

# Headache in patients infected with the novel coronavirus (Covid-19): An integrative literature review

Cefaleia em pacientes infectados pelo novo coronavírus (Covid-19): uma revisão integrativa da literatura

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## ABSTRACT

**Introduction:** The disease caused by the new coronavirus was named by the acronym Covid-19 which means “CORona Vlrus Disease”, while “19” refers to the year 2019, when the first cases in Wuhan, China, were identified. **Objective:** Our objective was to identify the prevalence of headache and to know its clinical characteristics in COVID-19 patients, available in the literature. **Methods:** Based on a literature search in the major medical databases and using the descriptors “headache and coronavirus”, “headache and 2019-nCoV”, “headache and SARS-CoV-2”, “headache and coronavirus and 2019-nCoV” and “headache and coronavirus and SARS-CoV-2” we include articles published between January 2019 and April 2020. We found 94 articles, but only 13 met the inclusion criteria. **Results:** In 13 articles analyzed in this review, a total of 3,105 Chinese patients (51.6% men and 48.4% women) had laboratory diagnoses of COVID-19. In 240 (7.7%) patients, headache was an associated symptom of COVID-19, but in only 52 (21.7%) of them there was some information about the characteristics of this headache. **Conclusions:** COVID-19 patients have several clinical manifestations, including headache that is nonspecific with a prevalence of 7.7%.

**Keywords:** Headache; Coronavirus; Covid-19; 2019-nCoV; SARS-CoV-2

## RESUMO

**Introdução:** A doença causada pelo novo vírus Corona foi batizada com o acrônimo COVID-19, que significa “Doença de Corona Vlrus”, enquanto “19” refere-se ao ano de 2019, quando foram identificados os primeiros casos em Wuhan, na China. **Objetivo:** Nosso objetivo é identificar a prevalência da cefaleia e conhecer suas características clínicas em paciente com COVID-19, disponíveis na literatura. **Método:** Com base em uma pesquisa bibliográfica nas principais bases de dados médicos e utilizando os descritores “headache and coronavirus”, “headache and 2019-nCoV”, “headache and SARS-CoV-2”, “headache and coronavirus and 2019-nCoV” and “headache and coronavirus and SARS-CoV-2” incluímos artigos publicados entre janeiro de 2019 e abril de 2020. Foram encontrados 94 artigos, mas apenas 13 preencheram os critérios de inclusão. **Resultados:** Em 13 artigos analisados nesta revisão, um total de 3.105 pacientes chineses (51,6% homens e 48,4% mulheres) tiveram diagnóstico laboratorial de COVID-19. Em 240 (7,7%) pacientes, a cefaleia foi um sintoma associado ao COVID-19, mas em apenas 52 (21,7%) deles havia alguma informação sobre as características dessa cefaleia. **Conclusão:** Os pacientes com COVID-19 apresentam várias manifestações clínicas, inclusive cefaleia que é inespecífica e com uma prevalência de 7,7%.

**Descritores:** Cefaleia; Coronavirus; Covid-19; 2019-nCoV; SARS-CoV-2

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## INTRODUCTION

The disease caused by the novel coronavirus (2019-nCoV) was named by the acronym COVID-19 which means “CORona Vlrus Disease”, while “19” refers to the year 2019, when the first cases in Wuhan, China, were identified. The virus that causes this disease, a beta coronavirus, is called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and it is the same

virus that causes Severe Acute Respiratory Syndrome (SARS), identified in 2002, and Middle East Respiratory Syndrome (MERS), identified in 2012. Transmission of 2019-nCoV

from humans to humans has been confirmed in China and the USA and occurs mainly with the contact of respiratory droplets from infected patients<sup>1</sup>.

In December 2019, in China, a novel coronavirus was identified as

the cause of a severe acute respiratory syndrome and received worldwide attention. It is a new emerging zoonotic agent that results in a severe syndrome that, in some patients, leads to the need for intensive respiratory treatment with specialized management in intensive care units<sup>2</sup>.

In January 2020, the World Health Organization (WHO) declared the outbreak in China as a public health emergency of international interest. In March 2020, with the spread of the virus in different countries, the infection caused by SARS-CoV-2 was considered a pandemic and called COVID-19. In early April, WHO recorded more than 1 million cases of patients infected with SARS-CoV-2 worldwide and more than 65,000 deaths caused by the pandemic worldwide. In Brazil, at the time of writing this manuscript, there are more than 18,000 cases of infection and more than 1,000 deaths<sup>3</sup>.

