

## Brucellosis, a Rare Cause of Muscle and Joint Pain Following Covid-19 Treatment in Endemic Regions

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**Abstract:** In our area, where endemic Brucella is present, we intended to demonstrate the frequency of Brucella among patients who applied malaise, muscle, and joint pain following Covid-19 treatment in the Long Covid period. In this study, 86 patients who were PCR positive between April 2020 and May 2022, diagnosed with Covid-19, and completed their treatment, were retrospectively analyzed. Thirteen patients with ongoing complaints of brucella agglutination and/or brucella coombs agglutination of 1/160 and above were included in the study. Five (38 %) patients in the study were male (31 to 69, median age 55 years), and eight (62 %) were female (40 to 57, median age 43.5). Muscular-joint pain (62 %), malaise (62 %), fatigue (30 %), and sweating (15 %) were common symptoms. The duration of onset of symptoms in the Long Covid period ranged from 41 days to 220 days. Brucellosis should be considered in the differential diagnosis of patients diagnosed with Covid-19 in endemic regions and presenting to the hospital with symptoms of muscle-joint pain and malaise after treatment. © 2023 NTMS.

**KeyWords:** Brucella; Covid-19; Muscle-Joint Pain.

## 1. Introduction

Covid-19 infection was first described in the Chinese city of Wuhan in the province of Hubei on 12 December 2019<sup>1</sup>. The World Health Organization (WHO) declared it a pandemic on 11 March 2020<sup>2,3</sup>. Symptoms generally associated with Covid-19 include fever, cough, respiratory difficulty, headache, and muscle-joint pain<sup>4</sup>.

Muscle-joint pain, malaise, and fever can persist in the Long Covid period<sup>5</sup>. In NICE guidelines: Acute Covid-19: Symptoms up to 4 weeks, ongoing symptomatic Covid-19: Symptoms between 4 and 12 weeks, post-Covid-19: Symptoms that develop after 12 weeks and persist for longer<sup>6</sup>. The term "Long Covid" includes both post-Covid and ongoing symptomatic Covid

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syndrome, according to NICE guidance <sup>6</sup>. Symptoms such as muscle-joint pain, weakness, and fever that continue in the Long Covid period are not specific. In some studies, similar symptoms can be seen in the underlying autoimmune disease, chronic fatigue syndrome, and post-chikungunya syndrome, a seronegative disease that progresses with an insufficient inflammatory response in endemic areas <sup>5</sup>. Patients with brucellosis generally present to the hospital with symptoms such as fever, shivering, fatigue, and diffuse muscle joint and back pain <sup>7</sup>. Because brucellosis symptoms are similar to Long Covid symptoms, it may be confused and even the diagnosis of brucellosis may be missed. Since there is no study on brucellosis, we aimed to present the patients who were diagnosed with brucella after presenting with Long Covid symptoms in areas where brucella is endemic.

## 2. Material and Methods

This retrospective study was performed in Adiyaman University Faculty of Medicine Infectious Diseases Clinic. In this retrospective study, 86 patients with Covid-19 PCR (+) between 01.04.2020 and 01.05.2021 were retrospectively analyzed. Brucella agg. test 1/160 and, brucella coombs agg. patients with (+) (n=13) were included. Although the pain continues, brucella Agg. test 1/160 and brucella coombs agg. Patients with (-) (n=73) were excluded.

Inclusion criteria for the study; history of Covid-19 infection, Covid-19 PCR positivity, over 18 years of age, and symptoms of muscle-joint pain and weakness. Exclusion criteria of patients; Covid-19 PCR negativity at the time of symptoms, being under the age of 18, patients with ongoing Covid-19 treatment and lung involvement, and patients with no regression in Covid-19 symptoms.

Brucella diagnosis was made by serology in the presence of accompanying symptoms. Titers of  $\geq 1/160$  were considered positive in the anti-human globulin (Coombs) test. Age, gender, history of Covid-19 disease, duration of symptoms, and serology results of the patients were recorded.

### 2.1. Statistical Analysis

Data were analyzed on Statistical Package for Social Sciences Statistical Software, version 21.0 (SPSS Inc). Descriptive statistics were produced. Data were expressed as numbers (percentage) and median (minimum-maximum).

## 3. Results

Brucella was diagnosed in 13 of 86 patients who had ongoing muscle-joint pain, weakness, fatigue, fever, sweating, and headache complaints during the Long covid period. Five (38 %) patients in the study were male (31 to 69, median age 55 years), and eight (62 %) were female (40 to 57, median age 43.5). Muscular-joint pain (62 %), malaise (62 %), fatigue (30 %), and sweating (15 %) were common symptoms. The duration of onset of symptoms in the Long Covid period ranged from 41 days to 220 days.

The onset of symptoms ranges from 41 days to 220 days, with a mean duration of 119 days. The positivity in brucella agg./brucella coombs agg. test ranged from 1/160 to 1/5120. The symptoms and characteristics of the patients included in the study are shown in Table 1. Since the study is retrospective, the study was conducted by considering the laboratory results registered in the system. There are cases of acute and chronic brucellosis among the patients.

