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**Reply to the letter: Headaches durin/after SARS-CoV-2
infection/vaccination can be primary and secondary as well as acute
and chronic, by Finsterer J and Mehri S**

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LETTER TO THE EDITOR

Reply to the letter: Headaches during/after SARS-CoV-2 infection/vaccination can be primary and secondary as well as acute and chronic, by Finsterer J and Mehri S

Dear Editors,

We sincerely thank Dr Finsterer and Dr Mehri for taking the time to carefully read our article titled 'Headaches and facial pain attributed to SARS-CoV-2 infection and vaccination: a systematic review' [1]. Dr Finsterer and Dr Mehri make five comments concerning our article that warrant a reply [2].

POINT ONE

No distinction has been made between headache/facial pain in the acute stage of the disease and long COVID syndrome or between acute COVID vaccination syndrome and post-acute COVID vaccination syndrome.

Reply. We state on page 2 that this article aims to cover acute COVID-19, after the resolution of acute COVID-19 and SARS-CoV-2 vaccines. The phase after the resolution of acute COVID-19 refers to the so-called long COVID-19. Thus, we discuss in detail the prevalence and the features of headaches during this phase of COVID-19.

POINT TWO

The absence of facial pain as a complication is incomprehensible. There are several reports about trigeminal neuralgia (TN) following COVID-19 or after SARS-CoV-2 vaccination/infection [3].

Reply. There are only three cases of TN reported in the recent literature (two of which were published after the literature search window of our study), among millions of people vaccinated with SARS-CoV-2. Notably, in a case of TN reported after SARS-CoV-2 mRNA vaccination [4], the diagnosis was disputed by the author [5] of this letter [2]. In the context of COVID-19, there is only one report of TN, with a time lag of 18 months [3]. In conclusion, the anecdotal cases published after our literature review do not change our conclusion that there is limited evidence that facial pain is a major clinical manifestation of SARS-CoV-2 infection or vaccination.

POINT THREE

The classification of SARS-CoV-2 infection- or vaccination-associated headaches as only primary headaches is incomprehensible. Associated headaches can also be secondary, as they are triggered by SARS-CoV-2 infection or vaccination complications.

Reply. We are aware of this distinction and there is a paragraph devoted to this issue on page 9, which reads as follows: 'SARS-CoV-2 infection may be associated with an increase in migraine attacks, which could indicate the involvement of inflammatory mediators in the pathophysiology of migraine and can impact the intrinsic threshold for upcoming attacks. In the case of an increase of a primary headache, the migraine diagnosis is still a primary headache. The same applies to the case of pre-existing tension-type headache (TTH). In the case of a new headache occurrence that is attributed to SARS-CoV-2 infection, it should be coded as a secondary headache even if the phenotype resembles migrainous characteristics. Distinguishing headaches attributed to systemic SARS-CoV-2 infection from primary headache disorders such as migraine or TTH might be difficult, but previous history of headaches can be helpful in that case. Characterization of frequently recurring headaches generally requires a headache diary to record information on pain and associated symptoms' [1].

POINT FOUR

Several causes of secondary headaches in patients with SARS-CoV-2 infection or after SARS-CoV-2 vaccination have not been considered, for example central nervous system (CNS) vasculitis, reversible cerebral vasoconstriction syndrome and venous sinus thrombosis.

Reply. Our aim was not to review the potential causes of secondary headaches in patients with SARS-CoV-2 infection or vaccination, but rather to present common features for headaches in the context of SARS-CoV-2 infection or vaccination and classify them phenomenologically according to the International Classification of Headache

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Disorders [6]. CNS vasculitis, reversible cerebral vasoconstriction syndrome and venous sinus thrombosis are very rare complications of SARS-CoV-2 infection or vaccination that might present with severe headaches. Regardless, headaches that often occur in SARS-CoV-2 infection or vaccination are basically either an aggravation of a pre-existing primary headache, most likely migraine or TTH, or a secondary headache due to systemic inflammation closely associated with the infection. Thus, we state in our article that 'Cytokine storm, with endothelium disruption and blood-brain barrier damage, possible microglia, and amyloid cascade activation, might be the cause of a more severe acute COVID-19 syndrome including headache as an accompanying symptom. Potential mechanisms of pre-existent primary headache, along with indirect activation of the trigeminovascular system and persistent inflammation, catabolism syndrome and endothelial dysfunction, have been suggested as possible pathophysiological mechanisms of persistent headache during the phase after the resolution of acute COVID-19. No diagnostic criteria for headache attributed to SARS-CoV-2 vaccines are suggested because headache is a common adverse event in all vaccines and may share nocebo features' [1].

POINT FIVE

Cerebral sinus thrombosis is not rare in the context of SARS-CoV-2 infection or vaccination.

Reply. A systematic review that investigated CNS magnetic resonance imaging findings following SARS-CoV-2 vaccination across various vaccine types identified several CNS conditions, including cerebral sinus thrombosis, vaccine-induced immune thrombotic thrombocytopenia, acute disseminated encephalomyelitis and autoimmune encephalitis, among others, all of which might present with headaches. The authors state that 'The incidence of these neurological complications is extremely rare, and the benefits of vaccination outweigh the risks. The reviewed studies were primarily case reports or case series, and thus large-scale epidemiological studies and controlled clinical trials are needed to better understand the underlying mechanisms and risk factors associated with these neurological complications following COVID-19 vaccination' [7]. We therefore stand by our statement that cerebral sinus thrombosis is a rare complication of SARS-CoV-2 vaccination.

In conclusion, we thank Dr Finsterer and Dr Mehri for their interest in headaches attributed to SARS-CoV-2 infection or vaccination. Indeed, the title of their letter, 'Headaches during/after SARS-CoV-2 infection/vaccination can be primary and secondary as well as acute and chronic', echoes our view.

AUTHOR CONTRIBUTIONS

Dimos-Dimitrios D. Mitsikostas: Conceptualization; writing – original draft; validation. **Edoardo Caronna:** Writing – review and editing. **Marina De Tommaso:** Writing – review and editing. **Christina I. Deligianni:** Writing – review and editing. **Esme Ekizoglu:** Writing – review and editing. **Hayrunnisa Bolay:** Writing – review and editing. **Carl**

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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