

## Urgent Need for ICHD Criteria for COVID-19-Related Headache: Scrutinized Classification Opens the Way for Research

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### To the Editor,

Headache is a prevalent COVID-19 symptom and the most frequent presentation is bilateral, and long-lasting with only partial or no response to analgesics (1). Furthermore, this headache showed a higher incidence of anosmia, in line with previous research in our recent paper (1). Some patients presented with a headache at the onset of symptoms, which lasted for at least 15 days in 15% of these patients (2). Furthermore, the rate of headache with COVID-19 is probably higher than that of other common cold viruses (mainly rhinoviruses and other CoVs) (3). Headache described under the rubric of acute headache attributed to systemic viral infection, (code 9.2.2.1) is described in the ICHD-3 (International Classification of Headache Disorders) classification. Unfortunately, the underlying mechanisms of this entity are not illuminated so far (4). In our analyses, the association of headache with fever seems not to be decisive (1). Therefore, for COVID-19-related headache, the simplistic view of a "causal" relationship with fever or respiratory symptoms is not adequate.

COVID-19-related headache is one of the most important newly emerging forms of headache in this century and deserves a special place in our headache classification. Therefore, we want to propose preliminary criteria (Box 1), based on our experience and accumulating literature.

The rationale for separating the COVID-19-related headache is trifold. A) The pandemic is still influencing the whole world with an increased number of affected patients. B) Moreover, headache with the distinguishable profile can occasionally be seen alone as the first sign of the disease and it is of utmost importance to recognize those headache patients with COVID-19 early. C) Although having some heterogeneous characteristics, (like many other headache syndromes), the characteristics of COVID-19-related headache are still distinguishable and showed differentiating value from primary headaches.

Headache attributed to COVID-19

Diagnostic criteria:

- A) The presence of a headache fulfilling all of the below criteria in C
- B) The presence of a laboratory confirmed COVID-19 as the causative disorder (PCR or IG evidence)
- C) Evidence of causation demonstrated by all of the following:
  - 1) Headache has developed in temporal relation to the onset of COVID-19 (-2+9 days)
    - a. Either new emerging headache or
    - b. New emerging headache has different characteristics in a patient with a known/diagnosed type of primary headache
  - 2) It resolves in 1 month in parallel with clinical and laboratory improvement (di-dimer etc.)
  - 3) Headache has at least two of the following characteristics
    - a. Bilateral (frontal or frontotemporal location predominant)
    - b. Long-lasting (>48 hours)
    - c. Resistant to simple analgesics (or to previously successful drugs for primary headache sufferers)
    - d. Association with ageusia/anosmia
- D) Not better accounted for by another ICHD-3 diagnosis

A re-analysis of our series (1) by binary logistic regression was computed with these proposed 4 variables (anosmia, bilateral occurrence, analgesic resistance and duration over 48 hours). The model summary showed a -2 Log likelihood ratio of 791.813 (Nagelkerke R Square: 0.294) and using this model 87.6% of the COVID-19 patients could be classified correctly with a cut off value of 0.5. For any of the two of these criteria,

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we calculated a high specificity of 0.95 but a low sensitivity of 0.379, with a positive predictive ratio of 0.516 (relative risk: 7.517 and OR: 11.490). Low sensitivity is understandable for a heterogeneous condition with still discussed laboratory confirmation (we take PCR positive cases only) but high specificity is secure for research guidance.

The underlying mechanisms of headache related to COVID-19 are not uncovered yet (5) though the involvement of trigeminal system and inflammasome activation were implicated (6,7). The close relation between headache and anosmia/ageusia may give us some clues and support a direct invasion of cranial nerves by the virus. To conceive appropriately designed comparable translational studies, the acceptance of ICHD criteria will be guiding the researcher. This will also make the pandemic disaster an opportunity, and improve our limited understanding to unravel the mysteries of the triggering mechanisms of viruses for the headache mechanisms.

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