Headaches and COVID-19 Infection: Epidemiology and Outcomes in a North African Sample

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Abstract

Objectives: This study aims to describe the epidemiological features of headaches in patients with COVID-19 infection.
Methods: This is a cross-sectional study. Patients older than eighteen and diagnosed with a COVID-19 infection were included. We excluded patients aged less than eighteen, those whose headache could not be assessed, those with a history of psychiatric or cognitive impairment, those who did not consent to participate, and deceased patients.
Results: The study involved 728 patients, 371 had headaches due to the SARS-Cov2 infection. The distribution of clinical forms of the COVID-19 infection in the entire population was as follows: 87.2% asymptomatic or mild forms (n= 634), 8% moderate forms (n= 58), 4.8% severe forms (n=35). Headaches were the second reported symptom, after anosmia (n= 400; 54%). Most patients reported a headache in the first week of symptoms. The intensity of headaches was mild to moderate in 74.8% of cases (n=275) and they improved within 5.7±4 days.
The univariate analysis showed an association between headaches and the following factors: female gender ($p<0.001$), the clinical form of COVID-19 infection ($p<0.001$). Patients with a mild form had a higher risk to develop COVID-19 infection-related headaches. Patients with comorbidities had also a significantly higher risk to develop COVID-19-related headaches ($p=0.012$). The independent predictors of acute COVID-19 infection-related headaches presence were only clinical forms of COVID-19 infection, fever, myalgia, abdominal pain, and sore throat ($p<0.05$).
Conclusion: Headaches associated with COVID-19 infection are frequent, with a female predominance. They are generally moderate, holocranian paroxysmal, and pulsatile. Red flags are present in most cases.

Keywords: Headaches, COVID-19, SARS-CoV-2, Acute onset; Outcomes.

INTRODUCTION

COVID-19 is a new infection and is becoming a public health burden worldwide. The first case was declared in December 2019 in Wuhan, China (1, 2). Common acute symptoms include headaches, fever, joint and muscle pain, cough, dyspnea, anosmia, and agnosia (3, 4). Digestive signs like abdominal pain, nausea, vomiting, and diarrhea are fewer common symptoms (5). Many studies focused on respiratory symptoms of COVID-19; however, few ones have treated headaches, one of the most frequent symptoms of SARS-CoV-2 infection. Moreover, the frequency, severity, and characteristics of this symptom varied from one study to another (6, 7). In all variants, headaches are the fifth most frequent symptom after fever, cough, myalgia, and chills/rigor. They are reported in 20% to 56% of the cases (8). In addition, some studies have concluded that there is a relationship between headaches and anosmia and/or agnosia (9, 10, 11). This work aimed to describe the epidemiological features of acute COVID-19 infection headaches among a Tunisian sample. We also aimed to assess the predictor factors of these headaches.

METHODS

Clinical setting

This is a cross-sectional study conducted for 3 months (from 1st, Feb 2021 to 30th, Ap 2021). The study population consisted of randomly selected subjects among the patients who were managed at the emergency department, in the COVID-triage unit, for a confirmed COVID-19 infection. A confirmed COVID-19 case was defined as a positive result in the nasal or oropharyngeal swab specimen analysis made by PCR analysis.

This COVID-19 emergency unit is the major one in the governorate. Subjects with suspected or confirmed COVID-19 infection present to this unit where their management is initiated. This unit is also a surveillance unit for patients needing hospitalization.

Ethical considerations

The study proposal was approved by the Institutional Ethical Committee. The nature and the aim of the study were explained for each patient before inclusion. Informed oral consent was obtained from all participants before enrolment.

Sample size

Until 1st January 2021, we counted around 20, 000 positive cases in our city. The sample calculation was based on the previous studies conducted estimating a prevalence of COVID-19 infection-related headaches at 20 to 50% (6, 7). To have a 99% confidence level with a 5% margin of error, we had to include at least 653 participants. According to the previous cross-sectional studies conducted in our department, the participating rate varies between 50 and 75%, and the follow-up is not possible in 30% of cases. We used Excel software to select a randomized sample of 2, 000 patients among whom 754 had accepted to participate in the study.

Eligibility criteria

Selected patients were older than eighteen, and diagnosed with a COVID-19 infection. We did not include patients with psychiatric and/or cognitive impairment. Deceased patients were excluded.

