Beyond the Lung: Exploring Musculoskeletal and Rheumatological Complications in Post-COVID-19 Survivors

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ABSTRACT

Background: Post-COVID-19 infection patients often present to rheumatology clinics with a variety of musculoskeletal complaints; some objective findings in particular merit special attention.

Objective: The goal of this study was to assess post-COVID-19 survivors who have recently developed musculoskeletal problems and to ascertain whether there is a relationship between the current presentation and the course of the prior infection.

Methods: In this cross-sectional research, 102 post-COVID-19 patients with musculoskeletal complaints were recruited from the Outpatient Rheumatology Clinic. A detailed medical history of the current complaint as well as prior to COVID-19 infection was analyzed. Joints, mucocutaneous, proximal and distal muscles, and peripheral nerves were evaluated and neurophysiological studies were also conducted.

Results: 64 males and 38 females with mean age of 41.6 ± 12.7 years and duration of COVID-19 infection was 13.6 ± 7.3 days. Duration of the current musculoskeletal complaints was 3.6 ± 1.8 weeks. Arthralgia and myalgias were reported by 58.8 % and 36.3% respectively, while arthritis was observed in 17.6%. Paresthesia, and motor weakness were reported by 19.6% and 22.5% respectively. 39.2% of the involved group exhibited objective findings and 31.4 % of patients had neurophysiological abnormalities.

Conclusions: Arthralgia, myalgias, arthritis and mononeuritis are the most prevalent manifestations in post-COVID-19 survivors with new onset musculoskeletal complaints. Increasing age, smoking history, increased duration and severity of prior infection are predisposing factors for neuritis.

Keywords: Post COVID-19, Musculoskeletal pain, Nerve conduction studies, Neuritis.

INTRODUCTION

In December 2019, Wuhan, Hubei Province, China, reported a pneumonia outbreak of unknown cause. Epidemiological data linked most of these illnesses to the Huanan seafood wholesale market. Human airway epithelial cells and the Vero E6 and Huh7 cell lines were exposed to broncho-alveolar lavage material from individuals with pneumonia of unknown origin. This exposure led to the discovery of SARS-CoV-2, formally known as Covid-19 [1]. On March 2020, the fictitious SARS-CoV-2 outbreak went global [2].

Patients with COVID-19 infections may develop various clinical symptoms, ranging from mild to severe. The most typical symptoms include fever, coughing, and shortness of breath. In both lung fields, computerized tomography (CT) revealed several features, including ground-glass opacities, interstitial infiltration, crazy-paving pattern, and numerous patchy consolidations, in addition to vascular enlargement, thick interlobar septa, and air bronchograms. Patients with severe pneumonia had a respiratory rate of at least 30 breaths per minute, an oxygen saturation of 93%, or a PaO₂/FiO₂ of 300 mmHg [3].

Although most coronavirus infections occur in the lungs, the heart, gastrointestinal tract, kidney, liver, and eyes are other organs that require careful management [4–7]. In recent systematic reviews, cutaneous manifestations have been discussed. COVID-19 patients have reported a wide variety of skin abnormalities, including urticarial rash, confluent erythematous/maculopapular/morbilliform rash, papulovesicular exanthem, an acral pattern resembling chilblains, livedo reticularis/racemosa pattern, and purpuric "vasculitic" pattern [8].

Little data suggest that COVID-19 involves the central nervous system (CNS). COVID-19 may exhibit neurological symptoms such as headaches, ataxia, confusion, and a loss of taste and smell. A few patients displayed cerebrovascular illness or seizure activity. Whereas additional routes, such as via the cribriform plate of the ethmoid bone close to the olfactory bulb, should be considered in patients who manifest loss of taste and smell, the hematogenous route appears to be the most likely conduit for SARS-CoV2 to reach the brain [9].

