Musculoskeletal Manifestations of COVID-19: A Cross Sectional Study in Egyptian Patients

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Musculoskeletal Manifestations of Coronavirus Disease 2019: A cross-Sectional Study in Egyptian Patients

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Abstract

Objectives: We conducted this cross-sectional study to explore the relation between coronavirus disease 2019 (COVID-19) and frequency of musculoskeletal manifestations and the possible cause of rheumatoid arthritis as one of the autoimmune diseases.

Background: COVID-19 has the capability to trigger the immune response and induce cytokine release, which is directly linked to musculoskeletal pain initiation, besides fever and cough.

Patients and methods: A cross-sectional study was conducted among a number of 120 critically hospitalized Egyptian patients and home-isolated patients proved positive for COVID-19 tested with RT-PCR aged 20\textendash;70 years. These patients were drawn randomly in the period from March 2020 to July 2020. Clinical assessments were done by sociodemographic data, assessment of musculoskeletal system, and severity of COVID symptoms. Data were analyzed using SPSS.

Results: The characteristic features of patients with COVID-19 were fever (48.3\%), fatigue (80.8\%), myalgia (72\%), and arthralgia (60\%). Some patients developed peripheral neuritis (54\%), neck pain in 40.0\% of patients, Guillain-Barré in 31.7\%, back pain in 29\%, and rheumatoid arthritis in 24.2\%.

Conclusion: COVID-19 may be manifested by musculoskeletal manifestation and rheumatoid arthritis as one of the autoimmune diseases.

Keywords: Arthralgia, Autoimmune diseases, Coronavirus disease 2019, D-dimer, Musculoskeletal manifestations

1. Introduction

Coronavirus infections, as well as other respiratory infections, may cause musculoskeletal problems; however, the symptoms may range from arthralgia to specious and chronic arthritis [1,2]. Arthralgia was found in 15\% of patients with coronavirus disease 2019 (COVID-19), and myalgia is much more common (44\%) [2,3].

Musculoskeletal symptoms may not seem to be associated with COVID-19 severity [3\textendash;7]. Myalgia is also common in severe acute respiratory syndrome coronavirus (SARS-CoV) which was reported in 49\textendash;68\% of severe cases [4,5], whereas arthralgia is less common (11\%). Arthralgia and myalgia are also common in patients with other viral infection as Middle East respiratory syndrome-CoV (32\%) [5].

Finally, in another point of view, there is a relationship between coronaviruses and arthritis, which is associated with increased risk of developing rheumatoid arthritis. In a Korean study, authors reported the increased susceptibility of rheumatoid arthritis observed in patients infected with endemic human coronavirus, parainfluenza virus, and metapneumovirus [8].

Although COVID-19 pandemic could potentially lead to an increase risk of rheumatoid arthritis no reports confirmed the development of autoimmune inflammatory arthritis, as rheumatoid arthritis, after infection by SARS-CoV-2 or any of the other human
coronaviruses. SARS-CoV-2, like SARS-CoV and Middle East respiratory syndrome-CoV, has the capability to trigger a massive immune response associated with a cytokine storm [9], leading to ARDS, which can be lethal in the most serious cases of COVID-19 [10–12]. Hence, anti-cytokine intervention does not increase the risk of viral infection and might not affect viral clearance but would inhibit the hyperinflammatory state in COVID-19, which might be beneficial [6–13].

Inhibition of IL-1β, which is generated by AT2 cells after infection with SARS-CoV [14] and is an essential innate immunity effector cytokine that controls neutrophil and macrophage function, appears to make sense in the treatment of COVID-19. In fact, IL-1β suppression with high-dose anakinra or canakinumab is currently being studied as a COVID-19 therapy [15,16].

One hypothesized mechanism may link the musculoskeletal pain and myalgia in COVID-19 to the distribution of angiotensin-converting enzyme 2 and the development of cytokine storms. SARS-CoV-2 may use angiotensin-converting enzyme 2 as a receptor (SARS-COV-2) [9–12]. Furthermore, some studies suggest that inflammatory cytokines cause myalgia by stimulating the production of prostaglandin E2. Patients with COVID-19 had higher plasma levels of IL-2, IL-7, IL-10, IL-6, TNF, and lymphopenia. Overall, pharmacological and non-pharmacological interventions are used to treat COVID-19 musculoskeletal pain patients, as various treatments have several advantages [7]. The aim of this study was to explore the relation between COVID-19 and frequency of musculoskeletal manifestations.

2. Patients and methods

This is a cross-sectional study that included COVID-19 patients diagnosed with a positive nucleic acid amplification test and chest computed tomography. This study included patients admitted in the Mataria Teaching Hospital, Egypt, as one of the isolation hospitals in Egypt, from March 2020 till July 2020. COVID was a pandemic and lots of patients attended to the hospital (either hospitalized or outpatient clinics); there was difficulty accessing such large data at this period of pandemic with a small number of medical stuff with mass quarantine and lockdown. Thus, we updated our manuscript with this information.

