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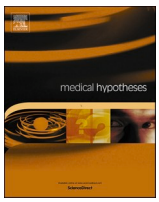

Can COVID-19 vaccines relieve severe tension-type headache and migraine?

Jordi González-Menacho [a], Mónica Villas-Roca [a], Helena Castañé [b], Jorge Joven [b], Jordi Camps [b,*], Simona Iftimie [c]

[a] Neurology Unit, Hospital Universitari de Sant Joan, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain
[b] Unitat de Recerca Biomèdica, Hospital Universitari de Sant Joan, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain
[c] Department of Internal Medicine, Hospital Universitari de Sant Joan, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain

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ABSTRACT

Chronic headache is a frequent disorder that can cause a significant deterioration in the quality of life of the affected person. The COVID-19 pandemic is compelling all countries to develop a complete vaccination protocol for the entire population. In this article, we present 8 clinical cases of patients suffering chronic headache which resolved completely or partially after vaccination. Five patients had migraine, 2 had a post-viral headache typical of COVID-19, and one had a headache induced by sexual activity. Resolution was complete in 3 cases, almost complete in 2 others, and a great improvement was observed in the other 3. We hypothesize that the administration of vaccines for COVID-19 can produce an improvement or the disappearance of symptoms in our patients by inhibiting synthesis of pro-inflammatory cytokines.

Introduction

Chronic headache is a common disorder that can impact all areas of a person's life, including the ability to fully participate in family, social and work activities. This disorder can cause considerable suffering, reduce quality of life and cause economic losses to the affected patient as well as to businesses and to society as large. Tension-type headache is usually associated with pain of moderate intensity, but migraine can cause severe and disabling pain, nausea, vomiting, and intolerance to light and sound [1]. COVID-19 has recently been added to the causes of chronic headache, as it is a common symptom of this disease, during infection and sometimes up to several months after [2,3]. The rapid spread of SARS-CoV-2 virus has meant that several vaccines were authorized within just a few months of the start of the pandemic and many laboratories obtained vaccines very quickly [4]. In Spain and the rest of the European Union, the vaccines that were initially distributed were Comirnaty® (Pfizer/BioNTech), based on mRNA, and AZD1222® -previously ChAdOx1®- (Astra-Zeneca), developed on a chimpanzee non-replicative adenovirus vector. Both vaccines are directed against fragments homologous to the Spike protein of SARS-CoV-2.

Between January and July 2021, and during their routine attendance at our Neurology outpatient clinic, eight patients with severe chronic headaches (in some cases caused by COVID-19 and in others not) spontaneously commented that their pain had decreased in frequency and/or intensity after the administration of the COVID-19 vaccine. In this article we describe these cases in detail and develop a hypothesis that can justify this unexpected observation.

The hypothesis

We hypothesize that the administration of vaccines for COVID-19 can produce an improvement or the disappearance of symptoms in our patients by inhibiting synthesis of pro-inflammatory cytokines (Fig. 1).

Criteria for the clinical evaluation of patients

Patients were attended to the Neurology outpatient clinic of the Hospital Universitari de Sant Joan de Reus, which is the reference consultation for headache patients in our geographic area. During the study period, the Unit attended to a total of 177 patients, of whom 120 had migraine. For patients who had not had COVID-19, chronic headache was established according to the criteria of the current classification of the International Headache Society (ICHD-3) [5,6]. However, for patients who had suffered COVID-19, the ICHD-3 classification could not

* Corresponding author at: Unitat de Recerca Biomèdica, Hospital Universitari de Sant Joan, C. Sant Joan s/n, 43201 Reus, Spain.
E-mail address: jorge.camps@salutsantjoan.com (J. Camps).

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be applied since it dates from 2018. In order to define this diagnosis, therefore, we set the following criteria, all of them required to be met: 1) the background of COVID-19 confirmed by PCR or serology, 2) the appearance of headache during or immediately after the diagnosis of COVID-19, 3) the patient had not suffered from similar episodes prior to the diagnosis of COVID-19, 'similar' meaning those with the same quality, location and symptoms, 4) other possible causes of headache having been excluded according to ICHD-3.

