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Evaluation of cognitive status, depression levels and sleep disorders of individuals with fatigue after COVID-19

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Abstract. Objective: Post covid syndrome is one of the most intriguing topics related to Coronavirus disease 2019. Fatigue is one of the most disabling symptoms of Post covid syndrome. In this study, we aimed to investigate cognitive function, depression levels, sleep disorders in persistent fatigue following Coronavirus disease 2019. Materials and Methods: 37 patients who had Coronavirus disease 2019 at least 12 weeks ago and continue to complain of fatigue and 37 healthy individuals were included in the study. The Fatigue Severity Scale and Fatigue Impact Scale questionnaires were administered to people with fatigue. The Montreal Cognitive Assessment scale, Beck Depression Inventory, Pittsburgh Sleep Quality Index, Epwoth Sleepiness Scale, Stanford Sleepiness Scale, Insomnia Severity Index scales were applied to all individuals in the study. Results: 70.3% of the patients with Post covid syndrome had increased fatigue severity. The Montreal Cognitive Assessment scale test scores were found to be significantly lower in individuals with Post covid syndrome. In addition, depression levels and insomnia severity were found to be significantly higher and sleep quality was significantly lower in individuals with Post covid syndrome. Conclusion**:** The treatment and rehabilitation of Post covid syndrome are important in terms of improving quality of life.

Keywords. Fatigue, post-covid syndrome, cognitive impairment, sleep disorder.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the cause of Corona virus Disease 2019 (COVID-19), has spread all over the world at an inconceivable rate and is estimated to have infected over 2.75 billion people if asymptomatic cases are included [1]. Although COVID-19 usually presents with respiratory symptoms in the acute period, its symptoms manifest in many different ways. It is also noteworthy that mainly the virus causes symptoms in the long term. Most patients with COVID-19 achieve a full recovery, however many patients report 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). The generally accepted view for diagnosing PCS is that “Illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within three months from the onset of COVID-19". Fatigue and cognitive impairment have been reported to be some of the most common and debilitating symptoms of PCS [2, 3]. Fatigue due to COVID-19 can be defined as “a decrease in physical and/or mental performance due to changes in central, psychological and/or environmental factors due to COVID-19 disease” [4, 5]. Despite significant efforts to elucidate the pathogenic mechanisms of fatigue, available information is limited. Potentially this is because the cause of fatigue cannot be isolated to a single source. Changes in neurotransmitter levels, inflammation, psychological disorders, stress levels, cognitive dysfunction, and substrate metabolism/availability are some potential contributors to fatigue. In addition, sleep disorders are frequently encountered following COVID-19 [5]. Sleep disorders are another potential cause of fatigue. In this study, we aimed to investigate the severity of fatigue, the effect of fatigue, cognitive status, depression level, sleep quality and sleep disorders in individuals who experience fatigue as a symptom in PCS.

2. Material and methods

37 patients who admitted to the neurology outpatient clinic 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 experienced fatigue at least 12 weeks after the improvement of acute infection symptoms, and 37 healthy individuals who had no complaints or any diseases including COVID-19 in the previous 6 months were included in the study. The study was approved by the Ankara City Hospital Ethics Committee. 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 a history of chronic drug use. The inclusion criteria for this study were: 1) Diagnosis of COVID-19 confirmed by RT-PCR at least three months before the inclusion in the study; 2) being referred for neuropsychological assessment after reporting subjective cognitive complaints; 3) being 18 + years old. Exclusion criteria included: Any cognitive complaint before COVID-19 and was documented medical history of neurological or psychiatric conditions before the infection. The Fatigue Severity Scale (FSS) was used to evaluate the effects of fatigue during daily activities in individuals with fatigue complaints, and the Fatigue Impact Scale (FIS) was used to measure the physical, social and cognitive effects of fatigue. In order to evaluate the cognitive functions of the individuals participating in the study, the Montreal Cognitive Assessment (MoCA) scale and Beck Depression Inventory

(BDI) were employed to evaluate the presence of depression, and the Pittsburgh Sleep Quality Index (PSQI), Epwoth Sleepiness Scale (ESS), Stanford Sleepiness Scale (SSS) and Insomnia Severity Index (ISI) were used to evaluate the sleep disorders and sleep quality. The data obtained were compared between individuals with fatigue due to COVID-19 and healthy individuals. 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 accepted as $p<0.05$.