A total of 398 patients were eligible for the study. Of them, 94 did not match our age range, 42 had malignant and autoimmune diseases, 106 passed away, and 36 had lost data.

Finally, a number of 120 participants met our inclusion criteria and were included in the statistical analysis. Our patients were furtherly divided into two groups: group 1 included critically hospitalized Egyptian patients and group 2 included the home-isolated patients, both of matched age ranged from 20 to 70 years. The sample size for the study was calculated by open-source epi info.com (version 3) utilizing ‘frequency in a population’ method.

The study was approved by the Ethics Committee of Mataria Teaching Hospital, Egypt (Date 2/9/2020. No.HM000128). This study does not contain any personal details as it is a secondary analysis of routine data that has been anonymized and was performed according to the Declaration of Helsinki.

The main inclusion criteria were to be positive for COVID-19 that was diagnosed by clinical manifestations and confirmed by RT-PCR (CDC Diagnostics, COVID-19 Multiplex Assay, Atlanta, Georgia, USA). Exclusion criteria were any history of chronic or acute inflammatory diseases in the preceding 3 months, malignancies, and/or autoimmune diseases.

2.1. All individuals underwent the following

History, clinical examination, and laboratory investigations including complete blood count and liver and kidney function tests using automated Sysmex KX-21 (Sysmex Corporation, Kobe, Japan). C-reactive protein (CRP), D-dimer levels, and rheumatoid factor were assayed according to manufacturer protocols using nephelometer MISPA-i2 protein analyzer from Agape Diagnostics, Switzerland.

Antinuclear antibodies were analyzed by Elisa kit from BioSource, California, USA. Computed tomography for the chest was done for all patients with respiratory problems to detect the presence or absence of ground-glass opacities.

2.2. Statistical analysis

Data were analyzed using IBM SPSS statistics for Windows (version 26.0 released 2018;IBM Corp., Armonk, New York, USA). Numerical data were summarized as means and SDs or median and range, while qualitative data were described as frequencies and percentages. Relations between qualitative data were done using χ² test or Fisher’s exact test as appropriate.

3. Results

This study represents information on a total of 120 participants. They included 53 (44.2%) males and 67 (55.8%) females, with a median age of 47 years. They were divided into two groups: hospitalized critical
group \( (N = 24) \) and home-isolated noncritical group \( (N = 96) \).

The characteristic features of patients with COVID-19 were fever (48.3%), fatigue (80.8%), myalgia (72%), and arthralgia (60%). Some patients developed peripheral neuritis (54%), neck pain in 40.0% of patients, Guillain–Barré in 31.7%, back pain in 29%, and rheumatoid arthritis in 24.2% (Table 1 and Fig. 1).

Ground-glass opacities were present in 86.6% of the patients, while 40.8% presented with consolidation was found in hospitalized critical cases.

Of the 120 participants, 24 patients were admitted with respiratory failure defined as peripheral oxygen saturation of less than 90%, which showed a high significant difference between critical and noncritical cases.

The hospitalized critical group showed higher inflammatory markers than that of the home-isolated noncritical group with a significant difference in the levels of CRP and D-dimer especially in

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Noncritical ( (N = 96) ) ([n (%)])</th>
<th>Critical ( (N = 24) ) ([n (%)])</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>26 (27.1)</td>
<td>9 (37.5)</td>
<td>0.315</td>
</tr>
<tr>
<td>Neck pain</td>
<td>32 (33.3)</td>
<td>16 (66.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0</td>
<td>24 (100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>48 (50.0)</td>
<td>10 (41.7)</td>
<td>0.465</td>
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<tr>
<td>Fatigue</td>
<td>74 (77.1)</td>
<td>23 (95.8)</td>
<td>0.042</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>48 (50.0)</td>
<td>24 (100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>68 (70.8)</td>
<td>24 (100.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Guillain–Barré</td>
<td>8 (33.3)</td>
<td>30 (31.3)</td>
<td>0.844</td>
</tr>
<tr>
<td>Peripheral neuritis</td>
<td>49 (51.0)</td>
<td>16 (66.7)</td>
<td>0.169</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>26 (27.1)</td>
<td>3 (12.5)</td>
<td>0.136</td>
</tr>
<tr>
<td>CRP</td>
<td>21.2 (0.1–380)</td>
<td>123.5 (8–200)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D-dimer</td>
<td>525.0 (40.0–5510.0)</td>
<td>1112 (500.0–2500.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ground-glass opacity</td>
<td>80 (83.3)</td>
<td>24 (100.0)</td>
<td>0.039</td>
</tr>
<tr>
<td>Consolidation</td>
<td>30 (31.3)</td>
<td>19 (79.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total ( (N = 120) ) ([n (%)])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>85 (70.8)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>35 (29.2)</td>
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<tr>
<td>ICU admission</td>
<td>96 (80.0)</td>
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<tr>
<td>Respiratory failure</td>
<td>24 (20.0)</td>
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<tr>
<td>Fever</td>
<td>62 (51.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>58 (48.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>48 (40.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>72 (60.0)</td>
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<tr>
<td>Guillain–Barré</td>
<td>82 (68.3)</td>
</tr>
<tr>
<td>Peripheral neuritis</td>
<td>55 (45.8)</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>65 (54.2)</td>
</tr>
<tr>
<td>CRP</td>
<td>24 (0.1–380)</td>
</tr>
<tr>
<td>D-dimer</td>
<td>551 (40–5510)</td>
</tr>
<tr>
<td>Ground-glass opacity</td>
<td>16 (13.3)</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein.
patients with arthralgia and myalgia who showed a higher significant difference between the two groups (Table 2 and Fig. 2).