As this is an observational study, a cause-effect relationship between the administration of the vaccines and the improvement of headache cannot be established with certainty. However, it can be estimated through the evaluation of criteria such as those of Karch and Lasagna for adverse effects of medications [7]. These criteria are the following: 1) Not defined: no temporal relationship between vaccine and clinical improvement has been confirmed. 2) Possible: the temporal relationship is clear, but the clinical effect on headache is incomplete and transitory. 3) Probable: the temporal relationship is clear and the clinical effect on the headache is complete and/or permanent. 4) Defined: the case is considered probable and the scientific community also accepts as plausible the relationship between vaccination and headache improvement.

To consider a case as measurable, we required the headache to be present for a minimum of 3 months, for more than 10 days a month, prior to vaccination.

Clinical observations

We report a series of 8 patients (7 women and 1 man) aged between 30 and 72 years (mean = 52 years) that suffered from episodic migraine without aura (3 cases), chronic migraine (2 cases), post-viral headache (2 cases), or sexual activity-related headache (1 case). Results are summarized in Table 1.

SARS-CoV-2 infection was confirmed in one of the patients with post-viral headache, but not in the other case. The pre-vaccination frequency of headache episodes reported by our patients was high. Four patients reported having a daily headache and three, for more than 20 days a month, with the mean headache value being 25 days a month. The patients had no relevant medical history, except for one case of fibromyalgia and one case of systemic lupus erythematosus. Their headache treatments were primarily pain relievers on demand; only two patients had previously tried preventive therapies such as amytriptiline or topiramate. No patients were taking preventive medication when they were vaccinated.

After vaccination, the average headache days per month decreased to 5, meaning a reduction of 80% in headache days per month. Remission was complete in 3 cases, almost complete (improvement greater than 95%) in 2 cases, and partial (improvement between 65 and 95%) in 1 case. Two more cases reported a clear improvement of intensity of pain but no change in frequency. The causal relationships between the vaccination for COVID-19 and the headache improvement was identified as 'probable' in 7 cases and 'possible' in the other one.

Evaluation of the hypothesis

The pathophysiological explanation of this hypothesis is currently mere speculation, but it may be related to the fact that most patients suffered from some type of headache associated with inflammatory processes: Five patients suffered from migraine, one had a persistent headache post-COVID-19, and another one met the WHO criteria for a suspected case of COVID-19. All patients met the ICHD-3 criteria to be considered as post-viral headaches as well as new-onset chronic daily headaches [7]. The evidence suggests a relationship of these headaches with elevated levels of pro-inflammatory molecules, such as calcitonin gene-related peptide (CGRP) or interleukin (IL)-6, among others. A causal relationship of CGRP with migraine was reported two decades ago and is widely accepted today [8], but the circulating concentrations of this peptide are not higher in COVID-19 patients. Indeed, it has been reported that patients with COVID-19 have lower levels of CGRP than the healthy population [9]. This finding suggests that the effect of vaccines is either not due to an inhibition of the action of CGRP or that it

