

COMMENTARY

Headache with SARS-CoV-2 infection: A matter of concern

Lukas Dearing | Felix Müller | Johann Sellner 

Department of Neurology, Landeskrankenhaus Mistelbach-Gänserndorf, Mistelbach, Austria

Correspondence

Johann Sellner, Department of Neurology, Landeskrankenhaus Mistelbach-Gänserndorf, Mistelbach, Austria.

Email: johann.sellner@mistelbach.lknoe.at

Keywords: COVID-19, headache, long COVID-19, meta-analysis, new daily persistent headache, post-infectious, SARS-CoV-2, viral illness

The world has been kept in suspense since early 2020 by coronavirus disease 2019 (COVID-19), a multi-organ disease caused by the highly contagious severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Cephalalgia, the most frequent early symptom of COVID-19, not only is painful but is a disabling condition that causes substantial personal suffering, impaired quality of life, and economic burden [1]. Headache in acute viral illness is seen as a consequence of the immune response, whereas the mechanism of action leading to its persistence thereafter is not well understood.

In this issue, Fernandes-de-las-Penas et al. [2] confirm that headache is not only frequent in the acute phase of SARS-CoV-2 infection but is a notable COVID-19 sequela in a subgroup of patients. Their findings are based on a meta-analysis of various scientific databases up to May 2021, which involved 28,438 COVID-19 survivors from 35 studies (longitudinal design in 40%). The cohort's mean age was 46.6 years, 57% were male, and the methodological quality was high in 45% of the studies. The overall rate of headache as an onset symptom or on hospital admission was 47.1%. The rate of headache did not differ between hospitalized and non-hospitalized patients, indicating that the immune response per se but not disease severity may be of relevance. The prevalence of post-COVID-19 headache declined during the disease course but remained at a frequency of 8.4% after 6 months.

Using the numbers provided by the meta-analysis, approximately 99 million people have developed headache during acute COVID-19 so far, and almost 16 million survivors were still experiencing headache half a year later (as of 20 March 2021). This staggering number shows the need to build awareness in the medical community and prevent disparities in healthcare [3]. In this regard, headache in acute COVID-19 is more intense in women and is characterized by bilateral headache predominantly affecting the forehead, with pressing quality and severe intensity, and is frequently accompanied

by typical migraine symptoms [1]. Individuals with headache during acute COVID-19 are generally younger and have a higher frequency of fever.

Investigations to understand the pathogenesis of headache in acute viral illness and as a persistent symptom are still only beginning. Interestingly, the anti-inflammatory cytokine interleukin-10 is higher in individuals with acute COVID-19 headache, which could reflect a homeostatic response to counteract an intense pro-inflammatory immune response [4]. Concerning post-viral headache, central sensitization, a process in central pain pathways associated with synaptic plasticity and increased neuronal responsiveness induced by neuroinflammatory stimuli, may play a decisive role. There is currently minimal understanding of the clinical spectrum and predisposing factors for post-COVID-19 cephalalgia. There is also a need to determine the relevance of somatic and psychiatric comorbidities and the significance of persistent headache in the long COVID-19 symptom complex. A wide range of symptoms are discussed as part of long COVID-19 and include fatigue, headache, shortness of breath, lack or distorted smell function, muscle weakness, low fever, and cognitive dysfunction. Notably, some individuals with post-COVID-19 headache had a pre-existing primary headache syndrome, and SARS-CoV-2 infection might have triggered exacerbation or chronification. There is also speculation that a subgroup of individuals with post-COVID-19 headache may be experiencing new daily persistent headache (NDPH), one of the most treatment-refractory primary headache disorders [5]. NDPH is characterized as a "headache that is daily from the onset, and very soon unremitting, typically occurring in individuals without prior headache history". NDPH may have features suggestive of migraine or tension-type headache. A unifying pathway leading to post-COVID-19 headache is therefore unlikely. There is much to be done before eagerly awaited therapeutic options and preventive strategies can be developed.

CONFLICT OF INTEREST

All authors report no disclosures relevant to the manuscript.

AUTHOR CONTRIBUTIONS

Lukas Dearing: Formal analysis (equal); Methodology (lead); Writing – original draft (lead). **Felix Müller:** Methodology (equal); Project administration (equal); Writing – review and editing (supporting). **Johann Sellner:** Conceptualization (lead); Formal analysis (lead); Project administration (lead); Supervision (lead); Writing – review and editing (lead).

DATA AVAILABILITY STATEMENT

Not relevant.

ORCID

Johann Sellner  <https://orcid.org/0000-0001-8749-5533>

REFERENCES

1. Garcia-Azorin D, Sierra A, Trigo J, et al. Frequency and phenotype of headache in covid-19: a study of 2194 patients. *Sci Rep.* 2021;11(1):14674.
2. Fernandez-de-Las-Penas C, Navarro-Santana M, Gomez-Mayordomo V, et al. Headache as an acute and post-COVID-19 symptom in COVID-19 survivors: a meta-analysis of the current literature. *Eur J Neurol.* 2021;28:3820-3825. <https://doi.org/10.1111/ene.15040>
3. Sellner J, Jenkins TM, von Oertzen TJ, et al. A plea for equitable global access to COVID-19 diagnostics, vaccination and therapy: the NeuroCOVID-19 Task Force of the European Academy of Neurology. *Eur J Neurol.* 2021;28:3849-3855. <https://doi.org/10.1111/ene.14741>
4. Trigo J, Garcia-Azorin D, Sierra-Mencia A, et al. Cytokine and interleukin profile in patients with headache and COVID-19: a pilot, CASE-control, study on 104 patients. *J Headache Pain.* 2021;22(1):51.
5. Rozen TD. Daily persistent headache after a viral illness during a worldwide pandemic may not be a new occurrence: lessons from the 1890 Russian/Asiatic flu. *Cephalalgia.* 2020;40(13):1406-1409.

How to cite this article: Dearing L, Müller F, Sellner J. Headache with SARS-CoV-2 infection: A matter of concern. *Eur J Neurol.* 2021;28:3554–3555. <https://doi.org/10.1111/ene.15084>