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Brief Communications

High Prevalence of Headaches During Covid-19 Infection: A Retrospective Cohort Study

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Objectives.—To document the prevalence of new headaches in patients with Covid-19 infection and the potential association with other neuro-sensorial symptoms (anosmia and ageusia). The persistence of these symptoms 1 month after recovery was also documented.

Background.—Headaches are a very common symptom of viral infections. Surprisingly, early Chinese studies reported a relatively low prevalence (12-15%) of headaches associated with Covid-19.

Methods.—All the patients with laboratory-confirmed or chest-CT-confirmed Covid-19 infection, diagnosed between February 27th and April 15th, 2020 in the dedicated laboratory of Clermont-Ferrand University Hospital were followed for 1 month after recovery.

Results.—A total of 139 consecutive patients (mean [SD] age, 48.5 [15.3] years; 87 women [62.6%]) were interviewed 1 month after disappearance of fever and dyspnea (semi-structured phone interview). Overall, 59.0% (82/139) of people with Covid-19 had mild disease, 36.7% (51/139) had severe disease, and 4.3% (6/139) had critical illness. Eighty-two (59.0%; 95% CI: 50.3 to 67.3) reported new headaches during the acute phase and 3.6% (5/139) had persistent headaches 1 month after fever and dyspnea remission. Anosmia and ageusia were also very common, occurring in 60.4% (84/139) and 58.3% (81/139) of the patients, respectively. These 2 symptoms persisted in 14.4% (20/139) and 11.5% (16/139) of Covid-19 patients 1 month after recovery. Headaches were neither clearly associated with anosmia, nor with ageusia, and were not associated with disease severity (ie, requiring hospitalization or intensive care unit).

Conclusion.—This specific study highlights the high prevalence of new headaches during Covid-19 infection in French patients. Further studies are needed to refine the characterization of patients with Covid-19-associated headaches.

Key words: headache, Covid-19, SARS-CoV-2, anosmia, ageusia

Abbreviations: ACE2 angiotensin converting enzyme 2, Covid-19 coronavirus disease 2019, ICHD-3 International Classification of Headache Disorders, third edition, ICU intensive care unit, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, SD standard deviation, 95% CI 95% binomial confidence interval

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INTRODUCTION

Covid-19 is a coronavirus disease, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that started in Wuhan, China on December 1, 2019 and was recognized by the WHO as a global pandemic on March 11, 2020.[1] Covid-19 cases spread throughout the world, including other Asian countries, Europe and America. Due to the recent nature of the Covid-19 outbreak, an extensive list of clinical characteristics has yet to be established. Initially, only a limited number of clinical manifestations were systematically assessed, mainly focusing on respiratory and cardiovascular features. Other symptoms were later identified such as digestive or neurological disorders, especially anosmia, ageusia, delirium, or headaches. As these symptoms were not routinely recorded, and because of the lack of studies designed to specifically investigate them, it is likely that the prevalence of headaches (12-15%) reported previously in Covid-19 patients is underestimated.[2-4]

We hypothesized that headaches prevalence was probably underestimated in previous studies and could be associated with other neuro-sensorial symptoms. Therefore, the goal of this study was to document the prevalence of new headaches during the acute phase of Covid-19 infection and assess their evolution 1 month after recovery. The secondary objective was to look for a possible association between headaches and neuro-sensorial symptoms, namely anosmia and ageusia.

METHODS

Patients.—All the patients with laboratory-confirmed or chest-computed tomography-confirmed (typical pattern including ground glass opacity, consolidation, nodule, reticulation, interlobular septal thickening, crazy-paving pattern, linear opacities, subpleural curvilinear line, bronchial wall thickening, lymph node enlargement, pleural effusion, and pericardial effusion) Covid-19 infection, diagnosed between February 27th and April 15th, 2020 in the dedicated laboratory of Clermont-Ferrand University Hospital were followed for 1 month after recovery, and were included in this retrospective cohort study. Patients were tested as they were presenting with fever, cough, or dyspnea.

Subsequently, to the diagnosis of outpatients or after discharge of inpatients, a systematic clinical follow-up via phone call was made at least twice a week until recovery. Last call was made 1 month (30-35 days) after disappearance of fever and dyspnea. During this last call, a semi-structured interview was conducted, and patients were systematically asked for the presence of new headaches, anosmia and ageusia during the acute phase of the infection (retrospective self-report) and if these symptoms had persisted. Demographic characteristics (age and sex) were also noted for each patient.

Considering the observational status of our study and the questionnaire being part of a systematic clinical follow-up, the French law on biomedical research does not apply to this retrospective study (IRB00008526, 2020/CE35). Nonetheless, oral informed consent was obtained from each subject for a potential use of the collected data for further research.

