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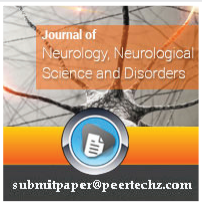

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Research Article

Evaluation of neuromuscular junction functions with single fiber electromyography in individuals with persistent fatigue after Coronavirus disease 2019

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Keywords: Coronavirus disease 2019; Post COVID syndrome; Post viral fatigue syndrome; Single fiber electromyography; Jitter; Neuromuscular duysfunction

Abstract

Purpose: Post COVID Syndrome (PCS) is one of the most intriguing topics related to coronavirus disease 2019 (COVID-19). Fatigue is one of the most prevalent and disabling symptoms of PCS. In this study, we aimed to investigate the neuromuscular junction functions in people who have had long-term fatigue due to COVID-19 and to investigate whether the neuromuscular junction is the cause of fatigue.

Methods: 37 patients who had COVID-19 at least 12 weeks ago and continued to complain of fatigue and 37 healthy individuals were included in the study. The Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS) questionnaires were applied to people with fatigue. Single Fiber Electromyography (SFEMG) was applied to all individuals and the obtained data were compared between the two groups.

Results: 70.3% of the patients with Post Viral Fatigue Syndrome (PVFS) had increased fatigue severity. 45.9% of the patients experienced mild fatigue, 35.1% of them experienced moderate fatigue, 13.5% experienced significant fatigue and 5.4% of them had severe fatigue according to FIS. The number of fibers with pathologically increased jitter and the mean jitter values of patients with PVFS were significantly higher than those of healthy individuals. 59.4% of patients with PVFS had moderate motor end plate dysfunction on SFEMG and 13.6% had apparent motor end plate dysfunction.

Conclusion: Patients with PVFS caused by COVID-19 have neuromuscular junction dysfunction. It is unclear why these individuals are affected, but abnormal immune responses can lead to this dysfunction.

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Abbreviations

PCS: Post COVID Syndrome; COVID-19: Coronavirus Disease 2019; FSS: The Fatigue Severity Scale; FIS: Fatigue Impact Scale; SFEMG: Single Fiber Electromyography; PVFS: Post Viral Fatigue Syndrome; EMG: Electromyography; MCD: Mean Consecutive Difference; BBB: Blood-Brain Barrier; CRS: Cytokine Release Syndrome; CNS: Central Nervous System

Introduction

The world has been unpleasantly surprised by the unforeseen pandemic of coronavirus disease 2019 (COVID-19) since 2019. Compared to the seasonal flu, COVID-19 is more contagious, more deadly, has a longer incubation period, and is associated with prolonged hospital stays [1,2]. However, unlike other infections, the disease commonly often affects individuals who have the disease after the acute phase. Most patients with COVID-19 achieve a full recovery, however many patients experience a recurrence of some symptoms of the infection or the development of new symptoms after the infection has cleared up, a condition known as Post-COVID Syndrome (PCS). Although there is an increasing amount of knowledge in the literature related to the acute phase of COVID-19, PCS is the main attraction of the disease, and persistent symptoms that develop following the acute phase of the disease also need to be clarified [3].

The frequency of individuals experiencing fatigue as a symptom in PCS is quite high at 53%, and this condition is called Post-Viral Fatigue Syndrome (PVFS). "Peripheral fatigue" is attributed to the progressive failure of peripheral nervous system function, while "Central fatigue" is the progressive decrease in the ability of the central nervous system to activate the muscles at the maximum level and depends on spinal and supraspinal mechanisms [4]. To date, studies investigating fatigue in patients with SARS-CoV-2-related neurological symptoms recovering from COVID-19 have not clarified whether the fatigue is central or peripheral origin. In this study, we aim to provide a comprehensive clinical, neurophysiological profile of patients with PVFS recovering from the acute phase of COVID-19 to reveal the features of neurotransmission at the neuromuscular junction and to show whether the dysfunction of neuromuscular transmission is the cause of persistent fatigue in these patients.

Materials and methods

37 patients who presented with a complaint of fatigue between 01 June 2021 and 31 August 2021 and had confirmed COVID-19 at least 12 weeks prior to admission and at least had fatigue 12 weeks after the improvement of acute infection symptoms, and 37 healthy individuals had no complaints or any diseases including COVID-19 in the last 6 months were included in the study. The study was approved by the Ankara City Hospital Ethics Committee No.1. Informed consent was obtained from all individuals participating in the study. Detailed medical evaluations of the patients were made in the neurology outpatient clinic. None of the individuals participating in the study had a known chronic or neurological disease and chronic drug use.

