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LETTER TO THE EDITOR

Cluster headache after COVID-19 vaccination with Comirnaty: A signal in pharmacovigilance database[☆]

Keywords COVID-19; Vaccines; Cluster headache

Abbreviations

BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
MRI	magnetic resonance imaging
ROR	reporting odds ratio
SUNCT	short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

We report a case of probable cluster headache, which occurred 8 hours after a third dose of COMIRNATY[®] vaccine in December 2021.

A 26-year old male patient, with a body mass index (BMI) of 31.3, received 2 doses of COMIRNATY[®] (Pfizer) in May and July 2021, followed by a booster dose of COMIRNATY[®] on 9 December 2021 in the left arm (Pas-de-Calais region, France). Eight hours later, he experienced unilateral left periorbital headache, pulsatile, intense and lasting up to 3 hours, recurring twice a day, associated with homolateral lacrimation and nasal obstruction, without myosis or ptosis. Neurological examination was strictly normal. Among the main differential diagnoses, seizure duration of more than 10 minutes was not suggestive of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and the number of seizures limited to 2 per day was not suggestive of paroxysmal hemicrania. Treatment with ibuprofen 400 mg and/or intranasal sumatriptan 10 mg/0.1 mL calmed the pain. We did not perform a magnetic resonance imaging (MRI); the pain gradually disappeared until 3 January, not justifying any further examination. This first episode of probable cluster headache for this patient, meeting the other criteria for cluster headache according to the international classification of headache disorders [1], was notified to the regional pharmacovigilance center in Lille (registered on December 14 2021; registration number CRPV215772). In this case, the global imputation

was determined as I2 by the French drug reaction assessment method [2].

In the international pharmacovigilance database, we found 628 cases of cluster headache with the COMIRNATY[®] vaccine at the date of 3 January 2021. These observations are 5 times more frequent with this vaccine (reporting odds ratio ROR = 5.1; 95% confidence interval CI: 4.7–5.6) than with the other drugs, suggesting a pharmacovigilance signal [2]. When extended to the other COVID-19 vaccines in the national pharmacovigilance database, we also find a signal with the 913 cases of cluster headache after VAXZEVRIA[®] vaccine (ROR = 17.8; 95% CI: 16.5–19.1) and with 156 cases after SPIKEVAX[®] vaccine (ROR = 2.9; 95% CI: 2.5–3.3). An analysis on Google Trends does not show a significant increase in requests about cluster headache in 2021.

The European monographs for COMIRNATY[®] vaccine do not mention the occurrence of cluster headache as an adverse event. In the literature, we do not find any mention of cluster headache with COMIRNATY[®] vaccine. Post-vaccination headaches have been described [3] and persistent migraines (status migrainosus) [4]. Cases of Parsonage-Turner syndrome have been reported a few hours or days after vaccination [5], as well as small fiber neuropathy at one week [6].

The association between headache and COVID-19 vaccines could be explained by the immune response occurring after vaccination: activation of CD4⁺ and CD8⁺ T cells leading to the activation of nociceptors [4,7], or by immune-mediated hypersensitivity to polyethylene glycol [6], or by an autoimmune mechanism.

Another pathophysiological explanation could be neuroinflammation related to injecting too close to a nerve in the deltoid during an intramuscular injection, which is recommended with COVID-19 vaccines—although the maximum of our immune cells are in the tissues in the dermis, and an intradermal injection has already shown a better immunological response with the flu vaccine [8].

Caution should be exercised in diagnosing cluster headache, given the need for five episodes. Differential diagnoses should be kept in mind by clinicians, such as acute sinusitis, ophthalmic zona, etc.

In conclusion, cluster headache after vaccination against COVID-19 is a possible adverse effect, although it may also be a concomitant event. In any case, informing clinicians about the identified signal may help to better report similar cases and to better understand their evolution. Obviously, vaccination against COVID-19 has long shown a favorable

[☆] This case has been declared to regional pharmacovigilance center of Lille on 14 December 2021 under the registration number CRPV215772.

benefit-risk balance which these observations do not call into question.

Disclosure of interest

The authors declare that they have no competing interest.

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Michaël Rochoy^{a,b,c,1,*}, Eric Billy^{b,1},
Franck Clarot^{b,1}, Victor Dumortier^c,
Sophie Gautier^c, Romain Barus^c

^a University of Lille, CHU de Lille, OULR
2964-METRICS, CERIM, département de médecine
générale, 59000 Lille, France

^b Collectif Du Côté de la Science, France

^c University of Lille, centre régional de
pharmacovigilance, service de pharmacologie
médicale, CHU de Lille, 59000 Lille, France

* Corresponding author. 20, rue André-Pantigny,
62230 Outreau, France.

E-mail address: michael.rochoy@gmail.com

(M. Rochoy)

¹ Collectif Du Côté de la Science, France
<https://ducotedelascience.org/>.

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