Data Collection and Study Design

A doctor examined the medical records, additional examinations if indicated, and then phone calls were made for additional data collection. Sociodemographic characteristics (gender, age) of all patients, prior history of hypertension, diabetes, cardiovascular diseases, chronic pulmonary diseases, cancer, and immune-compromised conditions, and their presenting symptoms (fever, caught, dyspnea, anosmia, agnosia, diarrhea, abdominal pain …) were evaluated.

Asymptomatic patients are those with documented COVID-19 infections and without clinical signs of COVID-19 infection. For symptomatic patients, the grading of COVID-19 severity was stratified, according to WHO classification, into mild, moderate, or severe as follows:

- *Mild COVID-19*: Clinical signs (anosmia, agnosia, headache…) but no evidence of viral pneumonia or hypoxia (12).
- *Moderate COVID-19*: Patients with clinical signs of pneumonia (fever, cough, dyspnea) but no signs of severe pneumonia (SpO2 <90%under room air) (12).
- *Severe COVID-19*: Patients with clinical signs of pneumonia plus one of the following: Respiratory rate >30 breaths/min; severe respiratory distress; or SpO2<90% on room air (12).

The data analysis of COVID-19-related headaches included the site of headaches, character, frequency, duration, intensity, and response to analgesics. We used the Simple Verbal Scale (SVS) and Numeric Scale (NS) to evaluate the severity of headaches. The time between the onset of headache and the positive diagnosis of COVID-19 infection, as well as other COVID-19 infection symptoms, were also recorded.

Red flags concerning prior medical conditions included the age over 50, the presence of immune-compromised states, and current or prior history of cancer.

Red flags regarding headaches included (13):

- Recent onset of headaches (headache coincides with Covid-19 symptoms onset),
- Change in the intensity of preexistent headaches (is defined by the patient as a similarity equal to or lower than 30% on a 0-100% scale, compared with the preceding headache episode).
- progressive worsening of headaches
- treatment resistance (defined as the complete lack of response to acute medications),
- exacerbation of headaches by sneezing, coughing, or exercise;
- interruption of the sleep
- ocular pain,
- positional pattern

Red flags concerning general symptoms include fever, chest pain, dyspnea, cough, rhinorrhea diarrhea, dizziness, generalized weakness, odynophagia, arthralgias, asthenia, and cutaneous rash.

We also noted whether our patients presented cardiorespiratory complications during the

infection such as thromboembolic complications, and dyspnea.

Statistical analysis

The normal distribution of the data was verified. Data reported in the text and tables indicate the mean ± standard deviation for numeric variables and percentages or ranges for dichotomous variables. To compare qualitative variables, we used the Person Chi square-test and the Fisher exact test. Significant parameters were analyzed by a multiple logistic stepwise regression procedure to precise the independent predictors of headaches. Odds ratios were estimated from the b coefficients obtained, with respective 95% confidence intervals (CI 95%). The significance level was $p < 0.05$.

RESULTS

The study population included 728 patients with a confirmed COVID-19 infection (Figure 1).

The distribution of clinical presentation of the COVID-19 infection in the entire population was as follows: asymptomatic or mild forms (n= 634; 87.2%), moderate forms (n= 58; 8%), and severe forms (n=35; 4.8%).

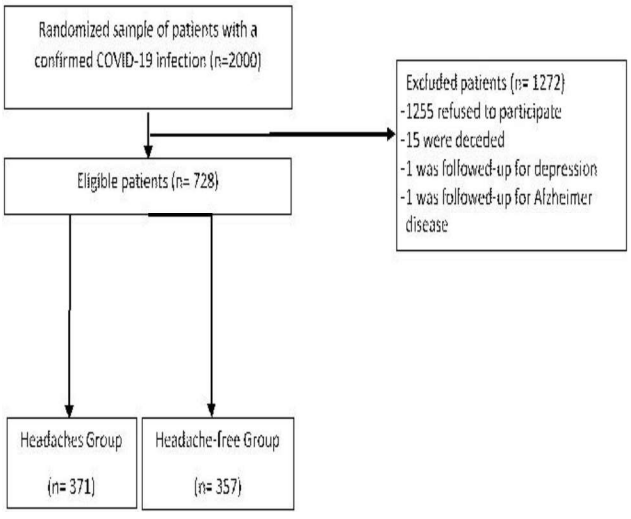

Figure 1: Flowchart for the patients' enrollment

More than half of the patients have had COVID-19 infection-related headaches (n=371 patients; 51%). None of the patients presented with focal neurological signs.