**Table 1:** Patients' symptoms and other characteristics.

Case	Sex	Age	Symptoms	Brucella Agg.	Time Elapsed
1	Female	40	Low Back Pain, Malaise, Fatigue	1/160	92 Days
2	Female	51	Night Sweats, Malaise	1/320	78 Days
3	Female	43	Muscle-Joint Pain	1/320	120 Days
4	Female	54	Malaise, Total Body Pain	1/160	88 Days
5	Male	49	Muscle-Joint Pain	1/5120	183 Days
6	Male	64	Muscle-Joint Pain, Malaise	1/320	136 Days
7	Female	43	Respiratory Difficulty, Fatigue	1/640	106 Days
8	Female	57	Muscle-Joint Pain, Malaise	1/640	94 Days
9	Male	69	Malaise, Headache, Vertigo	1/160	41 Days
10	Male	55	Muscle-Joint Pain, Fatigue	1/640	104 Days
11	Male	31	Muscle-Joint Pain, Malaise	1/160	180 Days
12	Female	42	Muscle-Joint Pain, Fatigue	1/2560	105 Days
13	Female	44	Muscle-Joint Pain, Malaise, Sweating	1/640	220 Days

#### 4. Discussion

Brucellosis was diagnosed in 13 cases with a history of Covid-19 disease, who applied to the hospital with muscle-joint pain, weakness, and fatigue during the Long Covid-19 period. In these cases, brucella agg./brucella coombs agg. tests were positive, varying over 1/160. The patients were diagnosed with brucellosis and treatment was started. We are currently facing an unprecedented epidemic. Uncertainties about the disease continue after (Long Covid).

This means that every detail about the disease needs to be evaluated in detail to remove uncertainties. Available evidence and WHO reports indicate that pain is a common symptom during SARS-CoV-2 infection. Muscle pain, joint pain, sore throat, and headache are the pain-related symptoms seen in Covid-19<sup>9</sup>.

In some cohort studies, muscle pain, arthralgia, and fatigue have been reported in Covid-19 patients<sup>9, 10, 11</sup>. Symptoms of Covid-19 disease may persist even if the disease resolves, and the PCR is negative. Most of the symptoms in the Long Covid period show features similar to those that developed in the acute phase of Covid-19<sup>12</sup>. These symptoms are usually fever, cough, shortness of breath, headache, muscle-joint pain, and fatigue. One or more of these symptoms continue to be seen during the Long Covid period<sup>4, 13</sup>.

Brucellosis is a ubiquitous zoonotic disease widely seen in the Mediterranean region, the Indian subcontinent, the Middle East, Africa, Central America, and Central Asia. The most frequent symptoms of brucellosis are muscle-joint pain, fatigue, back pain, and shivering<sup>14</sup>.

Another study showed that 80% of individuals with a confirmed diagnosis of Covid-19 continued to have at least one symptom two weeks after acute infection. Fatigue is the most common of these symptoms in acute Covid-19 and Long Covid periods. Some symptoms may persist even 100 days after the first acute Covid-19 symptom<sup>15</sup>. Brucella spondylodiscitis is a disease with cardiac involvement and cranial involvement<sup>16</sup>. Long covid symptoms in endemic areas should not delay the diagnosis in patients with brucellosis. Times to presentation to hospital in the Long Covid period among the 13 cases in the present study ranged between 41 days and 220 days. We attribute the prolonged time to diagnosis of brucellosis in these patients to the symptoms seen in these patients being ascribed to Long Covid symptoms.

Symptoms seen during the Long Covid period may resemble those of various other diseases. Although clinical examination results and patient symptoms vary, chronic fatigue syndrome is one of the most frequently seen conditions in the Long Covid-19 period. Chronic fatigue syndrome is compatible with dysautonomia<sup>17</sup>. Covid-19 also plays a probable triggering role in the immune system, as in Guillain-Barre syndrome and other autoimmune diseases. A possible underlying autoimmune disease should therefore also be considered in the differential diagnosis of young women presenting with muscle-joint pain in the Long

Covid period<sup>12</sup>. In addition, studies have suggested that post-chikungunya syndrome, a seronegative disease progressing with insufficient inflammatory response, should also be considered in the differential diagnosis of patients presenting with high fever, headache myalgia, and diffuse joint pain in the Long Covid period<sup>5, 13</sup>.

In this study, A diagnosis of brucellosis was made in 13 patients whose complaints continued after the treatment of Covid-19 and who applied to the hospital. In these cases, brucella agg./brucella coombs agg. tests were found to be 1/160 and above positivity. The patients were diagnosed with brucellosis and treatment was started.

#### 5. Conclusions

Brucellosis is a condition that can lead to more serious complications if its diagnosis is delayed. For this reason, in Long Covid cases, especially in brucella endemic regions, cases with symptoms that may overlap with the brucellosis clinic should be evaluated in terms of brucellosis. This approach will be useful in preventing more serious complications that may develop later.

#### Limitations of the Study

It is our limitation that it is a retrospective study, and the number of cases is low. Among the other limitations of my study, it could not be distinguished clinically and laboratory, that all the cases may not have been admitted to the hospital, that their covid history may have increased the susceptibility to immune suppression and therefore to brucellosis-like infective conditions. The fact that they were not evaluated for other pain syndromes and that only patients from one clinic were included may have caused possible population bias. Considering these situations, we think that more comprehensive similar studies will make a great contribution to the literature.

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#### Conflict of Interests

The authors accept their responsibilities in the study. There is no conflict of interest between the authors.

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#### Author Contributions

SA and HSS designed the study; SA and HSS collected the data; SA ve HSS analyzed the data; SA wrote the first draft of the manuscript. All authors contributed to the study's conception and design. All authors read and approved the final manuscript.

#### Ethical Approval

This study was approved by the ethics committee of Adiyaman University (No. 2021/03-20).

#### Data sharing statement

All data relevant to the study are included in the article.

#### Consent to participate

Written informed consent was obtained from every patient at the time of the operation.

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