The Fatigue Severity Scale (FSS) was used to evaluate the effects of fatigue on daily living activities in individuals with fatigue complaints, and the Fatigue Impact Scale (FIS) was used to measure the physical, social, and cognitive effects of fatigue.

The Fatigue Severity Scale (FSS) was developed by Krupp, et al. [5] in 1989. The Turkish validity and reliability of the scale were performed by Armutlu, et al. [6] in 2007. In the scale, which consists of nine items that patients can apply on their own, each item is scored between 1 and 7. The cut-off value for pathological fatigue was determined as 4 and above. Fatigue is decreased with decreasing total scores [6].

The Fatigue Impact Scale (FIS) consists of forty questions and evaluates the effects of fatigue on life. High scores indicate the occurrence of problems caused by fatigue in terms of cognitive, physical, and psychosocial aspects [7,8]. Nerve conduction study and needle electromyography (EMG) were performed within the procedure described below to exclude possible neurogenic and myogenic involvement in all individuals included in the study. A single fiber EMG (SFEMG) test was applied to the patients whose classical nerve conduction study and needle EMG were normal, in order to evaluate neuromuscular transmission based on the following criteria. We did not perform repetitive nerve stimulation on the patients because single-fiber EMG is a much more sensitive test than repetitive EMG.

Electrophysiological study

Electrophysiological studies were performed using a Dantec-Keypoint EMG device. Firstly nerve conduction studies were applied to all individuals. Needle EMG examination was performed in patients whose nerve conduction studies were within normal limits. Concentric needles were used in the needle EMG study. A band-pass filter range of 10 Hz - 10000 Hz was used. The sweep rate was 10 ms/cm at rest and light muscle, and 100 ms/cm in full muscle; sensitivity was used at 100 µV/cm at rest, at 200 µV/cm-1 mV/cm in mild muscle, and 1 mV/cm in full muscle. A needle EMG examination was performed in at least one distal and one proximal muscle, including at least one lower and upper extremity, and an SFEMG study was applied to patients with normal needle EMG results. The upper-frequency filter was 10 kHz for SFEMG recording; the lower-frequency filter was set to 500 Hz. At least 100 traces were recorded for each jitter analysis. Ten different single-fiber potential pairs were recorded from each individual. Ten individual jitter values were calculated for each individual. The mean sequential difference value (Mean Consecutive Difference - MCD) was used as the "jitter". Jitter values of 55 microseconds and above were considered abnormal, and those below were considered normal. Motor endplate functions were interpreted according to the number of fibers with increased jitter recorded from individuals. Accordingly, motor endplate functions were considered normal when all of the recorded jitter values were normal or 1 of them was above 55 microseconds. Patients with 2 out of 10 jitter values were considered to have borderline impairment in motor endplate functions, and patients with 3 or more elevations were considered to have

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impaired motor endplate function, and analysis was performed accordingly. The IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Program was used for statistical analysis and calculations. The statistical significance level was set as $p < 0.05$.

Results

While the mean age of the individuals in the study with PVFS was 48.4 ± 12.6, the mean age of the healthy individuals was 46.3 ± 12.6. 70% of both individuals with PVFS and healthy individuals were female and 30% were male. There was no difference between the groups in terms of age and gender. The mean time between SARSCoV-2 polymerase chain test positivity and electrophysiological test time of individuals with PVFS was 6.8 ± 3.0 months. While only one of the 37 patients with PVFS required intensive care follow-up during the active infection period, intensive care follow-up was not required in the remaining 36 patients. The mean values of the FSS scores of individuals with PVFS were 39.2 ± 18.5. Accordingly, 70.3% of the patients with PVFS had increased fatigue severity, while 29.7% of them exhibited no fatigue. The mean FIS scores of individuals with PVFS were 76.6 ± 24.7. According to the FIS, there were no patients with the level of feeling the effect of fatigue as 'none', while 45.9% of the patients felt the effect of fatigue mildly, 35.1% of them moderately, 13.5% of them significantly, and 5.4% of them very important.