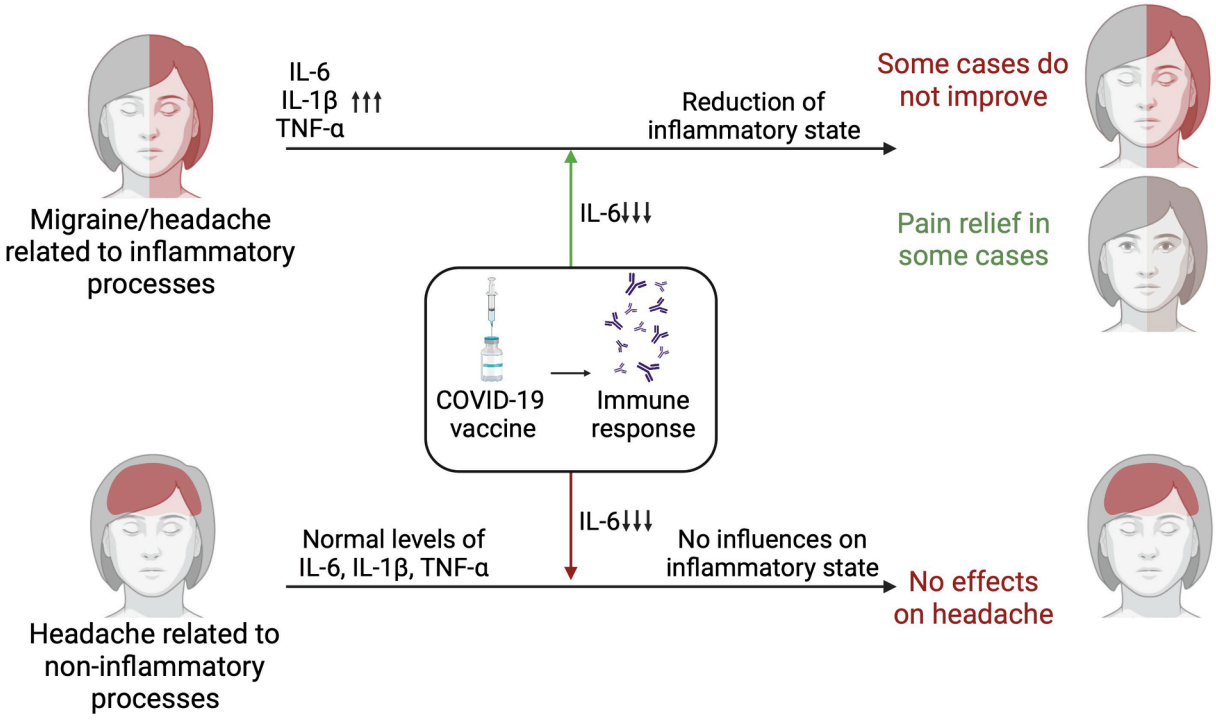

Fig. 1. We hypothesize that the immune response induced by COVID-19 vaccines decreases circulating levels of IL-6, which could lead to relief or even disappearance of pain in some patients with migraine or other types of inflammatory headache with high levels of cytokines. Abbreviations: IL, interleukin; TNF, tumor necrosis factor. Figure created with BioRender.com.

Table 1
Demographic and clinical characteristics of the studied patients.

Variable	Patients							
	1	2	3	4	5	6	7	8
Age	30	60	38	47	51	70	51	72
Sex	F	F	F	F	M	F	F	F
Smoking	No	No	Ex-smoker	No	No	No	No	No
AHT	No	No	No	No	Yes	No	No	No
T2DM	No	No	No	No	No	No	No	No
DLP	No	No	No	Yes	Yes	Yes	No	No
CVD	No	No	No	No	No	No	No	No
Cancer	No	No	No	No	No	No	No	No
Diagnosis	Migraine TTH ONN	Migraine	CIH	Migraine VH	HISA	VH	Migraine MAH	Migraine
HET, months	60	180	3	13	15	8	>300	>528
C19B	No	No	Yes	No	No	No	Yes	No
Vaccine	PF	AZ	PF	AZ	PF	AZ	PF	PF
DFDV	12/27/2020	04/01/2021	01/14/2021	03/05/2021	05/19/2021	04/19/2021	06/07/2021	04/06/2021
DSDV	01/18/2021	06/21/2021	02/08/2021	06/07/2021	06/09/2021	No	No	04/27/2021
PREFREQ	11	20	30	30	30	30	26	27
POSTFREQ	0	10	25	0	30	0	2	1
RP	Probable	Probable	Probable	Probable	Possible	Probable	Probable	Probable
Headache intensity	Complete resolution	Great improvement	Great improvement	Complete resolution	Great improvement	Complete resolution	Almost complete resolution	Almost complete resolution

