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Evaluation of COVID-19-Related Pain Symptoms and Assessment of Neuropathic Pain

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ABSTRACT

Myalgia, arthralgia, headache, chest pain, back pain, abdominal pain, sore-throat may be present in COVID-19. The purpose of this study is evaluating the frequency, intensity and the regional characteristics of pain related symptoms in hospitalized COVID-19 patients as long as neuropathic pain and its components.

In this retrospective study, for the assessment of pain, myalgia, arthralgia, headache, sore-throat, chest pain, back pain and abdominal pain were questioned. Intensity of pain was evaluated by an 11-point Numerical Rating Scale. Neuropathic pain detection was performed by Identification Pain Questionnaire (ID-Pain).

The frequency of pain in hospitalized patients was 68.5%. The frequency of COVID-19-related symptoms were 53.4% myalgia, 39.7% arthralgia, 41.1% headache, 21.2% sore-throat, 21.9% chest pain, 28.1% back pain and 15.8% abdominal pain. A statistically significant relationship was observed between headache and hyposmia development (odds ratio= 6.53; 95% CI: 3.14-13.60; *P<0.001*). In neuropathic pain assessment, ID-Pain scores of 6 (4.1%) of patients were found ≥ 2. For neuropathic pain components, it was observed that hot/burning type was accompanying to pain in 12 (8.2%) of patients while pins and needles type was accompanying in 8 (5.5%) of the patients.

In hospitalized COVID-19 patients, myalgia, arthralgia and headache are most frequent pain types. Headache was found to be related with hyposmia. Neuropathic pain or mixed pain with a neuropathic component is not a rare condition in COVID-19 disease. Finally, we suggest routine assessment of neuropathic pain in patients with COVID-19.

Keywords: Chest Pain; COVID-19; Headache; Myalgia; Neuralgia; SARS-CoV-2

Introduction

COVID-19, which is caused by SARS-CoV-2 virus have a wide clinical spectrum. The clinical characteristics of COVID-19 have a lot of similarities with many other viral diseases. Pain is among the most frequent clinical manifestations in COVID-19 along with fever, cough, dyspnea and fatigue (1). Clearly description of the symptoms and features of COVID-19 is crucial for early diagnose and treatment and establishing the quarantine measures.

SARS-Cov-2 enters the cell body using angiotensin converting enzyme (ACE-2) receptor. ACE-2 receptors exist in many types of tissues like lungs, endothel cells, intestines, heart, kidneys and brain. Damaging of the endothelial cells due to infections may result ischemia, edema, and hypercoagulability (2). In COVID-19, many organ systems are affected in proportion with the intensity of the infection.

In COVID-19, myalgia, arthralgia, headache, chest pain, back pain, abdominal pain and sore-throat may be observed (1,3). In the literature, there are some reports regarding pain frequency and intensity. However, distinguishing nociceptive pain and neuropathic pain is one of the most important contents of pain assessment. We conducted this study on hospitalized patients, which have more intense disease therefore more vulnerable for the effects of pain. The aim of this study is evaluating the frequency, intensity, and regional characteristics of pain as well as neuropathic pain components.

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Materials and methods

This retrospective study was conducted in Mugla Education and Research Hospital between May and October 2020. Institutional ethical committee approval (No. 200100) and approval from Turkish Ministry of Health were obtained before the study. Patients older than 18 years old with positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test results or have radiologic findings match with COVID-19 were included in the study. While patients who were followed in intensive care unit (ICU) composed Group ICU, patients who did not require ICU treatment composed Group Non-ICU. Patients with cooperation disorders, who cannot remember the symptoms of pain, and who had need deep sedation in ICU were excluded from the study. Demographic features of the study group and COVID-19-related data were taken from the software data system of the institution.

Patients' age, gender, RT-PCR results, hyposmia existence, and pain complaints were recorded. A pain medicine specialist via phone conversations conducted detailed questioning of pain. In pain assessment, one-week duration from the beginning of the first symptom was regarded. Presence of myalgia, arthralgia, headache, sore throat, chest pain, back pain, and abdominal pain were asked. In existence of overlapping pain, each pain type evaluated separately. In the assessment of frequency of pain, every single of these pain types were considered. Intensity of pain was evaluated by an 11-point numerical rating scale (NRS). The NRS consists of numbers between 0 and 10 where 0 indicates "no pain" and 10 indicates "maximum pain. Regarding the NRS scores, the intensity of pain was classified as 'no pain' (NRS = 0), 'mild pain' (NRS = 1-3), 'moderate pain' (NRS = 4-6) and 'severe pain' (NRS = 7-10). Neuropathic pain detection was performed by 'Identification Pain Questionnaire' (ID-Pain).