The mean and standard deviation values of the number of fibers with pathological jitter increase and the jitter values of the individuals included in the study are shown in Table 1. The number of fibers with pathologically increased jitter and the mean jitter values of patients with PVFS were significantly higher than those of healthy individuals (p= 0.009, p=0.001, respectively). In addition, 27% of patients with PVFS exhibited normal SFEMG findings, 59.4% had moderate motor end plate dysfunction on SFEMG, and 13.6% had apparent motor end plate dysfunction. The SFEMG of all healthy individuals was within normal limits and there was no pathological increase in jitter in any of the examined muscle fibers of healthy individuals.

When the individuals in the patient group were examined, no significant relationship was found between the fiber number with pathologically increased jitter and MCD values, and the FSS and FIS scores.

Discussion

In this study, we discovered that patients with PVFS had a greater mean fiber number with pathologically increased jitter and higher MCD values than healthy individuals. In addition, we detected moderate motor end plate dysfunction in 59.4% of patients with PVFS and apparent motor end plate dysfunction in 13.6% of them in SFEMG. MCD is the average of the absolute differences of the times between two single fiber potentials of the same motor unit (stimulus artifact and one single fiber potential in evoked SFEMG) from one discharge to the other during sequential motor unit firing. Therefore, MCD reflects motor endplate functions. Our findings show that individuals with PVFS as a result of COVID-19 have motor end plate dysfunction. SFEMG is especially used as a diagnostic tool in Myasthenia Graves (MG) and has a very high sensitivity in detecting neuromuscular junction pathologies.

In patients with MG, the most prominent symptom is fatigue, and when SFEMG is applied to the symptomatic muscle in MG, it is almost impossible to be normal in the symptomatic muscle since in MG, postsynaptic acetylcholine receptors are blocked with antibodies, as a result of the ongoing immune reaction, the number of functional receptors is decreased, the crystals become shallow and the synaptic gap widens, and therefore neuromuscular junction functions are impaired, and SFEMG is extremely sensitive in measuring neuromuscular junction functions [9]. In our study, we chose the frontal muscle, which is one of the muscles with less prominent synaptic folds, less postsynaptic AChR, and smaller motor unit potentials exposed to high firing frequencies, in order to more clearly reveal neuromuscular junction functions.

Studies have claimed that SARS-CoV-2 infection disrupts the Blood-Brain Barrier (BBB), induces endothelial cell activation, and increases the number of activated myeloid cells in the brain parenchyma. It has also been reported that systemic cytokine imbalances can initiate BBB deterioration. Additionally, studies have shown that dysregulation of innate immune responses during COVID-19 leads to Cytokine Release Syndrome (CRS) characterized by an excessive elevation of proinflammatory cytokines. All of these events have been demonstrated to be the cause of neuroinflammation and neurological involvement during and after COVID-19 infection. However, it is still unclear how these events are related and whether neuroinflammation-induced neurological changes occurring after SARS-CoV-2 infection are related to CNS immune activation or direct neuroinvasion [10].

The neuromuscular junction dysfunction we found may also be due to an abnormal immune response due to COVID-19. Likewise, there are many publications reporting medulla spinalis, peripheral nerve, and muscle involvement due to COVID-19 because of direct virus invasion, molecular mimicry, and para and post-infectious immune mechanisms [11]. It also revealed that MG occurred in patients who had COVID-19 in a few cases [12].

Therefore, the neuromuscular junction may be one of the impacts on the nervous system as a result of neuroinflammation and excessive and disfunctioning immune system in the postcovid period, and this involvement may cause permanent fatigue in these patients. From a different point of view, many factors such as appropriate pH, free ion

Table 1: Comparison of fiber number and MCD values with pathologically increased jitter in patients with PVFS and healthy individuals.

Variables	Patient with PVFS Mean ± SS	Control Mean ± SS	Test Statistic
Number of fibers with pathologically increased jitter	0.72 ± 1.14	0 ± 0	0.001
MCD	30.72 ± 7.74	26.37 ± 4.35	26.37 ± 4.35

MCD: Mean Consecutive Differences; PVFS: Post Viral Fatigue Syndrome

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levels, and protein structure are required for a healthy junction function. Abnormal systemic inflammatory reaction may affect all of these necessary factors and impair function in the neuromuscular junction [13]. There is no previous research on this subject in the literature. It should be noted that despite the high sensitivity of SFEMG, it is not a specific test. High jitter values do not help determine whether motor endplate disease is presynaptic, synaptic, or postsynaptic. In addition, increased jitter reflects not only on motor endplate dysfunction, but also abnormal unreliable conduction in immature terminal motor axons, degenerated or immature motor endplate conduction, and threshold ephaptic conduction. The increase in jitter may also be due to blockage of acetylcholine release, axonal sprouting, and new synapse formation.