It's possible that COVID-19 does not directly harm nerves, roots, or anterior horn cells in the same way that West Nile or polioviruses do. In numerous cases of COVID-19-related Guillain-Barre syndrome (GBS) that have been documented, even the cerebrospinal fluid (CSF) and the polymerase chain reaction (PCR) for coronavirus have come back negative [10]. Due to molecular mimicry between the peripheral nerve's ganglioside components and the infectious pathogen's surface antigens, it is likely to be a Para-infectious or post-infectious complication resulting from an abnormal immune response, which can be considered a second
mechanism explaining GBS in COVID-19. However, there are increasing reports of various neuromuscular and rheumatologic consequences linked to COVID-19 infection and disease progression, including soft tissue abnormalities, myalgia, myositis, neuropathy, and arthropathy.

The SARS-CoV-2 virus may predispose peripheral nerves to damage through hypothetical mechanisms that are still unproven because iatrogenic peripheral neuropathy has been associated with COVID-19 at a higher rate than expected. Patients with COVID-19 may be more likely to experience iatrogenic nerve injuries due to virus-induced state of hyperinflammation or overlapping comorbidities that increase the risk of both severe nerve injury and symptoms of COVID-19 requiring hospitalization.

A positive antinuclear antibody (ANA), antiphospholipid antibodies, lupus anticoagulant assay and an elevated level of D-dimer have all been found in laboratory studies with COVID-19. These instances of COVID-19 imitating or causing rheumatic and musculoskeletal diseases suggest immunological dysregulation that may continue over an extended period. Molecular mimicry, epitope dissemination, bystander activation, the persistence of the latent virus, and poly/oligoclonal immune activation in an autoimmune mosaic are some viral processes that impair self-tolerance. Similar mechanisms may lead to autoimmunity following Covid-19 infection.

This study aimed to assess post-COVID-19 survivors who have recently developed musculoskeletal problems and to ascertain whether there is a relationship between the current presentation and the course of the prior infection.

PATIENTS AND METHODS

Studied population

Patients with musculoskeletal problems seen at Outpatient Rheumatology Clinic between April 21 and January 22 who had covid-19 and survived at least 3 months post-recovery were enrolled in this observation research. All patients were required to have a positive oropharyngeal or nasopharyngeal swab test to qualify for inclusion in the trial, and the authors considered the reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 to be the gold standard for inclusion. One hundred and two participants agreed to take part in the research.

Exclusion criteria: Patients under 18 years, pregnancy, lactation, endocrine disorders, cancer, autoimmune diseases, diabetes, CNS diseases, prior history of neuropathies and those who regularly take medications such as steroids, statins, cyclosporin, isoniazid, phenytoin and colchicine, or sulphonamides.

Clinical Evaluation and patient classification:

A thorough history was taken and detailed clinical evaluation for joints, skin, muscle power (proximal and distal) and peripheral nerves according to a predetermined protocol. Sensory and motor conduction studies, as well as an electromyography study were conducted as part of the electrodagnostic workup according to the American association of electrodagnostic medicine, the American academy of neurology, and the American academy of physical medicine and rehabilitation guidelines. Neuropack S1, MEB-9400K, four-channel electromyography measuring system (Nihon Kohden, Japan) was used in this research.

Classification of patients:

According to patient records and CT reports, patients were classified into mild, severe, and critical. Those with mild disease who were advised to continue their management at home (home-treated group). Those with severe and critical cases were hospitalized according to their progression (hospital- isolated group).

Laboratory assessment:

Laboratory tests were performed, including complete blood count (CBC), liver and renal function, Rheumatoid factor (RF) (Quantitative determination of RF by Immunoturbidimetry). Spinreact and Spain. Anti-cyclic citrullinated peptides (anti-CCP) by enzyme-linked immunosorbent assay (ELISA) and Eagle biosciences, Amhers, NH, US, antinuclear antibodies (ANA) by ELISA, anti-neutrophil cytoplasmic antibody (ANCA), anti-cardiolipin IgG and IgM, detected by ELISA.