There was no significant difference between critical and noncritical cases with regard to fever, fatigue, Guillain–Barré, peripheral neuritis, and rheumatoid arthritis.

4. Discussion

The pandemic of COVID-19 infection spread rapidly throughout the world with very high rates as well in Egypt. COVID-19 is still strange and unknown as its affection ranges from mild to severe according to personal immunity. Lots of studies have reported extrapulmonary manifestations together with other clinical manifestations including musculoskeletal manifestations varying from myalgias, arthralgias, neurological manifestations, and autoimmune diseases. Pathologically, several reports have suggested an inflammatory process affecting different systems of the body in addition to the musculoskeletal system.

In our study, myalgia was the commonest presenting symptom, which was reported in 72% of patients, followed by arthralgia which was presented in 60%, while the study of Hasan et al. [7] reported that myalgia/or arthralgia were present in 15.5%. Moreover, another systematic review reported the prevalence of myalgia over arthralgia by 19%. Up to 80% of patients may develop musculoskeletal manifestations that persist longer than 3 months leading to cases of chronic fatigue syndrome leading to impairment in their quality of life [17].

The mechanism of muscle pain and arthralgia in viral diseases is still unclear. However, it is believed to be due to increased proinflammatory cytokines and acute-phase proteins. In our study, there was a highly significant difference between arthralgia, myalgia (Fig. 2), CRP, and D-dimer \( P < 0.001 \) as shown in Table 2 in critical and noncritical cases as shown in Table 1, which goes with the study of Eren et al. [18], who showed that myalgia and arthralgia were found retrospectively causing chronic fatigue syndrome.

On the other hand, we found no significant difference between critical and noncritical cases as regards fever, fatigue, Guillain–Barré, peripheral neuritis, and rheumatoid arthritis unlike the study of Milan and Hasan, who reported more cases of Guillain–Barré syndrome in COVID-19 hospitalized individuals, and more extensive demyelinating neuropathy, which may be due to a larger sample size and longer duration of follow-up for their cases, or the sampled size cases were of the same chronicity as their patients or may due to personal variability of the patient affection [17].

The Liu et al. [4] study, a multicenter retrospective study conducted in Hubei, China, indicated that patients have developed autoimmune diseases as the Guillain–Barré syndrome post COVID-19 infection, which goes with our study that found patients who developed rheumatoid arthritis, Guillain–Barré syndrome which may be due to disturbance of the virus to patients’ self-tolerance and triggering the autoimmune responses through cross reactivity with the host cells, prognosis of autoimmune diseases and COVID-19 remains
controversial but the patients who closely adhere to medical treatment during COVID-19 infection prevents complications and disease flares [16].

Generally, there was great variation between different studies conducted all over the world to test the frequency of fatigue and musculoskeletal. Xu et al. [19] reported that the frequency of fatigue and musculoskeletal symptoms were 4 and 16%, respectively. Mo et al. [20] revealed the rate of fatigue as 73.2% and the rate of myalgia/arthralgia as 61%. Studies conducted in Europe reported myalgia as 59% and arthralgia in 31% of the cases [21]. Accordingly, further studies with a larger sample size are needed to clarify this relationship and reveal its underlying pathophysiology.

5. Conclusion

SARS-CoV-2 can produce a variety of musculoskeletal symptoms such as arthralgias, myalgias, neuropathies/myopathies, and rheumatoid arthritis, which need special attention.

Consent statement

Ethical approval and written informed consent was obtained from the Menoufia University academic and ethical committee.

Conflict of interest

None declared.

References