



ORIGINAL ARTICLE

Medicine Science 2023;12(1):238-43

## Miscellaneous neuromuscular symptoms and signs in long Covid

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Received 08 December 2022; Accepted 16 February 2023

Available online 24.02.2023 with doi: 10.5455/medscience.2022.12.259

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### Abstract

We have completed the 3rd year of the Covid-19 pandemic. In the early stages of the disease, we were faced with a wide variety of symptoms and signs, including the neuromuscular system, as well as life-threatening cardiopulmonary, neurovascular and immun complications. In our study, we questioned fatigue, myalgia, arthralgia, dyspnea, headache, dizziness, neck pain, back pain, low back pain, knee-hip-foot joint pain, vascular claudication (lower extremity pain/cramp), neuropathic pain, morning stiffness, joint swelling, pernio, imbalance in walking in patients (N=111; 65 female, 29 male) aged 20-59 years, who applied to our outpatient clinic in the last 1 year and had Covid-19. The mean time after Covid-19 was  $5.8 \pm 2.1$  months. The duration of Covid-19 treatment was a minimum of 5 days and a maximum of 12 days (median=5 days). Weight loss in 14.4% (median=3.5 kg), anorexia 17.1%, myalgia 41.4% (visual analog scale, VAS=5.1±1.9 cm), arthralgia 24.3% (VAS=5.1±2 cm), fatigue 63.1%, joint swelling 1.8%, pernio sign 0.9%, morning stiffness 7.2% (median=15 min, min 5-maximum 60 min), headache 39.6%, neuropathic pain 15.3%, effort dyspnea 38.7%, 30 second chair stand test=  $14.9 \pm 3.6$ , vascular claudication symptom 11.7%, neck pain 27.0%, low back pain 30.6%, back pain 36%, hip-knee-foot pain 18.0%, gait imbalance 1.8%, dizziness 18.9% were observed. While fatigue ( $p=0.05$ ), headache ( $p=0.04$ ), and dyspnea ( $p=0.021$ ) complaints were higher in males; VAS (arthralgia) was found higher in females ( $p=0.026$ ). In the post-Covid-19 period, we see many neuromuscular symptoms and signs, especially fatigue, myalgia, headache and back pain. In addition, lower extremity vascular claudication and neuropathic pain related with chronic pain should not be overlooked in these patients.

**Keywords:** Covid-19, neuromuscular symptoms, neuropathic pain, long covid

### Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China, and spread rapidly around the world [1]. Covid-19 is an RNA virus that has a viral structural spike (S) protein that binds to the angiotensin converting enzyme 2 (ACE2) receptor in human cells. The ACE2 receptor is found in high levels in the lung epithelium, heart, kidney, pancreas, spleen, gastrointestinal tract, bladder, cornea and blood vessels, as well as in the central and peripheral nervous systems and skeletal muscle. Viral replication in human cells is

followed by viral release through cell destruction. In addition, Covid-19 activates an inflammatory response that can cause a cytokine storm and consequent multi-organ damage [2].

Covid-19 can manifest in different ways, from asymptomatic clinical to mild upper respiratory tract disease symptoms to acute respiratory distress syndrome (ARDS). It is known to cause numerous extrapulmonary findings including gastrointestinal findings, liver, kidney, heart damage and acute coronary syndromes, neurological complications and skin findings. Although myalgia is common in Covid-19 infection, other

### CITATION

Koca TT, Erzurumluoglu O, Kocyigit BF. Miscellaneous neuromuscular symptoms and signs in long Covid. Med Science. 2023;12(1):238-43.



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musculoskeletal symptoms have rarely been identified early. As the number of Covid-19 patients and recoveries increases, increasing musculoskeletal complaints, neurological and rheumatic complications related to both the disease process and the post-treatment period have been reported [3,4].

Inflammation causes flu-like manifestations of the disease. When viral replication occurs, IL-6 and TNF-alpha levels increase in the blood. During viral reproduction, symptoms such as fever, weakness, cough, myalgia occur. Myalgia and fatigue, one of the most common symptoms at the beginning of the disease, occur as a result of IL-6 upregulation. Studies on myalgia in Covid-19 infection support that the symptom of myalgia is dependent on the general inflammation and cytokine response in the disease [5,6].

It is characterized by severe ischemic myalgia accompanied by physical fatigue and muscle weakness in patients in the acute period [7]. However, current data on miscellaneous symptoms and signs such as myalgia, arthralgia, fatigue, joint swelling, imbalance in walking, spinal pain, headache, pernio, neuropathic pain, dizziness etc...seen in the neuromuscular system in the long term period after Covid-19 are insufficient.