Ethical approval: The study was conducted following Helsinki Declaration and was approved by Faculty of Medicine’s Ethical Committee, Minia University (approval number: 24/2021). All patients signed informed consent forms.

Statistical analysis

IBM's Statistical Package for Social Sciences (SPSS) version 25 was used for data entry after collection, editing, and coding. Means and standard deviations were used to illustrate the quantitative information. Quantitative and percentage data were supplied for qualitative variables. Independent t-test was used to compare quantitative data from two groups. Pearson's Chi-Square or Fisher's Exact Test was used to examine the percentages. The margin of error allowed was 5%, and the confidence interval was set to 95%. This meant that a p-value ≤ 0.05 indicated statistical significance. When the expected frequency was less than 5, an Exact test was used.

RESULTS

102 patients were enrolled in the current study, 64 (62.7%) males and 38 (37.3%) females. Patients’ age ranged from 18 to 67 years with mean age of (41.6 ± 12.7), and their COVID-19 illnesses lasted between 7 to 40 days and the mean duration of illness was 13.6 ± 7.3, while musculoskeletal illness duration was 1-8 weeks with a mean of 3.6 ± 1.8. Smoking history was
12%. Fever was the main complaint and was reported by 96 (94.1%) patients, followed by cough and expectorations in 66 (64.7%) and dyspnea in 41 (40.2%) patients. 49 (48%) patients reported loss of smell and taste.

Among the musculoskeletal complaints, arthralgias was reported by 60 patients (58.8%) and myalgias was reported by 37 (36.3%). Sensory complaints of paresthesia, numbness, and hotness were reported by 19.6%. Weakness of small muscles of the hand, wrist drop, foot drop were the main motor complaint and reported by 23 (22.5%). On examination, arthritis was seen in 18 (17.6%) patients (13 knees, 4 ankles and 1 wrist). Arthritis in those patients was not associated by enthesitis or inflammatory back pain. Sensory examination showed impaired sensation at the distribution of median, ulnar, radial and sural nerves. Distal muscle weakness related to peripheral nerves distributions were found in 23 (22.5%, 5 median, 8 ulnar, 6 radial and 4 common peroneal nerves). NCS abnormalities were seen in 31.4% of the studied population (7.8% sensory, 16.7% motor and 6.9% combined sensory-motor abnormalities). Furthermore, tendopathy, malar rasha, oral ulcers, alopecia and Raynaud’s phenomenon were reported by 2% of the invoved sample. Palpable purpura was seen in 4 (3.9%) cases (Table 1).