ID-Pain is a simple and easily applicable neuropathic pain-screening tool that can be performed by patients themselves. The questionnaire includes 6 items, which 5 are sensorial items and 1 is for assessment of joint pain. Items include: 1- Did the pain feel like pins and needles? 2- Did the pain feel hot/burning? 3- Did the pain feel numb? 4- Did the pain feel like electrical shocks? 5- Is the pain made worse with the touch of clothing or bed sheets? and 6- Is the pain limited to your joints? Scores between -1 and +1 are given for each item. The 6th item is for joint pain and -1 score is given if this item is positive. Other 5 items are for neuropathic pain and +1 point is given for their positivity. Therefore, a total score between -1 and +5 are given in ID-Pain Scale. For scores between zero and -1 are neuropathic pain is considered improbable; scores equal to 1 are considered possible; between 2 and 3 it is considered probable; between 4 and 5 it is considered highly probable (4,5).

Statistical Analysis: The statistical analysis was performed with software IBM SPSS Statistics for Windows, version 22.0. Continuous variables are displayed as means ± standard deviations and categorical variables as counts and percentages. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine relationship with headache. A *P* value <0.05 was considered statistically significant.

Results

A total of 341 patients were initially included in the study. However, 32 of them were excluded due to loss of life in ICU, 102 were excluded due to lack of establishing a phone conversation, and 61 were excluded because they were not able to give detailed information about their COVID-19 process. The data of 146 patients (83 males, 63 females) were considered in the study. While Group ICU was including 18 members, Group Non-ICU was including 128 members. The mean age of the patients was 50.77±16.94 years. Mean age of Group ICU was 67±13.85 years and it was higher than Group Non-ICU.

In assessment of frequency of pain, at least 1 pain complaint was observed in 68.5% (n=100) of the patients. The frequency of pain was 66.4% (n=85) in Non-ICU Group, and 83.3% (n=15) in ICU Group. Demographic features are given in Table 1.

The frequencies of COVID-19-related myalgia were 53.4%, arthralgia 39.7%, headache 41.1%, sore-throat 21.2%, chest pain 21.9%, back pain 28.1% and abdominal pain was 15.8%. The distribution of patients regarding to pain intensity was given in Table 2. Hyposmia had developed in 45.9% of the patients (n=67).

According to logistic regression results, a statistically significant relationship was observed between headache and hyposmia development (odds ratio (OR) = 6.53; 95% CI: 3.14-13.60; *P*<0.001). But there was no relationship between headache and age, sex (Table 3).

Table 1. Demographics and Baseline Characteristics of Patients

	All Patients (n=146)	Non-ICU (n=128)	ICU (n=18)
Age (mean±SD)	50.77±16.94	48.42±16.02	67.50±13.85
Sex			
Female n (%)	63 (43.2%)	57 (44.5%)	6 (33.3%)
Male, n (%)	83 (56.8%)	71 (55.5%)	12 (66.7%)
RT-PCR positivity, n (%)	113 (77.4%)	99 (77.3%)	14 (77.8%)
Hyposmia, n (%)	67 (45.9%)	57 (44.5%)	10 (55.6%)
Frequency of pain, n (%)	100 (68.5%)	85 (66.4%)	15 (83.3%)

Values are expressed as mean±standard deviation (SD) or number (percentage)