In about 10% of patients who recover after Covid-19, the symptoms may persist for a long time. Covid-19 infection negatively affects the quality of life and daily life of the person by causing many symptoms and signs in the neuromuscular system with multiple pathophysiological mechanisms (endothelial dysfunction, immune reaction, mitochondrial dysfunction, ischemia etc...) in the long term. While focusing on respiratory and cardiac problems after Covid-19, neuromuscular symptoms and signs are ignored. These symptoms and signs are also frequently seen after Covid-19 and reduce the quality of life of people. In our study, these symptoms and signs and related factors were comprehensively reported in the view of the current literature.

## Material and Methods

### Study design and sample

Our study was designed as cross-sectional analytical. Patients who applied to the Physical Medicine and Rehabilitation outpatient clinic and had Covid in the last 1 year (with a history of Covid-19 PCR positivity) were included in the study. Those with concomitant chronic rheumatic disease, orthopedic disorder, history of trauma, systemic disease, infection, and malignancy were excluded from the study.

### Data collection

Data were recorded by the same experienced clinician through physical examination and a simple questionnaire. Demographic data (age, gender) of the patients were recorded. In the questionnaire, duration after covid (months), the duration of treatment with covid (days), the presence of weight loss, the amount of weight loss (kg), anorexia, myalgia and visual analog

scale (VAS) (0- 10 cm), arthralgia and VAS (0-10 cm), fatigue, joint swelling, pernio (chillblain) findings in fingers and toes (bruising, pain, discoloration), morning stiffness and its duration (minutes), headache, neuropathic pain (assessed with PAIN DETECT), effort dyspnea, 30-second sit and stand test, vascular claudication findings such as leg cramps and pain, neck pain, low back pain, back pain, hip-knee-foot pain, gait imbalance, and dizziness were questioned.

### Visual analog scale (VAS)

It is a scale used to digitize some values that cannot be measured numerically. Numbers 0-10 are written on a horizontal or vertical 100 mm long line. For the value to be measured, the person is asked to mark the point he feels and thinks. For example, for pain, a value of 0 means 'no pain' and a value of 10 means 'unbearable pain'.

### Chair stand test

For this test performed to determine leg strengths; A straight-back chair with a seat height of 43.18cm (12-in) without armrests and a Casio HS-5 M stopwatch were used. The individual was allowed to sit in the middle of the chair with his back straight, feet on the ground and arms crossed in front of his chest (right hand on left shoulder, left hand on right shoulder). While the individual was in this position, he started the test with the start command and took off as fully as he could during 30 seconds. The number of full take-offs made during 30 seconds formed the score of the subject. Each subject was both shown and explained how to do the test, and the test was started after making sure that each subject had 2-3 attempts to do the test [8].

### Pain detect

The PainDETECT questionnaire was first developed to detect the neuropathic component of pain in patients with low back pain. Patients with a total questionnaire score of 12 or less are considered to have no neuropathic pain component. If the total score is in the range of 13-18, the result is uncertain, but it is accepted that neuropathic component may be present, that is, possible neuropathic pain [9]. The Turkish validity and reliability study of the questionnaire was done by Alkan et al. [10].

### Statistical Analysis

Statistical evaluation will be done with the Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA) program. Concerning categorical data, frequencies and percentages were applied to distinguish these values. Differences between groups were contrasted using the Chi-squared test. Numerical data will be given as ratio, mean±standart deviation (std), median (minimum/maximum). With the Kolmogorov Smirnov test and histogram analysis, it will be checked whether the data is normally distributed. According to the analysis result, appropriate parametric or nonparametric tests is used. Statistical significance level was accepted as  $p < 0.05$ . As a result of the power analysis, type 1 error was accepted as 0.05 and the power

of the test was 0.80, and the minimum sample size was calculated as 86 patients.

### Ethics

In our study, approval was obtained from the Ministry of Health and Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Clinical Research Ethics Committee (date: 08.03.2021; protocol number: 87). The study is in compliance with Helsinki Declaration principles. A voluntary consent form was obtained from the participants.