Sample Size Justification.—To allow for a maximum 95% confidence interval of ±10% for the proportion of patients with new headaches whatever its prevalence, it was necessary to include at least 97 patients. We included a convenience sample of 139 patients that were tested in our hospital during the main phase of the epidemics.

Statistics.—Statistical analyses were performed using Stata software, version 15 (StataCorp, College Station, TX, USA). Analysis of new headaches prevalence and association of these headaches with demographic characteristics (age and sex), clinical characteristics (fever, asthenia, and hospitalisation requirement), anosmia, and ageusia was pre-planned. Looking for an association with persistent anosmia or ageusia was post hoc. Binary variables (sex, hospitalization, asthenia, fever, new headaches, anosmia, and ageusia) were expressed using frequencies and percent and were compared between the groups (new headaches during the acute phase yes/no) using chi-squared or Fisher's exact tests. For new headaches

Louis Poncet-Megemont and Pauline Paris are contributed equally to the study.

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during the acute phase, 95% binomial confidence interval (95% CI) was estimated. Continuous data (age) were expressed with mean and standard-deviation (SD) or median and range, according to their statistical distribution. The assumption of normality was assessed using the Shapiro-Wilk test. The comparisons between groups were performed using 2-tailed independent *t*-test. The level of significance was set at 5% ($P < .05$).

RESULTS

Overall, 180 patients tested positive for Covid-19 between February 27th and April 15th, 2020, 168 presenting a positive PCR test and 12 having negative PCR but a typical chest-CT. Nineteen patients died (7 women, median age 83 [53-95], 3 had negative PCR). Five patients declined to participate in the cohort (subsequent follow-up by the general practitioner or not speaking French) and 17 patients were unreachable. Thus, 139 patients were interviewed 1 month after recovery (Table 1). Among these patients, 82 (59.0%; 95% CI 50.3-67.3) presented with new headaches during the acute phase and 5 (3.6%) of them were still presenting headaches 1 month after resolution of fever and dyspnea. These 5 patients were female, with a median age of 51 (range 24-62) and 2 of them had been hospitalized (none in ICU). Three out of 5 had initially both anosmia and ageusia and 1 of them had persistent anosmia and ageusia. There was a strong association between anosmia and ageusia ($P < .001$), as expected. Among 84 patients with initial anosmia and 81 with initial ageusia, 75 had the 2 symptoms (ie, 89.3% of patients with anosmia and 92.6% of patients with ageusia).

DISCUSSION

This retrospective cohort study found a very high prevalence of new headaches (59.0%) during the acute phase of Covid-19 infection. Anosmia and ageusia were also very common since they were recorded in, respectively, 60.4% and 58.3% of the patients. One month after recovery, (ie, disappearance of fever and dyspnea), headaches, anosmia, and ageusia were still present in 3.6%, 14.4%, and 11.5% of patients, respectively. Headaches were not associated with disease severity.

The demographic and clinical characteristics of our cohort are similar to those of previous studies except for gender, where women represent a higher proportion than men [3]. According to the Chinese center for disease control report, the clinical spectrum of coronavirus infection is quite broad ranging from mild to critical disease.[5] In our cohort, 59.0% (82/139) of cases were reported to be mild, 36.7% (51/139) were moderate to severe, and 4.3% (6/139) were critical. Thus, while the proportion of patients with critical illness is consistent with that of previous investigations, there was a greater proportion of patients with moderate to severe illness requiring hospitalization than in other studies.[3] The most common symptoms of illness during the acute phase were fever and asthenia, in agreement with previous studies.[3]

Table 1.—Epidemiological and Clinical Characteristics of Patients With or Without New Headaches During the Acute Phase of Covid-19 Infection

Characteristics	Overall N = 139	Patients With Headaches N = 82	Patients Without Headaches N = 57	*P* Value
Age (years)	48.5 ± 15.3	47.1 ± 14.1	50.5 ± 16.8	.207
Female sex, n (%)	87 (62.6)	55 (67.1)	32 (56.1)	.190
Hospitalization, n (%)	57 (41.0)	32 (39.0)	25 (43.9)	.569
Hospitalization in ICU, n (%)	6 (4.3)	2 (2.4)	4 (7.0)	.227
Fever, n (%)	99 (71.2)	59 (72.0)	40 (70.2)	.820
Asthenia, n (%)	128 (92.1)	78 (95.1)	50 (87.7)	.125
Initial anosmia, n (%)	84 (60.4)	53 (64.6)	31 (54.4)	.224
Initial ageusia, n (%)	81 (58.3)	52 (63.4)	29 (50.9)	.140
Persistent anosmia, n (%)	20 (14.4)	9 (11.0)	11 (19.3)	.169
Persistent ageusia, n (%)	16 (11.5)	8 (9.8)	8 (14.0)	.437

ICU = intensive care unit. There was no missing data for these variables among the 139 respondents.