According to a Chinese study, the main clinical symptoms of patients with COVID-19 are fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), dyspnoea (18.6%), sore throat (13.9%) and headache (13.6%). Gastrointestinal symptoms, such as diarrhea (3.8%) and vomiting (5.0%) are less frequent<sup>4</sup>. Elderly and people with underlying diseases are susceptible to infection and more predisposed to severe outcomes, which may be associated with acute respiratory distress syndrome (ARDS) and the cytokine storm<sup>5,6</sup>.

Although headache is one of the clinical manifestations of COVID-19, this symptom is still poorly characterized. In this context, our objective was to identify the prevalence of headache and to know its clinical characteristics in a patient with COVID-19, available in the literature.

## METHODS

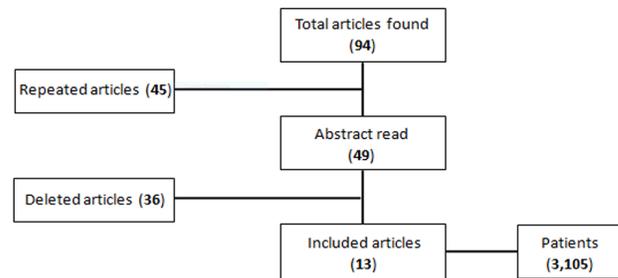
This study was an integrative and retrospective review of the articles on headache as a symptom of COVID-19 published in the last 16 months. The research was performed in the online databases *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILacs), Scientific Electronic Library Online (SciELO), Chinese National Knowledge Infrastructure

(CNKI) and Medical Literature and Retrieval System onLine (MEDLINE/PubMed®), from January 2019 to April 2020, given the current status of the pandemic by SARS-CoV-19. We have used the descriptors “headache and coronavirus”, “headache and 2019-nCoV”, “headache and SARS-CoV-2”, “headache and coronavirus and 2019-nCoV” and “headache and coronavirus and SARS-CoV-2”.

Articles written in all languages were included. Editorials, comments, letters to the editor, review articles, articles that were not fully available or those that did not have accurate information were excluded. To ensure the validity of these articles, the selected studies were analyzed in detail, by all authors, for the presence of headache in patients with COVID-19.

In our search, we found a total of 94 articles, but with the elimination of repeated articles, only 49 remained.

After reading the abstracts, we excluded articles that did not describe headache with associated symptom (36 articles). Only 13 articles describing case series were included and made up this review, totaling 3,105 patients (Figure 1).



**Figure 1.** Flowchart of search and selection of studies

Data were analyzed based on demographic and clinical characteristics and are presented as percentages. The percentage is always related to the total number of patients whose information was available for the specific issue.

## RESULTS

In 13 articles analyzed in this review, a total of 3,105 Chinese patients (51.6% men and 48.4% women) had laboratory diagnoses of COVID-19. In 7.7% (240/3,105) patients, headache was an associated symptom of COVID-19, but in only 21.7% (52/240) of them there was some information about the characteristics of this headache, as shown in Table 1.

## DISCUSSION

Coronaviruses are a large class of viruses that exist widely in nature and the newly discovered 2019-nCoV is the seventh coronavirus currently known to infect humans and also responsible for the current pandemic that started in China<sup>20</sup>.

To the best of our knowledge, this is the first study to assess headache characteristics in patients with COVID-19. We found that headache was an initial symptom of the disease in 3,105

patient with this disease. Its prevalence has been reported in most studies, but its semiological characteristics have rarely been addressed.

According to the International Classification of Headache Disorders, 3rd edition (ICHD- 3)<sup>21</sup>, headache attributed to systemic viral infection is characterized by its temporal relation to onset of viral infection and significant improvement or resolution in parallel with the improvement or resolution of systemic viral infection. Headache is usually diffuse and of moderate to severe intensity (Table 2).

Possibly, the neuroinvasive predisposition characteristic of coronaviruses is an explanation for patients with COVID-19 to develop headache. Genomic analysis shows that SARS-CoV-2 shares a highly

**Table 1.** Clinical characteristics of headache in 3,105 patients with coronavirus disease 2019 (Covid-19) in the period from January 2019 to April 2020 in China.