AHT: Arterial hypertension; AZ: Astra Zeneca; C19B: COVID-19 background; CVD: Cardiovascular disease; CIH; COVID-19-induced headache; DFDV: Date of the first dose of vaccine; DLP: Dyslipidemia; DSDV: Date of the second dose of vaccine; F: Female; HET: Headache evolution time; HISA: Headache induced by sexual activity; M: Male; MAH: Medication abuse headache; ONN: Occipital nerve neuralgia; PF: Pfizer; POSTFREQ: Postvaccine frequency. Number of days per month with headache episodes after vaccination PREFREQ: Prevaccine frequency. Number of days per month with headache episodes before vaccination; RP: Relationship probability; T2DM: TTH: Tension-type headache; Type 2 diabetes mellitus; VH: Viral headache.

may involve more complex regulatory mechanisms. Furthermore, recent analyses have not shown a clear relationship between the use of monoclonal anti-CGRP medications and the risk of COVID-19 [10].

On the other hand, several studies reported that patients with various types of chronic headache have elevated levels of IL-6 [11–13]. High levels of IL-6 have even been considered a reliable way to measure intensity and impact of headache due to COVID-19 [14]. It is also known that IL-6 is stimulated by CGRP and that this is one of the mechanisms by which CGRP produces migraine [15]. It would be logical to think, then, that in patients receiving a COVID-19 vaccine, IL-6 levels would decrease and lead to an improvement in headache. What is strange, however, is the speed at which the vaccination improved or resolved the headaches, because other medications given for headaches require much longer treatment times. Given that vaccines act differently from traditional or non-vaccine medications, conventional pharmacokinetic concepts may not fully apply in this case. It should be noted that the Pfizer vaccine technical sheet does say in the 'pharmacokinetics' section that this concept is not applicable to this substance.

Limitations and critical appraisal of our observation

Certain limitations condition the interpretation of our results. First, we have known these effects of vaccines *a posteriori*, and in most cases (6 of the 8) these patients had never been attended to by us before these events. This prevented biological samples from being obtained that would have allowed a deeper understanding of the underlying mechanisms of this supposed relationship. Furthermore, the experience is based wholly on the information given by the patients, and no system is known to date that is able to measure pain in terms of intensity or frequency from an objective point of view, so its assessment is always carried out using clinical scales. In the case of headache, it is mandatory to refer to the diagnosis of each patient according to the International Headache Society classification system [5], and in terms of measuring its impact, it is advisable to use the frequency of the headache (usually days of headache per month) as a parameter that enables comparisons between treatments in current pharmacological trials [6]. Most of our patients met the criteria recommended by the ICHD-3 guidelines regarding the baseline headache lasting at least one year before the pharmacological intervention, to exclude those cases with headaches that could remit spontaneously [6]. These guidelines also recommend considering as 'responders' people who have experienced an improvement of at least 50% of their condition, usually based on the frequency of pain, a rate that was met in all of our patients. It should be noted that patients reported their pain remission without any question being addressed by the clinician who attended them. This, together with the fact that the patients did not know each other and common data such as the period between vaccination and the appearance of improvement, which is practically identical in all cases, strengthens their evidence. It is further strengthened because the patients had thought before they were vaccinated that their condition would worsen, and then all of them described their improvement as 'unexpected' and 'surprising'. An improvement in their condition lasting more than 7 months post-vaccination, with no headache at all in some cases, would reasonably exclude the likelihood of a placebo effect, especially considering that in some of the patients the headache had lasted for more than 5 years, and more than 40 years in one of the cases. It is reasonable to suggest a probable causal relationship between the vaccine and the clinical effect beyond being merely subjective.

Conclusion

The cases described here point to the possibility that vaccines against COVID-19 provoke remission, or at least a significant improvement, in chronic headaches of various types, including those associated with chronic post-COVID-19 symptoms. More prospective studies are needed to further clarify this possibility.

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Consent statement/ethical approval

The study was conducted according to the guidelines of the

Declaration of Helsinki, and approved by the *Comitè d'Ètica i Investigació en Medicaments* (Institutional Review Board) of *Institut d'Investigació Sanitària Pere Virgili* (Resolution CEIM 040/2018, amended on 16 April 2020).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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