Patients with COVID-19-related headaches had a mean age of 45 ± 17.05 years. They were 232 females (62.5%). The clinical characteristics are summarized in Table 1.

Headaches were the second most reported symptom (n=371; 51%) after anosmia (n= 400; 54%). Most patients (n=270; 79.2%) reported headaches onset within the first week of symptoms. One hundred and ninety-two patients (53%) presented holocranian throbbing headaches. The headaches were paroxysmal in 217 cases (60.3%) and pulsatile in 196 (52.8%). The headaches' intensity was mild to moderate in 76.8 % of cases (n=275). The mean Numeric Scale (NS) value was 5.2±1.9 (min: 1, max: 10), and the mean improvement time was 5.7± 4 (min: 1, max: 30) days. Table 2 details the characteristics of these headaches.

Red flags concerning prior medical conditions were noticed in 140 patients (37.7%). Red flags regarding the characteristics of the headaches were present in 20.5% of cases. The most frequent red flags were the sudden onset (20.5%) (Table 3).

Systemic symptoms were described in all patients. The most common systemic symptoms associated with headaches were fever (46.9%), arthralgia (41.8%), and asthenia (40.4%). The neurological signs most commonly associated with headaches were anosmia (60.1%) and agnosia (53.6%) (Table 4).

Table 1: Demographics and Clinical Characteristics of The Study Population

	Headaches Group n= 371	Headache-Free Group n= 357	P-value
Age (years; mean±SD	45.08±17.5	43.8 ± 17.1	**NS**
Age over 65 years; n(%)	57 (15.4)	47 (13.2)	
Male gender; n(%)	139 (37.5)	192 (53.8)	
Marital state; n(%)			**NS**
Single	84 (22.6)	99 (27.7)	
Married	268 (72.2)	248 (69.5)	
Profession; n(%)			**NS**
Medical or paramedical staff	39 (10.5)	25 (7.2)	
Student	33 (8.9)	41 (11.5)	
White-collar jobs	92 (24.8)	100 (27.6)	
Blue-collar jobs	95 (25.6)	95 (26.8)	
Past medical conditions; n(%)	140 (37.7)	102 (28.5)	**0.014**
COVID-19 severity; n(%)			**0.000**
Asymptomatic or Mild presentation	306 (82.5)	328 (92.1)	
Moderate presentation	40 (10.8)	18 (5.1)	
Severe presentation	25 (6.7)	10 (2.8)	
Hospitalization for COVID-19 infection ; n(%)	56 (16)	32 (9.8)	**0.022**
Evolution ; n(%)			**0.001**
Favorable	309 (91.2)	340 (97.1)	
With Complications (thrombo-embolic complication, dyspnea…)	30 (8.8)	10 (2.9)	

We have observed no case of speech disorder, visual disturbance, focal weakness, hypoesthesia, seizures, or ataxia.

Only one patient underwent Brain Computed Tomography and Magnetic Resonance Imaging. He had a complaint of very intense headaches with the meningeal syndrome. They were normal. The cerebrospinal fluid analysis was also normal.

Table 2: The characteristics of headaches associated with COVID-19

Headaches' characteristics	Value; n(%)
Time of onset; *n (%)*	**366 (%)**
At the onset of infection (in first 7 days)	290 (79.2)
During infection (between 7 and 10 days)	73(20)
In the end of infection (after 10 days)	3 (0.8)
Site; *n(%)*	**362 (%)**
Holocranian	192 (53)
Hemicranian	95 (26.3)
In helmet	75 (20.7)
Evolution in time; *n(%)*	**360 (%)**
Continuous	143 (39.7)
Paroxysmal	217 (60.3)
Pulsatile	196 (52.8)
Pressing / tightening	97 (26.1)
Intensity (SVS); *n(%)*	358 (%)
Mild	73 (20.4)
Moderate	202 (56.4)
Severe	60 (16.8)
Excruciating	23 (6.4)

The management of headaches associated with the COVID-19 infection has been based on the use of analgesics. Paracetamol was the most frequently used in 333 cases (89.8%). A combination of paracetamol with tramadol or codeine was used in 51 cases (13.7%). Many patients used traditional habits in association with the prescribed drugs to decrease their pain. They have tried herbal tea (n = 114; 30%), and staying in the darkness (n =25; 6.7%). In 300 cases (86.7%), headaches have improved under the used treatment.