Published studies	Number of patients	Age (years)		Sex	Headache prevalence		Clinical characteristics
		Average	Variation		n	%	
Tian et al., 2020 <sup>7</sup>	262	47.5	1-94	M=127; F=135	17	6.5	Mild to moderate intensity in 93.5% of patients and it appeared at the beginning of the disease
Xu et al., 2020 <sup>8</sup>	62	41.0	19-65	M=35; F=27	21	34.0	71.4% of patients and it appeared at the beginning of the disease
Huang et al., 2020 <sup>9</sup>	41	49.0	18-65	M=30; F=11	3	7.3	NR
Liu et al., 2020 <sup>10</sup>	30	35.038	21-59	M=10; F=20	16	53.3	It appeared at the beginning of the disease
Cheng et al., 2020 <sup>11</sup>	1,078	46.0	0.25-94	M=573; F=505	22	2.0	NR
Wang et al., 2020 <sup>12</sup>	31	7.1	0.5-17	M=15; F=16	3	9.7	NR
Li et al., 2020 <sup>13</sup>	54	51.5	25-82	M=22; F=32	?	Rare	NR
Chen et al., 2020 <sup>14</sup>	99	55.5313.1	21-82	M=67; F=32	8	8.0	NR
Liu et al., 2020 <sup>15</sup>	137	55.0316.0	20-82	M=61; F=76	13	9.5	NR
Mi et al., 2020 <sup>16</sup>	10	68.4318.5	34-87	M=2; F=8	1	10.0	NR
Jin et al., 2020 <sup>17</sup>	651	NR	NR	M=331; F=320	67	10.3	It was more frequent in patients with gastrointestinal symptoms (21.6% versus 8.8%)
Ding et al., 2020 <sup>18</sup>	5	50.239.8	39-66	M=2; F=3	2	40.0	NR
Zhang et al., 2020 <sup>19</sup>	645	NR	NR	M=328; F=317	67	10.4	It was more frequent in patients with abnormal pulmonary imaging findings (11.3% versus 2.8%)

Legend: M - male; F - female; NR - not reported.

**Table 2.** Diagnostic criteria of ICHD-3 for headache attributed to systemic viral infection.

- A. Headache of any duration fulfilling criterion C
- B. Both of the following:
  1. systemic viral infection has been diagnosed
  2. no evidence of meningitic or encephalitic involvement
- C. Evidence of causation demonstrated by at least two of the following:
  1. headache has developed in temporal relation to onset of the systemic viral infection
  2. headache has significantly worsened in parallel with worsening of the systemic viral infection
  3. headache has significantly improved or resolved in parallel with improvement in or resolution of the systemic viral infection
  4. headache has either or both of the following characteristics:
    - a. diffuse pain
    - b. moderate or severe intensity
- D. Not better accounted for by another ICHD-3 diagnosis

homologous sequence with SARS-CoV-1 and MERS-CoV, in addition to a similarity of receptors in human cells. This can affect the respiratory tract and also the central nervous system, especially the thalamus and brain stem<sup>20</sup>.

Headache was observed in patients of all age groups, both in adults<sup>7-13</sup>, as in children<sup>6</sup>. It is important to note

that headache is a characteristic symptom of pneumonia caused by coronavirus and not exclusive to COVID-19, and does not behave as a differential symptom between these viral infections<sup>13</sup>.

In the studied cases of COVID-19, headache was usually associated with other typical symptoms of the disease, such as gastrointestinal symptoms. When the

patient experienced nausea, vomiting and diarrhea, headache was more frequent, probably due to the higher fever and hydroelectrolytic imbalance<sup>17</sup>.

We found in the 13 studies a prevalence of headache equal to 7.7% (240 out of 3.105 patients), ranging from 2.0% to 53.3%. A factor that may determine a higher prevalence of headache in COVID-19 patients is pneumonia, considered a predictive factor for severe subtypes of the disease. We observed that in patients with changes in pulmonary radiological images there was a higher prevalence of headache when compared to patients with normal exams<sup>19</sup>.

The symptoms of COVID-19 are nonspecific, making the initial clinical presentation indistinguishable from other viral respiratory diseases. Initially, there is a predominance of systemic manifestations, such as fever, fatigue, myalgia and asthenia<sup>10</sup>. However, the headache that can also appear at the beginning of the disease should not be neglected, but contribute to the diagnosis, especially in those patients with a positive epidemiological history.

This review had some limitations. All patients were from China, so some articles found were written in Chinese and needed to be translated<sup>10-13</sup>. In addition, as it is pandemic, new studies were published almost daily and described the headache incompletely. However, we believe that these findings are consistent with the clinical manifestations of this disease.

## CONCLUSION

COVID-19 patients have several clinical manifestations, including headache that is nonspecific with a prevalence of 7.7%.

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## CONFLICT OF INTEREST

There is no conflict of interest.

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