Table (1): Comparisons between the studied groups regarding clinical, neurophysiological and laboratory results (n=102)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N= 102</th>
<th>Group I (hospitalized) n=36</th>
<th>Group II (Home treated) n=66</th>
<th>p</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/ years (m ± SD)</td>
<td>41.6±12.7</td>
<td>45.2±13</td>
<td>39.7±12.2</td>
<td>0.04</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>64 (62.7)</td>
<td>18 (50)</td>
<td>46 (69.6)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>38 (37.3)</td>
<td>18 (50)</td>
<td>20 (30.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of COVID illness/days (m ± SD)</td>
<td>13.6±7.3</td>
<td>21.4±7.1</td>
<td>9.3±1.6</td>
<td>0.0001</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration of MSK complaints/weeks (m ± SD)</td>
<td>3.6±1.8</td>
<td>4.1±2</td>
<td>3.3±1.7</td>
<td>0.03</td>
<td>0.22</td>
</tr>
<tr>
<td>Arthralgia, n (%)</td>
<td>60 (58.8)</td>
<td>19 (52.8)</td>
<td>41 (62.1)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Myalgia, n (%)</td>
<td>37 (36.3)</td>
<td>13 (36.1)</td>
<td>24 (36.1)</td>
<td>**1</td>
<td></td>
</tr>
<tr>
<td>Arthritis, n (%)</td>
<td>18 (17.6)</td>
<td>6 (16.7)</td>
<td>12 (18.2)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Palpable purpura, n (%)</td>
<td>4 (3.9)</td>
<td>4 (12.5)</td>
<td>0</td>
<td>0.006</td>
<td>0.27</td>
</tr>
<tr>
<td>Paresthesia, n, (%)</td>
<td>20 (19.6)</td>
<td>13 (36.1)</td>
<td>7 (10.6)</td>
<td>**0.002</td>
<td>0.31</td>
</tr>
<tr>
<td>Distal motor weakness, n (%)</td>
<td>23 (22.5)</td>
<td>16 (44.4)</td>
<td>7 (10.6)</td>
<td>**0.001</td>
<td>0.39</td>
</tr>
<tr>
<td>Neurophysiological study abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sensory neuropathy, n (%)</td>
<td>8 (7.8)</td>
<td>5 (13.9)</td>
<td>3 (4.5)</td>
<td>0.0001</td>
<td>0.39</td>
</tr>
<tr>
<td>Motor neuropathy, n (%)</td>
<td>17(16.7)</td>
<td>11 (30.6)</td>
<td>6 (9.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined sensory-motor, n (%)</td>
<td>7 (6.9)</td>
<td>5 (13.9)</td>
<td>2 (3)</td>
<td></td>
<td></td>
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<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive ANA, n (%)</td>
<td>18 (17.6)</td>
<td>10 (27.8)</td>
<td>8 (12.1)</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>Positive ANCA, n (%)</td>
<td>6 (5.9)</td>
<td>4 (11.1)</td>
<td>2 (3)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Positive Anticardiolipin, n (%)</td>
<td>16 (15.7)</td>
<td>6 (16.7)</td>
<td>10 (15.2)</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

MSK: musculoskeletal. ANA: Anti-nuclear antibodies, ANCA: anti-neutrophilic cytoplasmic antibodies. *P value was calculated by Independent t test, Pearson Chi square test or **Fisher exact test wherever suitable, highlighted values are significant.

Comparing between the two groups regarding neurophysiological results we found that 58.3% of hospitalized cases and 16.7% of home-treated cases showed abnormalities as shown in figure (1). Theses changes were statistically significant (p=0.0001, r=0.4). We studied factors that might predispose to neurophysiological changes among the studied population like age, sex, history of severe disease, duration of illness and minimum oxygen saturation during the infection time. Also, binary logistic regression was done and we found that hospitalized cases with severe disease were the most predisposing factor for neurophysiological changes (odd’s ratio=5.3), smoking history, (odd’s ratio=2.4), gender and duration of illness increased the risk (odd’s ratio=1.1) as shown in table (2). The anti-CCP antibody was positive in two patients, but no patient in our study sample had a positive RF. The ANA was positive in 17.6% of cases, while ANCA and Anti-cardiolipin antibodies were positive in 5.9% and 15.7%, respectively. Musculoskeletal complaints were more evident in hospitalized patients. Patients’ reports of arthralgias and objective findings of arthritis were positively linked to the ANA existence in both groups (p=0.004, r=0.28 and p=0.0001, r=0.6), despite the finding that ANA was significantly different between the two (p= 0.047).
DISCUSSION

Our data showed that rheumatic manifestations and musculoskeletal symptoms and signs were common among post-COVID-19 survivors. Arthralgia and myalgia were the most prevalent complaints that is consistent with previous researches \[21-24\]. Hospitalized patients were more prone to symptoms existence than home-treated cases. This observation was statistically significant as previously mentioned by other authors \[24\]. Mono- or oligo-articular arthritis was predominant in the lower limbs and not associated with enthesis or inflammatory back pain as reported by Taha et al. \[26\] and Demir et al. \[27\]. They studied 154 hospitalized cases, and their observations were reported during the admission period (71.4% and 55.8%, respectively) that is similar to our observation.