The Fatigue Severity Scale (FSS)*:* The FSS was developed in 1989 by Krupp et al. [6]. The Turkish validity and reliability of the scale, which questions the fatigue level within the last month, including the day it was filled out, was performed by Armutlu et al. [7] in 2007. In the self-administered scale, which consists of nine items, each item is scored between 1 and 7 (1 = I strongly disagree, 7 = I completely agree) and the total score is calculated by taking the average of nine items. The cut-off value for pathological fatigue was determined as 4 and above. The lower the total score, the less fatigue experienced by the individual.

The Fatigue Impact Scale (FIS): The FIS was developed to assess fatigue symptoms in chronic diseases or various conditions. It consists of forty questions and evaluates the effects of fatigue on life quality. The scale gives four different results: cognitive, physical, psychosocial impact scores and total score. Each question is graded between "0- no problem" and "4-maximum problem". The highest score is 160. High scores indicate the existence of cognitive, physical and psychosocial problems resulting from fatigue [8, 9].

The Montreal Cognitive Assessment (MoCA) Scale*:* The MoCA scale was developed to distinguish healthy individuals from individuals with mild cognitive impairment. It consists of questions that assesses attention and concentration, executive functions, memory, language, visuospatial skills, abstract thinking, calculation and orientation. It can be applied in ten minutes. The total score is calculated out of 30. The threshold value is 21 (20 and below points of cognitive dysfunction). The Turkish validity and reliability study was performed by Selekler et al. [10].

Beck Depression Inventory (BDI): The BDI's efficacy and reliability allow accurate diagnosis by detecting both physical and emotional depression. Based on this scale, a total of 21 titles and four options for each title are created and questions are asked. It is filled out by asking people to give their answers according to themselves, and depression is classified according to the score obtained [11]. According to this scale, 0-9 points are within the range of normal (no signs suggesting depression), 10-18 points are mild, 19-29 points are moderate depression, and 30-63 points denote the probability of severe depression.

The Pittsburgh sleep quality index (PSQI): PSQI was established in 1989 by Buysse et al [12]. The validity and reliability study of the PSQI, which was developed by Agargun et al. [13], was performed in Turkey. PSQI, which evaluates the sleep quality in the last month, includes a total of 24 questions. Of these, 19 are self-report questions and answered by the patient and five questions were answered by a spouse or roommate and used for clinical information only and not included in scoring. The last of the self-declarative questions (question 19) is about the availability of a roommate or spouse and is not used in scoring. The total score has a value between 0-21. A total score higher than 5 indicates poor sleep quality.

Epworth Sleepiness Scale (ESS): **It is a test** used to evaluate daytime sleepiness and indicates the possibility of napping or sleeping in various situations in the past month. It consists of 8 questions in total and each question is filled in by the patient themselves to give 0-3 points. While the highest score is 24, a total score of 10 and above indicates the presence of excessive daytime sleepiness [14].

Stanford Sleepiness Scale (SSS): It is a seven-step subjective test used to determine the level of daytime sleepiness. Daytime sleepiness was graded as "1" for the least severe and "7" for the most severe [15].

Insomnia Severity Index (ISI): This scale, which was developed to determine the degree of insomnia symptoms, can be used in normal population screenings and in the clinical evaluation of insomnia. It is a five-point Likert-type scale consisting of seven items. Each item is scored between 0 and 4, and the total score ranges from 0 to 28. A score of 0-7 of the scale indicates clinically insignificant insomnia, 8-14 insomnia sub-threshold, 15-21 clinical insomnia (moderate), and 22-28 denotes clinical (severe) insomnia. The Turkish validity and reliability study was performed by Boysan et al. in 2010 [16].

3. Results

While the mean age of the individuals in the study with fatigue was 48.4±12.6, the mean age of the healthy individuals was 46.3±12.6. 70% of both fatigued and healthy individuals were female and 30% were male. There was no difference between the groups in terms of age and gender. The mean values of the FSS scores of the individuals with fatigue were 39.2±18.5. According to this, 70.3% of the patients with fatigue had increased fatigue severity, while 29.7% were considered to experience no fatigue. The mean FIS scores of individuals with post-COVID-19 fatigue were 76.6±24.7. According to the FSS, no patients experienced no effect of fatigue at all, while 45.9% of patients felt the effect of fatigue mildly, 35.1% patients felt moderate, 13.5% significant, and 5.4% patients felt very significantly affected by fatigue.