### Results

Our study included 65 women (58.6%) and 46 men (41.4%), with a mean age of 37.3±11.3 years (20-59 years), with a total of

N=111 patients who had covid-19 in the last 1 year. The duration after Covid-19 was 5.8 ± 2.1 months. The duration of Covid-19 treatment was a minimum of 5 days and a maximum of 12 days (median=5 days). There was weight loss in 14.4% of the patients, with a median weight loss of 3.5 kg (2-10 kg). The prevalence of anorexia 17.1%, myalgia 41.4% (VAS=5.1±1.9 cm), arthralgia 24.3% (VAS=5.1±2 cm), fatigue 63.1%, joint swelling 1.8%, pernio sign 0.9%, morning stiffness 7.2% with median=15 minutes (min 5-maximum 60 minutes), headache 39.6%, neuropathic pain 15.3%, effort dyspnea 38.7%, 30 seconds sit and stand test= 14.9±3.6, vascular claudication symptom 11.7%, neck pain 27.0%, low back pain 30.6%, back pain 36%, hip-knee-foot pain 18.0%, gait imbalance 1.8%, and dizziness 18.9%. Descriptive data of the study are summarized in Table 1.

**Table 1.** Analysis of sociodemographic and descriptive data of the study

	Mean±std	Median	N/%	Minimum-maximum
Age (year)	37.3±11.3	-	111	-
Gender(female/male)			65/58.6 46/41.4	
Duration after covid-19 (months)	5.8 ±2.1	-	111	1-12
Duration of Covid-19 treatment (days)	-	5	111	5-12
Weight loss	-	-	16/14.4	
The amount of Weight (kg)	-	3.5	-	2-10
Anorexia			19/17.1	
Myalgia			46/41.4	
Myalgia VAS (0-10 cm)	5.1±1.9	-	-	-
Arthralgia			27/24.3	
Arthralgia VAS (0-10 cm)	5.1±2			
Fatigue	-	-	70/63.1	
Joint swelling	-	-	2/1.8	
Pernio	-	-	1/0.9	
Morning stiffness	-	-	8/7.2	
Duration of morning stiffness (minutes)	-	15	-	5-60
Headache			44/39.6	
Neuropathic pain			17/15.3	
Effort dyspnea			43/38.7	
30-second chair stand test	14.9±3.6	-		
Vascular claudication	-	-	13/11.7	
Neck pain	-	-	30/27	
Low back pain	-	-	34/30.6	
Back pain	-	-	40/36	
Hip-knee-foot pain	-	-	20/18	
Walking imbalance	-	-	2/1.8	
Dizziness	-	-	21/18.9	

When we analyzed the whole group in terms of gender, the complaints of fatigue ( $p=0.05$ ), headache ( $p=0.04$ ), and effort dyspnea ( $p=0.021$ ) were higher in males; VAS, arthralgia was higher in females ( $p=0.026$ ) (Table 2). Other parameters were in similar distribution.

**Table 2.** The Comparison of the parameters according to gender (Only statistically significant parameters are indicated in the table)

	P
<b>Fatigue</b>	0.05*
<b>Headache</b>	0.04*
<b>Effort dyspnea</b>	0.021*
<b>VAS (arthralgia)</b>	0.026*

\*Mann Whitney U test.  $p<0.05$ , statistically difference

## Discussion

Coronavirus is a life-threatening virus that can infect humans and some animals, ranging from the common cold to serious respiratory problems in humans. Covid-19 is a virus with a high mutation ability, and the continuation of some symptoms after the disease or the emergence of other new findings in individuals who have had the disease negatively affect people both psychologically and physically. It has been observed that some symptoms persist for a while in individuals who survived the disease. While there is still no clear treatment method for acute infection, it is an important health problem to manage the symptoms and long-term complications of the disease in the post-covid-19 period of patients.

We frequently see neuromuscular symptoms and signs in the post covid period especially fatigue, myalgia, headache and back pain (in order of high frequency). Additionally neuropathic pain and vascular claudication symptoms associated with chronic pain are seen in patients in long term follow up. We think that the development of neuropathic pain is related with chronic pain; the development of vascular claudication is related to the thrombosis effect of the virus.

We also find differences in terms of gender. The complaints of fatigue, headache, and effort dyspnea were higher in males; VAS, arthralgia was higher in females. Differences in chronic pain in females vs. males are well known, and a lot of laboratory tests have demonstrated that females are more sensitive to pain than males.