Subjective complaints were more common among home-treated patients while objective findings like arthritis and motor neuropathies were more evident in hospitalized cases. 300 post-COVID-19 survivors were included in the study by Karaarslan et al. \[21\] who collected their data from hospitalized patients after their discharge at 3 and 6 months post-COVID-19. They noted that arthralgia and myalgia were reported by 18.6% and 15.1% respectively, that is in contrast to our findings. The observed differences could be explained due to different study design, different sample size, and the exclusion of patients admitted to critical care units. Additionally, during their follow-up period, they had missing data.

Our data reported a significant number of cases with objective features of neuropathy in the post-COVID-19 survivors, sensory, motor and combined sensory-motor impairment as evidenced by neurophysiological studies. Searching PubMed and midline revealed a lack of studies regarding peripheral nerve affection in post-COVID-19 survivors. However; previous reports recorded axonal and demyelinating polyneuropathy during the acute stage of viral infection and diagnosed as Guillain barre syndrome during the first 3 weeks of infection \[28\].

According to our data, neurophysiological abnormalities were found in 58.3% and 16.7% in hospitalized and home-treated patients, respectively. These findings were noteworthy when compared to mild patients who received home-based care. These results are in agreement with earlier researches \[29\].

Our results demonstrated that cutaneous manifestations such as Raynaud's phenomenon, malar rash, oral ulcers, and alopecia were insignificant findings among the studied group, possibly due to the small number of patients and lack of a follow-up period in this study, as opposed to past data reports, which noted a sizable number of patients with Raynaud's phenomenon, livedo reticularis, and other cutaneous symptoms of COVID-19 that persisted over...
time who reported these findings during the infection periods. 

Patients in the studied group with ANA positivity were correlated with arthralgias and arthritis and hospitalization. Previous record by Pascolini et al. reported that ANA positivity was correlated with hospitalization and critical illness although they didn’t study musculoskeletal manifestations but pulmonary sequelae. Zhou et al. studied the autoimmune characteristics of 21 cases with severe presentation of acute respiratory distress and found ANA to be present in about half of their sample, which is much far from our results owing to different study designs and greatly difference in the inclusion criteria. Moreover, Karahan et al. studied the antiphospholipid antibodies in critically-ill patients with COVID-19 and non COVID-19 patients. They found that these autoantibodies existed with the same percentage in the critically-ill patients irrespective to the aetiology. Our data support the presence of Anti-cardiolipins antibodies to be found in 16.7% of the hospitalized group that was closer to findings from their data. Our findings provided additional information to earlier reports, which declare that ANA positivity is associated with a higher probability of hospitalization and a worse outcome.

Evaluation of patients during their critical illness and follow-up is one of the major limitations in this study moreover a larger sample size will add a significant value, lack of previous laboratory results prior to COVID-19 infection has also a major concern. Therefore, additional researches are needed in this arena.

CONCLUSION

The most striking findings among post-COVID-19 survivors presenting with musculoskeletal and rheumatological complaints are arthritis and neurophysiological abnormalities. Hospitalization during the first stages of infection, longer disease duration, and older populations were all observed to increase the risk of rheumatological consequences in this study. Patients with this condition were also found to have the autoantibodies ANA and ANCA.

Conflict of Interest: Authors had no competing interests.

Funding: The authors certified that no public, commercial, or non-profit grants were awarded to support this study.

Author Contributions: Faten Ismail and Ahmed Hafez conceptualized the study. Salma Taha did research in the field of neurophysiology and gathered data. Ahmed Kasem collected data related to COVID-19 infection from patient reports. Amel Kamal analyzed lab work. Data analysis, interpretation of results and figure creation were the responsibility of Tasneem M. Ali and Ahmed Hafez. Manuscript revision and approval were all accomplished by Ahmed Hafez, Faten Ismail, Ahmed Kasem and Salma Taha.

Compliance with ethical standards: The authors affirmed that they have no known financial or interpersonal conflicts that would have appeared to impact the research presented in this study.

Funding: The authors confirmed that no specific grant was provided for this research by funding organizations in the public, private, or nonprofit sectors.

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