In other words, this increase in jitter can be detected in SFEMG in cases where axonal loss and reinnervation are observed, such as axonal neuropathy and motor neuron disease [14]. In our investigation, we applied nerve conduction studies and needle EMG with appropriate procedures to exclude peripheral nerve and muscle involvement, which are frequently involved in COVID-19 patients, and included patients without electrophysiological signs of neuropathy and myopathy. Because SFEMG can be abnormal in neuropathic and myopathic diseases as well. Therefore, another mechanism of the increase in jitter we found may be a moderate polyneuropathy or myopathy that was not reflected in the conduction studies and needle EMG in these patients, or the fact that we applied EMG during the healing process of these diseases, that is, during the reinnervation process. If SFEMG was performed during the reinnervation process of polyneuropathy and the motor endplates have not yet matured, we may be detecting an abnormal jitter increase.

We found the mean values of the FSS scores as 39.2 ± 18.5 in individuals who had experienced COVID-19 at least 12 weeks ago, and who presented with the symptoms of fatigue, and 70.3% of the patients had increased fatigue severity. In addition, the mean FIS scores of individuals with PVFS were 76.6 ± 24.7. While there were no patients without the level of feeling the effect of fatigue none, 45.9% of patients felt the effect of mild fatigue, 35.1% felt moderate fatigue, 13.5% significant fatigue, and 5.4% patients felt very significant Fatigue. Our data show that the SARS-CoV-2 infection has a significant effect on both fatigue and exhaustion in accordance with the literature [4]. It is important to measure the objective dimension of fatigue in patients who experience fatigue as PCS. A general decline in quality of life has been observed 1 year after major coronavirus Outbreaks [2].

Fatigue is thought to have had a large impact on this decline, as fatigue has been reported in 28% to 87% of individuals following coronavirus infection. Considering the number of cases around the world, fatigue should be effective and an effective rehabilitation program should be developed for these patients. Seven studies evaluated the association between fatigue and COVID-19 severity [15,16-19]; four found greater fatigue in severely ill individuals [15,16,19] and one study reported greater fatigue or physical decline with increasingly long hospital stays [20]. In our study, only one patient was followed up in the intensive care unit, so no connection between severe illness and fatigue was found. Fatigue has been reported in both severe cases of COVID-19 (requiring hospitalization) and milder cases. In addition, in our study, we found the time elapsed between the active infection period and the EMG test time to be 6.8 ± 3 months. For severe acute respiratory syndrome and Middle East respiratory syndrome, fatigue was reported to be one of the most persistent long-term symptoms, accounting for up to 39 months after initial infection [21]. For COVID-19, several studies have found that fatigue improves from acute illness to follow-up [22-24]. Sun, et al. [25] reported that the median duration of fatigue was 14 days in mild COVID-19 patients and 32 days in patients with severe disease. In our study, the duration of fatigue was quite long. Our study of patients with really long-lasting fatigue may increase the accuracy of our findings.

A limitation of our study was that we only had access to a small number of patients. In addition, the evaluation of neuromuscular junction functions in patients with a history of COVID-19 but do not exhibit fatigue symptoms may be important in interpreting the pathogenesis. Neurological signs and symptoms of PCS are a matter that requires clarification since our knowledge of this subject is still in its infancy. This subject requires extensive study.

Description of authors' contribution

Sadiye Gumusyayla: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Gonul Vural: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – review & editing.

Serdar Baraklı: Conceptualization, Methodology, Resources, Software, Validation, Writing – review & editing.

Rezzan Yıldız: Conceptualization, Data curation, Formal Analysis, Methodology, Validation, Visualization, Writing – review & editing.

Orhan Deniz: Investigation, Methodology, Resources, Software, Supervision, Validation.

Imran Hasanoglu: Conceptualization, Data curation, Resources, Software, Supervision, Validation, Visualization.

Hatice Rahmet Guner: Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Ethical publication statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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