Table 2. COVID-19-Related Pain Types, Severity and Frequency

	All patients (n=146)	Non-ICU (n=128)	ICU (n=18)
Myalgia			
No pain	68 (46.6%)	63 (49.2%)	5 (27.8%)
Mild pain	22 (15.1%)	20 (15.6%)	2 (11.1%)
Moderate pain	43 (29.5%)	36 (28.1%)	7 (38.9%)
Severe pain	13 (8.9%)	9 (7.0%)	4 (22.2%)
Arthralgia			
No pain	88 (60.3%)	80 (62.5%)	8 (%44.4)
Mild pain	18 (12.3%)	15 (11.7%)	3 (%16.7)
Moderate pain	26 (17.8%)	23 (18.0%)	3 (%16.7)
Severe pain	14 (9.6%)	10 (7.8%)	4 (%22.2)
Headache			
No pain	86 (58.9%)	79 (61.7%)	7 (38.9%)
Mild pain	16 (11.0%)	13 (10.2%)	3 (16.7%)
Moderate pain	32 (21.9%)	27 (21.1%)	5 (27.8%)
Severe pain	12 (8.2%)	9 (7.0%)	3 (16.7%)
Sore throat			
No pain	115 (78.8%)	101 (78.9%)	14 (77.8%)
Mild pain	17 (11.6%)	16 (12.5%)	1 (5.6%)
Moderate pain	10 (6.8%)	8 (6.3%)	2 (11.1%)
Severe pain	4 (2.7%)	3 (2.3%)	1 (5.6%)
Chest pain			
No pain	114 (78.1%)	103 (80.5%)	11 (61.1%)
Mild pain	17 (11.6%)	14 (10.9%)	3 (16.7%)
Moderate pain	10 (6.8%)	7 (5.5%)	3 (16.7%)
Severe pain	5 (3.4%)	4 (3.1%)	1 (5.6%)
Back pain			
No pain	105 (71.9%)	94 (73.4%)	11 (61.1%)
Mild pain	4 (2.7%)	4 (3.1%)	0 (0%)
Moderate pain	18 (12.3%)	13 (10.2%)	5 (27.8%)
Severe pain	19 (13.0%)	17 (13.3%)	2 (11.1%)
Abdominal pain			
No pain	123 (84.2%)	106 (82.8%)	17 (94.4%)
Mild pain	12 (8.2%)	11 (8.6%)	1 (5.6%)
Moderate pain	10 (6.8%)	10 (7.8%)	0 (0%)
Severe pain	1 (0.7%)	1 (0.8%)	0 (0%)

Values reported are n (%) for categorical variables

Table 3. Regression Analysis of Headache Associated With Age, Sex and Hiposmia

	OR (95% CI)	P-values
Age	1.0 (0.99-1.02)	0.988
Sex	1,275 (0.60-2.69)	0.524
Hyposmia	6.23 (2.95-13.13)	<0.001

OR: Odds ratio; CI: Confidence intervals

Table 4. ID-pain Scores, n (%)

Score	All Patients (n=146)	Non-ICU (n=128)	ICU (n=18)
0 and -1	134 (91.8%)	121 (94.5%)	13 (72.2%)
1	6 (4.1%)	3 (2.3%)	3 (16.7%)
2-3	5 (3.4%)	4 (3.1%)	1 (5.6%)
4-5	1 (0.7%)	0 (0%)	1 (5.6%)

Values reported are n (%) for categorical variables

In neuropathic pain assessment, ID-Pain scores were 2 or more in 4 patients in Non-ICU and 2 patients in ICU. There was only one patient, who was in Group ICU with ID-Pain score 4-5. The classification of patients regarding ID-Pain scores is given in Table 4. In the assessment of neuropathic pain components, it was observed that hot/burning type was accompanying in 12 (8.2%) patients while pins and needles type was accompanying in 8 (5.5%) of patients. The distribution of neuropathic pain components is given in Table 5.

Discussion

The number of infected people is rapidly increasing as a result of high contagious characteristics SARS-CoV-2 and lack of specific treatment. In this period, the main goal is to control the pandemic by vaccination facilities. In other hand, mutation of the virus has the potential to prevent to reach this goal. Therefore, supportive treatments remain as the major treatment option currently.

Many of the people experience COVID-19 in asymptomatic, mild or moderate severity. With older age and concomitant chronic diseases, the severity of COVID-19 increases and some patients may require ICU treatment (6). In this study, the mean age of ICU Group was found higher than Non-ICU Group. Effective pain treatment may have a beneficial role on the course of the disease particularly in patients who need respiratory support in ICU. Untreated pain can prevent effective respiration, increase the respiratory work, have negative effects on other treatments, and may cause delirium and anxiety (7-9).