While the mean MoCA score of the individuals who participated in the study and had fatigue was 23.3±4.7, the mean MoCA score was 25.7±2.7 in healthy individuals. MoCA test scores of individuals with fatigue were significantly lower than those of healthy individuals ($p=0.008$) (Table 1). While the MoCA score was below the cut-off value in 27% of the individuals in the patient group, none of the healthy individuals had the MoCA score below the cut-off value. The average BDI score of individuals with fatigue was 17.0±9.9, while the average of BDI scores of healthy individuals was 9.2±8.9. The average BDI score of the individuals with fatigue was significantly higher than the healthy individuals ($p=0.001$)

(Table 1). 48.6% of individuals with fatigue had moderate or severe depression. The mean PSQI score of individuals with fatigue was 9.1±3.8, while that of healthy individuals was 3.1±2.0. Sleep quality of individuals with fatigue was significantly lower than that of healthy individuals (p=0.001). Sleep quality was poor in 83.6% of individuals with fatigue. While the mean ISI score of the individuals with fatigue is 11.1±7.0, the mean of the ISI score of the healthy individuals is 5.1±4.9. The mean ISI scores of individuals with fatigue were significantly higher than those of healthy individuals (p=0.001) (Table 1). 35.1% of individuals with fatigue had clinically moderate or severe insomnia. The mean MoCA scores of the female patients included in the study with fatigue were 22.2±5.7, while the mean MoCA scores of the male patients were 25.9±2.3. MoCA test scores of female patients were significantly lower than those of males (p=0.04). There was a negative and significant correlation between age and MoCA score in patients with fatigue. MoCA test scores decreased with increasing age (p=0.006). In addition, there was a significant and negative correlation between MoCA test scores and BDI, SSS and FIS scores. It was observed that while MoCA test scores decreased, BDI scores, SSS and FIS scores increased, p values (0.02, 0.01, 0.03), respectively. There was a positive and significant correlation between BDI score and SSS, FIS and ISI scores. It was observed that while the BDI scale scores increased, the SSS, FIS and ISI scores also increased, respectively, p values (0.001, 0.001, 0.006). PQSI scores and ISI scores were positively correlated (p=0.001). There was a positive and significant correlation between FSS and ISI and SSS (p =0.001, p=0.04, respectively). There was a significant and positive correlation between SSS and FIS and ISI (p=0.01, p=0.01, respectively). There was a significant and positive correlation between FIS and ISI scores (p=0.001).

Table 1. Comparison of MoCA, BDI, PSQI, and ISI test scores for patients with fatique due to PCS and healthy individuals

Variables	Patients with fatique Mean ± SD	Control Mean ± SD	Test Statistic
MOca	23.3 ± 4.7	25.7 ± 2.7	*0.008*
BDI	17.0 ± 9.9	9.2 ± 8.9	*0.001*
PSQI	9.1 ± 3.8	3.1 ± 2.8	*0.001*
ISI	11,1±7,0	5,1±4,9	*0.001*

SD; Standard Deviation, MoCA; Montreal Cognitive Assessment Scale, BDI; Beck Depression Invantory, PSQI; Pittsurg Sleep Quality Scale, ISI; Insomnia Severity Index

4. Disscussion

In our study, the MoCA test scores were found to be significantly lower in individuals with PCS with fatique. In addition, depression levels and insomnia severity were found to be significantly higher and sleep quality was significantly lower in individuals with PCS with fatigue. In addition, the MoCA scores of the women in the patient group were significantly lower than those of the male patients.

