the CNS.^[12] In particular, cases of OCNP have been described after COVID-19 infection (table 1.4). Consequently, a possible mechanism of oculomotor nerve palsy after COVID-19 vaccination could be a similar triggering of a misdirected immune response against myelin sheaths and surrounding axons, as in COVID-19 infection, for example via antigenic mimicry, bystander activation, or "superantigens" mechanism.^[12,13] As we have already mentioned above, OCNP after COVID-19 vaccination have been actually described, while RPON could be described as a Painful OCNP.

The next steps of AEFI algorithm are also met. We have excluded any other possible explanation for the condition of our patient, while until now there is not such kind of data that would *reject* a potential

causal association.^[13] It is worth noting the necessity of lumbar puncture to rule out other conditions, such as infectious, inflammatory, or neoplastic processes, especially in the first episode of RPON, where results should be normal.^[14] Possibly inflammatory CSF findings have been described in only two cases, one case with a single oligoclonal band, and another with an elevated IgG index, both, however, involving the fourth nerve, raising the question of a possible different etiologically form of RPON.^[15] A case of increased CMV IgG levels in CSF, is of doubtful significance, since it is a common finding in general population.^[16] Proceeding to the reasoning of the AEFI algorithm, neurologic symptoms and signs 9-11 days after vaccination can be considered as post-vaccinal,^[4] while similar previous cases of RPON after immunization, have been surprisingly described also around 10 days after vaccination.^[3,4] Finally, the booster vaccine dose was more commonly associated with headache, and CN palsies have been also described after a booster dose,^[17] which is in accordance with the mechanisms of adaptive immunity, that takes some days or weeks to develop, while for example some cytokines achieve higher titers after the 2nd vaccine dose.^[18] Our patient developed the episode of RPON after a booster vaccine dose, which is compatible with this theory.

In conclusion, it is important to highlight the possible trigger factors of RPON, in order to better understand its pathogenesis, which still remains unclarified. Taking into consideration this case and similar other cases of cranial and OCNP after vaccination, we may accept with more certainty, that the core problem of RPON is a neuropathy, while headache could be a secondary event that takes place in some individuals whose anatomical structures and physiology endeavour the earlier triggering of an ipsilateral headache. For this reason, we believe that this case report, is important not only because it is the first case report that describes a clear recurrence of RPON after COVID-19 vaccination, but also because it is the first report of relapse of RPON after immunization, and especially with an mRNA vaccine, *in the adult population*, adding valuable information into the pathophysiology of the syndrome and secondary to the study field of COVID-19 infection, COVID-19 vaccines and their potential side effects. The rarity of these cases in adults can be explained by the fact, that since recently adult vaccination was not common, and RPON is also a rare entity. However, neurologists should be aware of this and similar potential side effects of COVID-19 vaccination, and vaccines in general, which in no case outweigh their life-saving benefits, in order to act properly. According to ICHD-3, "treatment with corticosteroids is beneficial in some patients" and is actually the common practice.^[11] In a literature review, 96.2% of patients who received corticosteroids alone, benefited from the therapy. A benefit from Non-

Steroid Anti-inflammatory Drugs, like indomethacin, and anti-migraine medicine, has also been described in the past.^[2] Although RPON is also considered a self-limiting condition, that can be improved up to a couple of months later, there are patients prone to recurrent episodes with persistent eye misalignment, where injection of botulinum toxin or strabismus surgery may be considered.^[19]

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