In many of the studies, myalgia has been reported as the most common pain type. Although the mechanism of myalgia is not clearly understood, it is assumed that generalized inflammation and cytokine response are the main causes. In severe COVID-19 patients, high levels of cytokines such as TNF-α, IL-6, and IL-10 were reported, and it was suggested that cytokine storm and the intensity of the disease has a correlation (3-10). In a Turkish study, in hospitalized COVID-19 patients, the frequencies of myalgia, arthralgia and back pain were reported 68%, 43.3% and 22% respectively and it was suggested that only arthralgia has a correlation with the severity of the disease (11). We can say that the results of our study are similar with that study (53.4% myalgia, 39.7% arthralgia, and 28.1% back pain) but we did not observe a correlation between pain intensity and the severity of the disease.

COVID-19-related sore-throat and abdominal pain may mimic the other viral infections. We observed sore throat in almost one of every five patients and abdominal pain in almost one of every six patients. In a European study including 1420 mild-moderate COVID-19 patients, frequency of sore-throat was 52.9% and frequency of abdominal pain was 19.1% (1). It was reported that sensitivity of RT-PCR was 59% and the sensitivity of computer tomography (CT) is more sensitive for COVID-19 diagnosis (12). Therefore, we suggest that in existence of sore-throat or abdominal pain, COVID-19 diagnosis should not immediately excluded regarding the negative RT-PCR result.

Even though the frequency of neurological symptoms was reported 1/3 of COVID-19 patients, headache, anosmia, hyposmia, dysgeusia

Table 5. Frequency of neuropathic pain components

	All patients (n=146)	Non-ICU (n=128)	ICU (n=18)
Pins and needles	8 (5.5%)	5 (3.9%)	3 (16.7%)
Hot/burning	12 (8.2%)	9 (7.0%)	3 (16.7%)
Numb	0 (0%)	0 (0%)	0 (0%)
Electrical shocks	2 (1.4%)	1 (0.8%)	1 (5.6%)
Worse with touch	6 (4.1%)	3 (2.3%)	3 (16.7%)

Values reported are n (%) for categorical variables

are more common symptoms (1,13). Additionally, symptoms such as vision impairment, loss of consciousness, neuralgia, stroke, epileptic seizures, rhabdomyolysis, Guillain-Barre Syndrome, and ataxia may observe (13). Uygun et al. reported that headache may be strongly related with anosmia/ageusia (14). In our study, the frequencies of headache and hyposmia were 41.1% and 45.9% respectively and we observed a significant relationship regarding on their frequencies. Although the specific mechanism of headache in viral infections is not known, it is assumed that the overexpression of proinflammatory cytokines in cerebrospinal fluid (CSF) may stimulate the trigeminal ganglion (3). Coronaviruses have neurotrophic characteristics. Another suggested mechanism on the development of the neurological symptoms is the directly neural invasion of the virus. It is reported that muscle or joint pain in COVID-19 is more intense and may be irresponsible to classic analgesics (15). Similarly, analgesic resistant headache is proposed as an important variable to COVID-19 suspicion (14). Development of analgesic resistance may support that neuropathic pain components exist in COVID-19-related pain and different mechanisms may have role in pain generation.

Neuropathic pain is described as "pain caused by a lesion or disease of the somatosensory nervous system". Classic analgesics are (Non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol) are not effective enough and specific drugs (anti-epileptics, antidepressants etc.) are required for the treatment of neuropathic pain (16). Despite neuropathic symptoms are quite common in COVID-19, there is lack of comprehensive assessment of neuropathic aspects of pain in the literature. Aksan et al. reported a case with very intense burning type pain (17). In our study, we observed that neuropathic pain components are very frequent in COVID-19-related pain. In this study we observed that 4.1% patients have 2 more ID-Pain scores. When we assessed the neuropathic pain components, we observed that burning type and pins and needles types were more frequent. We observed that neuropathic pain was more frequent in ICU patients. Regarding these results we suggest that effective pain assessment in ICU required COVID-19 patients should be performed and administration of neuropathic pain specific drugs such as pregabalin or gabapentin should be considered.

In conclusion, myalgia, arthralgia, and headache are most frequent pain types in hospitalized COVID-19 patients. We suggest that headache is closely related with hyposmia. Neuropathic pain is not a rare condition in COVID-19, and always should be considered. Finally, we suggest routine assessment of neuropathic pain in patients with COVID-19.

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