Our data show that SARS-CoV-2 infection has a significant effect on both fatigue and exhaustion. Consistent with previous evidence, results from these scales show that PCS patients perceive physical exhaustion and experience feelings of fatigue and lack of energy that affect their daily lives [17-19]. Based on the fact that fatigue is a multifaceted condition, we investigated cognition, depression and sleep disorders in individuals with fatique due to PCS and attempted to determine whether these disorders also contribute to fatigue. In our study, we found the MoCA scores to be significantly lower in individuals with PCS, and while 27% of the individuals in the patient group were below the MoCA cut-off value, there was no individual with a MoCA score below the cut-off value in the healthy controls. This shows that cognition is impaired in individuals who experience persistent fatigue after COVID-19. There are studies in the literature showing that cognition is affected following COVID-19 [19-26]. Cognition impairment in patients with fatique due to PCS may be resulting from fatigue's effect on cognitive control [27]. According to previously published literature, it was reported that neuroinflammation causes a GABAergic balance disorder after COVID-19 and is associated with neuromotor and cognitive fatigue, apathy and fatigue due to stress [28-32] and thus cerebellar hypermetabolism in a PET study conducted in COVID-19 patients with fatigue [33, 34]. Although a correlation between cerebral hypometabolism and fatigue has been consistently demonstrated in patients with neurological disorders, it cannot be ruled out that cerebral hypometabolism is caused by other symptoms such as depression and cognitive impairment [35-37]. One of the interesting findings of our study was that being female was correlated with MoCA scores in individuals with PCS. In other words, cognitive impairment in female patients was significantly more pronounced than in males. In a meta-analysis, it was found that cognitive impairment was higher in female gender, but this did not reach a significant level [3]. We also found a significant and negative correlation between MoCA scores and BDI, SSS, and FIS scores. We observed that while MoCA test scores decreased, BDI scores, SSS and FIS scores increased. Many studies to date have reported that there is also cognitive impairment in depression, and this is due to the fact that both executive/attention functions and mood are regulated by common brain regions such as the prefrontal region and cortico-striatal-pallidal-thalamic circuits [38, 39]. In addition, one of the findings in our study was the correlation between MoCA scores and FIS scores. We observed that MoCA scores decreased while FIS scores increased. This shows that fatigue is one of the factors resulting in cognitive disorder. In our study, we found that individuals with fatique due to PCS had significantly higher BDI scores than healthy individuals. Previous studies have reported varying degrees of depression in patients with COVID-19, ranging from 4% to 31% [20-22]. It has been reported that neuroinflammation triggered by viral infections may cause long-term cognitive and psychological problems by affecting the central nervous system [20, 25, 40]. This relationship has been reported with SARS and MERS as well as COVID-19 [20, 45]. Some studies have found a relationship between systemic inflammation markers and depression levels [46, 47]. Gennaro et al. [47]. In our study, 48.6% of individuals with fatigue had moderate

or severe depression. Fatigue and apathy are closely related to affective disorders, including mood disorders [48, 49]. Our study is significant in terms of determining depression in those experiencing fatigue and determining the presence of depression at a very high rate. That is, we found a higher incidence of depression in COVID-19 patients without fatigue than previously reported levels of depression. Therefore, fatigue also indicates potential of experiencing affective disorders in this patient group. However, some studies did not find a relationship between fatigue and depression in COVID-19 patients or a sign of major depression even if the presence of depression was determined [19]. In addition, the significant and positive correlation between FIS and BDI scores that we found in our study does not support this information. In addition, the level of depression in our patients was also correlated with SSS and ISI scores. In other words, in patients with depression, this affect disorder was found to be related to sleep disorders by causing insomnia and daytime sleepiness due to a divided sleep state [50].

Post COVID-19 sleep disorder can be observed during the acute phase of the disease due to physical and psychological stress and proinflammatory cytokine release. However, sleep problems persist in some patients in the chronic phase and are considered a central complication of the disease [51, 52]. We also investigated the frequency of sleep disorders in those who experience fatigue following COVID-19, and examined whether sleep disorders also contribute to this very common symptom, and we found that the sleep quality was significantly worse and the severity of insomnia was higher compared to healthy individuals. In addition, the FSS and FIS scores were positively and significantly correlated with the ISI scores. In other words, the fatigue severity of COVID-19 patients with high insomnia severity was higher and they experienced fatigue at a higher level.

Our study is the first to examine cognitive functions, depression levels and sleep disorders in individuals experiencing fatigue as a symptom of PCS, and the relationships between these parameters. Our data clearly shows that fatigue cannot be isolated to a single source and is a complex symptom. Therefore, increased depression and sleep disturbance after COVID-19 contribute to fatigue, which also affects mental performance. Cognitive disorders, depression and sleep disorders are all directly related to quality of life and should be identified, evaluated, treated and rehabilitated in detail in this patient group.

Our investigation has certain limitations. Firstly, although these disorders develop due to possible inflammation, inflammatory parameters were not examined to help the pathogenesis. Another limitation is that we could not evaluate cognitive status, depression level, and sleep disturbances in patients who did not have PCS but had COVID-19. We also did not evaluate individual domains of present cognitive impairment. Further studies that take these factors into account are required.

5. Conclusion

Fatigue, cognitive dysfunction, depression and sleep disorders have increased in the long-term following Coronavirus disease 2019.The treatment and rehabilitation of these disorders are important in terms of improving quality of life.

Authors`contributions

SG, GV, OD, RY and SB planned the study. SG, GV, OD, RY, SB trained the patients and spouses. SG, GV and RY performed neuropsychological testing. All authors con-tributed to analysis and made the first draft of the manuscript and all authors have approved the final version of the manuscript.

Conflict of Interest Disclosures

The authors declare no conflicts of interest related to this report.

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