Up to now, headaches were not the focus of several previous studies about Covid-19. It was only registered as a generic symptom in some of these studies. A meta-analysis, including mostly Chinese studies, estimated headaches prevalence at 12% (4-23%).[3] In accordance with the results we obtained in a cohort of French patients, a recent European study found that headaches were common in patients with mild-to-moderate Covid-19, with a prevalence of 70%.[6] Several explanations can be given to clarify this huge discrepancy between Chinese and European studies. First, a symptom must be specifically studied to allow a precise estimation, which was not the case in previous published studies. Then, the genetic background of the population could potentially influence the prevalence of this neurological symptom, possibly via the polymorphisms and expression level in different tissues of angiotensin converting enzyme 2 (ACE2), which is the receptor of Covid-19.[7] In addition, Chinese patients seem less prone to headaches than Europeans, as the prevalence of primary headaches is also significantly lower in China compared to Europe.[8] Finally, the appearance of new SARS-CoV2 strains could be responsible for the emergence of new symptoms.[9] Concerning anosmia, the prevalence of this symptom when systematically assessed, varies from 15% in a large Korean study involving more than 3000 patients[10] to 70% according to a large cohort of European patients.[6] For anosmia and ageusia, the median time for recovery was approximately 7 days in both cohorts. We report longer follow-up and show for the first time that more than 10% of the patients still have a complaint 1 month after recovery from respiratory symptoms and fever.

The prevalence of headaches of 59.0% in the present study is similar to that (63%) reported in a very large cohort of French patients with laboratory-confirmed influenza.[11] Thus, the prevalence for this new viral infection that produces an influenza-like illness is not surprising but seemed underestimated in previous studies. Concerning the 3.6% of patients with persistent headaches 1 month after symptom onset, larger studies should be conducted to explore this subgroup. For now, it is not possible to be sure that these persistent headaches are due to the Covid-19 infection alone. Indeed, the current pandemic crisis associated with the confinement is likely to have increased the prevalence of tension-type headaches. Nonetheless, we can speculate that cytokine release syndrome can induce headaches and that the levels of circulating pro-inflammatory cytokines can be elevated for several weeks in a sub-group of patients, maintaining headaches, as shedding of virus RNA has been shown to persist in body fluids for more than 6 weeks.[12]

This study has several limitations, the first being the use of a retrospective self-report. Thus, information concerning the presence of headaches in patients whom died was not available. As the observed data only reflect 139/180 (77.2%) of the target sample, prevalence estimates could be biased in undetermined ways by such selection bias. Nonetheless, for patients alive at follow-up, the participation rate was very high (86%) and phone interview was performed only 1 month after investigated symptoms, which limits the risk of recall bias. Moreover, if a recall bias was present, it would probably tend to reduce the reported prevalence, although participants could remember experiencing headaches that did not occur or that occurred at a different time. Several more specific parameters could have been recorded, especially new headaches characteristics, history of previous headaches, and other past medical history. Although not specifically noted during the interview, many patients described headache exacerbations associated with fever exacerbation, well-controlled by acetaminophen intake, compatible with international classification of headache disorders (ICHD-3) criteria of *Acute headache attributed to systemic viral infection* (code 9.2.2.1).[13] Several patients described a second type of headache, in relation with cough, compatible with ICHD-3 criteria of *Primary cough headache* (code 4.1). These 2 types of headaches are well-described in a detailed case report, in which a third type is also described, namely *Headache attributed to hypoxia and/or hypercapnia* (code 10.1).[14] Making a proper inventory of headache characteristics and associations with other infectious symptoms or presence of previous primary headaches should be done in future studies. Finally, we can regret the absence of systematic brain MRI for all these patients to look for potential abnormalities associated with headaches. Indeed, various neurological disorders have been described, particularly in patients with severe infection, and the relationship of such pathological images with headaches is unknown.[15]

In conclusion, headaches are 1 of the most common symptoms during Covid-19 infection in French patients. Of note, compared to other viral infections, Covid-19 infection is also characterized by multiple sensory

impairments (anosmia and ageusia) that persist for several weeks after recovery in a subset of patients. Further studies are needed to analyze specifically headaches and the associated sensory deficits in Covid-19 patients.

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