The bivariate analysis showed a significant relationship between headaches and gender ($p< 0.001$). Women had a higher risk to develop

Table 3: Red flags related to the patients' prior medical conditions and to headaches characteristics

	Value n (%)
Red flags related to prior medical conditions; n(%)	371 (%)
Comorbidities	140 (37.7)
Age > 50 years	118 (31.8)
Neoplasm in history	0 (0)
Pathologies of the immune system	3 (0.8)
Red flags related to headache characteristics; n(%)	371 (%)
Pattern change	48 (12.9)
Prodromes	6 (1.6)
Worst headaches	45 (12.1)
Precipitating by sneezing, coughing or exercise	38 (10.2)
Painful eyes	36 (9.7)
Photophobia	6 (1.6)
Treatment resistance	46 (12.3)
Positional headaches	46 (12.3)
Sudden onset	76 (20.5)

COVID-19 infection-related headaches compared to men. Nevertheless, headaches did not differ in terms of age, profession, or marital state (P > 0.05 for each). Patients with comorbidities had a higher risk of developing COVID-19 infection-related headaches (p=0.012). The SVS and NS scores were higher in women than in men (respectively p=0.05 and p=0.01).

We found a relationship between headaches and the subtype of clinical form of COVID-19 infection; patients with a mild form had a higher risk to develop COVID-19 infection-related headaches (p<0.001). Among the systemic signs observed during COVID-19 infection, dizziness, fever, myalgia, arthralgia, asthenia, chest pain, abdominal pain, diarrhea, sore throat, palpitation, anosmia, and agnosia were commonly associated with headaches (Table 4).

The independent predictors of COVID-19 infection-related headaches were the clinical form of COVID-19 infection (p=0.03), fever (p= 0.007), myalgia (p=0.002), abdominal pain (p=0.032), and sore throat (p=0.021).

DISCUSSION

The main findings of this study are the high prevalence of headaches in COVID-19 infection (51%) in the southern region of Tunisia (21%). This rate is one of the highest reported in previous studies (3). In the literature, headaches have been associated with SARS-CoV2 infection in 6.5 % to 56% of cases (8). Most studies focused on respiratory symptoms for which patients are admitted, and the rates of headaches seem to be underestimated. A meta-analysis, including 60 studies with more than 40000 patients report an incidence of around 12% (14). Headaches are considered the fifth most frequent symptom after fever, cough, myalgia, fatigability, and dyspnea (14). These studies consider that headaches are not a minor symptom and it is necessary to investigate and treat these symptoms. In our sample, headaches associated with COVID-19 infection were the second most reported symptom, after anosmia. It affected namely women. Most patients reported headaches in the first week of symptoms. The intensity of headaches was mild to moderate in three-quarters of the cases.

The physiopathology of headaches related to the COVID-19 infection is not well known. Many mechanisms are plausible. First, the COVID-19 virus causes endothelial dysfunction and disturbs

Table 4: Red flags related to the presence of neurologic and systemic symptoms and facors associated with COVID 19 headache in bivariate analysis

Variable	Headache Group n=371 n (%)	Headache-Free Group n= 357 n (%)	p-Value
Red flags related to the presence of systemic symptoms; n(%)	371 (100)	357 (100)	
Fever	174 (46.9)	113 (31.6)	0.000
Arthralgia	155 (41.8)	59 (16.5)	0.000
Astheny	150 (40.4)	94 (26.3)	0.000
Sore throat	52 (14)	23 (6.4)	0.001
Otalgia	3 (0.9)	0	NS
conjunctivitis	1 (0.3)	0	NS
Rhinorrhea	37 (10)	43 (12)	NS
Cough	127 (34.2)	117 (32.7)	NS
Dyspnea	74 (19.9)	48 (13.4)	NS
Chest pain	70 (18.9)	18 (5)	0.000
Palpitations	9 (2.4)	0	0.003
Abdominal pain	88 (23.7)	34 (9)	0.000
Vomiting	29 (7.8)	15 (4)	NS
Diarrhea	96 (25.9)	47 (13.1)	0.000
Pregnancy	2 (0.5)	1 (0.2)	NS
Red flags related to the presence of neurologic symptoms; n(%)			
Myalgia	131 (35.3)	42 (11.7)	0.000
Anosmia	223 (60.1)	177 (49.5)	0.004
Agnosia	199 (53.6)	156 (43.6)	0.007
Dizziness	32 (8.6)	0	0.000
Meningeal syndrome	1(0.3)	0	NS