When we analyzed the participants in terms of gender in our study, it was found that the complaints of fatigue, headache, dyspnea were higher in the male gender. On the other hand, arthralgia and VAS scores were higher in females. When the literature research, it was reported that post-covid fatigue and shortness of breath were more common in females [11]. In another study conducted with 1027 participants, it was found that myalgia and fatigue were more common in females [12]. In a study conducted in a tertiary hospital, it was reported that

gender did not have any effect on post-covid symptoms [13]. In most of the studies conducted in the post-covid period, it was found that the female gender had more symptoms in the post-covid period than the males [14-16]. We think that the difference between the literature and our study may be due to the difference in the sample and the duration after covid.

41.4% of the participants had myalgia (VAS score  $5.1\pm 1.9$ ), and 24.3% had arthralgia (VAS  $5.1\pm 2$ ). Joob et al. in the study, the frequency of arthralgia was found to be over 2.5% [17]. Skyes et al. in the study, it was reported that 51.5% of the participants had post-covid myalgia [18]. In another study, myalgia was found to be between 4.5% - 36% and arthralgia was in the range of 6.0-27% [19]. Our scores were found similar to the literature.

In our study, the 3 most common musculoskeletal symptoms were fatigue in 63.1%, myalgia in 41.4% and back pain in 36%, respectively. In studies in the literature, the incidence of post-covid symptoms varies [20-26]. We think that this is due to the fact that our study consisted of not only inpatients, but also groups of patients who were hospitalized, received outpatient treatment and completed their home quarantine without any treatment, in other words, all patients with severe and mild disease.

Among the extrapulmonary symptoms associated with Covid-19, dermatological symptoms are increasingly being reported [27]. Pernio or chilblain, characterized by an acral pattern, is a localized inflammatory disease resulting from an abnormal response to cold [28]. It is characterized by a poor prognosis and is reported as an isolated cutaneous manifestation of hypercoagulable states [29]. It is thought that Covid-19 may also cause pernio by immune mechanisms as it is characterized by perivascular lymphocyte infiltration in histopathological examinations [30]. When we look at the literature, studies on pernio after covid are mostly case reports. Painful skin lesions on the hands and feet in the long term after Covid-19 should be evaluated in terms of pernio. Vascular claudication is characterized by aching pain, numbness, weakness, or fatigue in the lower extremity muscle groups. The frequency of vascular claudication in our patients was 11.7%. Vascular claudication symptoms in the lower extremities may have been caused by immobilization, lack of physical activity, and the virus itself (intramuscular microthrombosis, entodel damage, ischemia). Few publications related to Covid-19-related vascular claudication were observed in the literature [31]. The sit and stand test is a test that evaluates lower extremity muscle strength and dynamic balance. In our study, the average number of 30-second sit and stand test was  $14.9\pm 3.6$ .

A very common symptom of Covid-19 is pain. Since Covid-19 can often affect the peripheral or central nervous system, a number of chronic pain complications of Covid-19 are predicted to be neuropathic. A few publications were found in the literature on the relationship between Covid-19 and neuropathic pain [32,33]. Neuropathic pain refers to pain caused by nervous system pathology. Neuropathic pain reflects both peripheral and



central sensitization mechanisms. Abnormal signals originate not only from damaged axons, but also from intact nociceptors that share the innervation region of the damaged nerve [34]. We now know that chronic pain may develop due to primary damage to the central or peripheral nervous system, and that chronic pain causes neuropathic pain through sensitization [35,36]. We think that the neuropathic pain in Covid-19 patients may develop over time due to the neuroinvasiveness of the virus or other painful conditions (arthralgia, myalgia, back pain etc...) by sensitization.

The vascular endothelium provides a crucial interface between the blood compartment and tissues and is responsible for maintaining normal homeostasis. Our view of Covid-19 from the lens of endothelial disease helps us to explain the pathophysiology of a wide variety of symptoms of the disease [37]. We now know that Covid-19 causes immune response and life-threatening conditions as a result of microthrombosis and endothelial dysfunction in many vital organs. This immune reaction can trigger autoimmune diseases in the long run. In a small number of case reports, it was observed in the literature that arthritis and polyarthritis could develop in the acute / subacute period due to Covid-19 [38,39]. In our study, we detected joint swelling in 2 patients.

The limitations of the study are the patients consist of the patients who attend to Physical Medicine and Rehabilitation clinic with a complain, secondly there is no control group. Also small sample size is another limitation.

#### Conflict of interests

*The authors declare that there is no conflict of interest in the study.*

#### Financial Disclosure

*The authors declare that they have received no financial support for the study.*

#### Ethical approval

*In our study, approval was obtained from the Ministry of Health and Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Clinical Research Ethics Committee (date: 08.03.2021; protocol number: 87).*

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