Letter to the Editor

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Headache is an important symptom in patients with coronavirus disease 2019 (COVID-19)

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To the Editor,

Coronavirus disease 2019 (COVID-19), the new pandemic infectious disease sustained by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has already affected millions of people worldwide, causing over 150,000 deaths [1]. The clinical course of this new pathology can be mild in up to 75–80% of subjects, characterized only by onset of bland and common respiratory symptoms. Nevertheless, the epidemiological importance of diagnosing COVID-19 in mildly symptomatic patients should not be underestimated, as these subjects have theoretically the same risk of transmitting the disease as overtly symptomatic patients [2]. Moreover, a consistent number of COVID-19 patients initially presenting with mild symptoms are at risk of progressing to severe disease, with development of respiratory distress, severe inflammatory response syndrome (SIRS), even progressing to death, when not timely and appropriately treated [3]. In a French cohort of 64 COVID-19 patients consecutively admitted for ARDS, features of neurologic illness were observed in up to 91% of patients [4]. While it is established that headache is a common symptom in patients with coronavirus diseases [5], we aimed to explore here whether the incidence of this symptom may predict the risk of having COVID-19.

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We carried out an electronic search in Scopus, Web of Science and Medline (PubMed interface), using the keywords “headache” AND “coronavirus 2019” OR “COVID-19” in all fields, between 2019 and the present date (i. e., April 17, 2020), limiting our search to articles containing not less than 10 COVID-19 patients and published in the English language. The title, abstract and full text (when available) of all items that could be initially detected with these search criteria were read, and those articles describing the incidence of headache in patients diagnosed with COVID-19 were then included in a pooled analysis. The reference list of all documents was also carefully scrutinized for retrieving further potentially eligible studies. A pooled analysis of individual data was finally conducted, by estimation of odds ratio (OR) and the 95% confidence interval (95% CI) for the incidence of headache in COVID-19 patients compared to the incidence of headache in the same geographical area, as retrievable from the Global Health Data Exchange (GHDx) registry, the largest worldwide database of health-related data and human pathologies [6]. The statistical analysis was carried out using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). The study was carried out in accordance with the declaration of Helsinki and with the term of local legislation.

A total number of 76 documents were originally identified based on our search criteria, 64 of which were immediately excluded because they were review articles (n=10), editorial materials (n=9), case reports (n=5), contained no incidence data of headache in COVID-19 patients (n=7), or dealt with pathologies other than COVID-19 (n=33). Two additional studies were identified by reading the reference list of these articles, so that a final number of 14 studies, totaling 2863 COVID-19 patients, could be finally included in our analysis [7–20] (Table 1). Twelve of these studies were located in China, where the incidence of headache according to the GHDx registry is 2.69% (95% CI, 2.40–30.4%) [7–18], one in Korea (headache incidence, 2.98%; 95% CI 2.67–3.30%) [19], and one in India (headache incidence, 2.81%; 95% CI, 2.51–3.13%) [20]. In all except one of these epidemiologic investigations, the incidence of headache was

Figure 1: Odds ratio (OR) and 95% confidence interval (95% CI) of incident headache in coronavirus disease 2019 (COVID-19) patients vs. the general population of the corresponding geographical areas.

Table 1: Summary of studies reporting the incidence of headache in coronavirus disease 2019 (COVID-19) patients.

Study	Setting	n	Women, %	Headache		
				Yes	No	% Yes
Xu YH et al., 2020 [7]	China	50	42%	5	45	10.0%
Tian S et al., 2020 [8]	China	262	52%	17	245	6.5%
Chen N et al., 2020 [9]	China	99	32%	8	91	8.1%
Huang C et al., 2020 [10]	China	38	27%	3	35	7.9%
Xu XW et al., 2020 [11]	China	62	44%	21	41	33.9%
Mao L et al., 2020 [12]	China	214	59%	28	186	13.1%
Song F et al., 2020 [13]	China	51	51%	8	43	15.7%
Jin X et al., 2020 [14]	China	651	49%	67	584	10.3%
Liu K et al., 2020 [15]	China	137	55%	13	124	9.5%
Guan W et al., 2020 [16]	China	1099	42%	150	949	13.6%
Chang D et al., 2020 [17]	China	13	23%	3	10	23.1%
Wang DW et al., 2020 [18]	China	138	46%	9	129	6.5%
Korea CDC, 2020 [19]	Korea	28	46%	3	25	10.7%
Gupta N et al., 2020 [20]	India	21	33%	3	18	14.3%
Total		2863		338	2525	11.8%

higher in COVID-19 patients than in the general population of the corresponding geographical area (Figure 1). Overall, headache was hence cumulatively reported by 11.8% (95% CI, 11.5–12.1%) of COVID-19 patients, compared to the 2.8% cumulative incidence in the general population of the same geographical areas. Therefore, incident headache was associated with a nearly 5-fold higher risk (11.8 vs. 2.8%; OR, 4.95; 95% CI, 3.50–6.92; I², 55%) of being diagnosed as having COVID-19 (Figure 1).

In conclusion, the results of this pooled analysis of the recent scientific literature suggest that headache, especially that of new onset in subjects who do not regularly suffer from this condition, should raise early concern to the possibility of being infected by COVID-19.

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