the blood-brain barrier. The angiotensin-converting enzyme 2 receptors (ACE-2) are the primary target of the virus. It is mainly present in the respiratory epithelium. It is the main agent of blood pressure regulation. ACE-2 receptors are also present in the nervous system (15, 16). Second, the virus COVID-19 causes alveolar inflammation and edema. That leads to hypoxia and hypercapnia that disturb the regulation of intracranial pressure resulting in several neurologic symptoms ranging from headaches to coma (17). Third, the SARS-CoV2 generates a cytokine storm. It results in an inflammatory reaction and an immune-mediated injury that stimulates headache (18, 19).

Belvis R. described tension headaches during the seven first days of COVID-19 affection (8). He described it to be mild, pericranial, and possibly triggered by some factors like stress and insomnia. After the 7th or the 10th day of COVID-19 infection, headaches characteristics changed. They became continuous, diffuse, with moderate intensity, and worsened by routine physical activity and changes in the head position. This change in headaches characteristics was concomitant with the worsening of the patient's respiratory status and the cytokine storm (8). As we found in our sample, patients with fever were more likely to present COVID-19-related headaches compared with those without fever (7). Headaches related to COVID-19 infection can be a mixture of tension-type headaches, headaches attributed to systemic viral infection, cough, hypoxia, and hypercapnia (8). Their beginning or worsening after the 7th to the 10th day of SARS CoV2 infection should be considered as a predictor of the cytokine storm onset. Our study agrees with these hypotheses; most of our patients (79.2%) reported headache onset within the first week of infection. These headaches were usually described to be paroxysmal, holocranian, and moderate in

intensity. Headache is a frequent symptom of common upper airway infections. However persistent or refractory headaches should evoke meningoencephalitis and cerebral venous thrombosis in infected patients (16).

In our study, headaches associated with COVID-19 infection were associated with other nervous manifestations like myalgia, arthralgia, dizziness, and abdominal pain but we did not conclude to association with respiratory symptoms. This can be explained by the predominance of asymptomatic or mild COVID-19 infection forms in our sample, unlike the majority of studies that analyzed hospitalized patients.

The higher female prevalence of headaches can be explained by the association of genetic factors, anatomical physiological differences, and the variability in the modulation of endogenous opioid systems and sex hormones between the two genders. All these factors can influence pain sensitivity in males and females (20).

In this study, we also analyzed red flags. Many red flags should be assessed while managing headaches in the emergency department (21-24). In our sample, red flags were frequent, which reinforces how important the anamnesis and the clinical exam in particular while analyzing headaches, namely in the case of COVID-19 infection (13, 25). The most frequent red flags we found were the sudden onset, the change in the pattern of headaches, the positional headaches, and the resistance to treatment. Those related to general symptoms were fever, arthralgia, and asthenia.

Few studies focused on COVID-19 infection-related and persistent post-COVID infection headaches in the north African region. We describe headaches in moderate and minor forms of COVID-19 infection forms. Despite these strengths, some limitations are worth to be mentioned. The most important limitation of our study is its cross-sectional design. However, the same investigators made all phone calls. Second, we have no imaging data in patients with persistent headaches. Further prospective studies with systematic imaging and assessment of inflammation biomarkers are proposed.

CONCLUSION

SARS-CoV2 infection gives primarily respiratory and cardiovascular impairment. However, neurologic symptoms are also common and can lead to severe complications if not diagnosed and managed at the time. Red flags concerning prior medical conditions, headaches characteristics, and systemic symptoms are not uncommon.

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