Migration Letters

Volume: 20, No: S9(2023), pp. 742-752

ISSN: 1741-8984 (Print) ISSN: 1741-8992 (Online)

www.migrationletters.com

Post Covid-19 Fatigue Syndrome

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Abstract

Fatigue is an often-reported symptom in individuals infected with SARS-CoV-2, the virus responsible for the COVID-19 pandemic. Early reports on the clinical characteristics of COVID-19 patients mentioned fatigue as a common complaint among many of them. The purpose of this study was to assess both mental and physical fatigue. in patients recovered from COVID-19 and to study whether the severity can predict the possibility of developing Post COVID-19 fatigue for long time. A clinical retrospective study conducted in post Covid-19 fatigue syndrome by Clinical evaluation of fatigue was conducted using a questioning form in Iraq, on 22 February 2022 on patients between 18 - 59 years old to see the incidence of the fatigue syndrome in patients recovered from COVID-19. Post COVID-19 fatigue syndrome was 82% of the patients recovered from COVID- 19 in this study, the symptoms between malaise 59.7%, hair loss 41.7 %, cognition impairment 25 % and loss of appetite 50 % in these patients. The incidence rate of post covid-19 fatigue syndrome was 82% which considered as high rate of incidence compared to the number of patients who took part in this study.

Keywords: *Covid-19, Fatigue Syndrome, Post covid Syndrome.*

1. Introduction

Shortness of breath and fever are often seen in the early stages of COVID-19, a virus that primarily affects the respiratory system and is caused by SARS-CoV-2 [1]. Globally, there are more than 5.5 million confirmed cases of COVID-19, and more than 353,000 people have died as of May 28, 2020 [2]. Fatigue is often cited as a COVID-19 symptom [3], and anecdotal information shows that some people still have extremely high levels of protracted fatigue as they recover from this virus. This is not surprising considering how often post-infectious weariness has been noted in several other viral and non-viral infections [4,5].

The SARS-CoV2 pandemic's varying clinical presentations have presented a challenge to medical practitioners since it first appeared. The research of COVID-19 symptom prevalence and patterning has received a lot of attention [6] However, it's still worthwhile to investigate the post-COVID stage.

Recent information suggests that SARS-CoV2 may be a risk factor for postinfectious fatigue syndrome (PIFS). [7] When an infectious trigger, such as a virus, bacteria, or

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parasite, is followed by severe, incapacitating, persistent, or recurrent physical and/or mental fatigue, this condition is referred to as PIFS. [8] This disorder is also known by the names chronic fatigue syndrome (CFS), post-viral fatigue syndrome (PVFS) and myalgia encephalomyelitis (ME). [9]

It is still unclear what causes fatigue, a common and incapacitating sign of neurological illnesses. Despite considerable effort, little is known about the pathogenic pathways underlying weariness. This can be the case because there are multiple factors that contribute to weariness. There are several potential factors that can contribute to feelings of fatigue, including alterations in neurotransmitter levels, inflammation, psychological issues, levels of stress, cognitive dysfunction, and changes in substrate metabolism or availability. [10,11]

persistent tiredness the term "chronic fatigue syndrome" (CFS) refers to a condition that lasts for six months or longer without a different cause. This could be seen following numerous bacterial and viral illnesses [12] . Additionally, there have been connections between CFS and depression, however it is still unknown if one diagnosis occurs before the onset of the other [11]. Research on post-viral fatigue and chronic fatigue syndrome (CFS) often investigates alterations in the immune system, but there is currently no strong evidence to set up a causative or associative relationship. Numerous studies have explored immune dysregulation and activation in CFS, but findings have been inconsistent and no biologically plausible explanation has been consistently found. Contrasting results have been seen across various studies examining immune dysregulation and activation in individuals with CFS [12] . The various aetiologias that ultimately cause CFS may be the cause of the inconsistent results of earlier CFS investigations. Future study should focus on deciding whether changes in immune system activity are connected to any potential post-viral tiredness brought on by the new SARS-CoV-2. Prospectively studying individuals after SARS-CoV-2 infection results in a cohort with similar index infection that is well described, allowing for more precise descriptors of both disease state and disease features.

1.1. Definitions of Fatigue

Existing definitions of exhaustion differ greatly, and much research on the topic have failed to define weariness objectively. The causes of weariness also differ depending on the condition. Most disease-related research studies have either failed to distinguish between fatigue and other confounding factors, such depressed mood or sleep difficulties, or have failed to take comorbidities into account as sources of exhaustion. Consequently, Rudroff and associates [13] proposed a uniform taxonomy for fatigue in neurological illnesses; in our opinion, this taxonomy can serve as a model for post-COVID-19. The decline in physical and/or mental function brought on by modifications in central, psychological, and/or peripheral components because of the COVID-19 disease is what we refer to as post-COVID-19 weariness. We'll also go through how the environment and the work at hand could interact with these physiological elements to increase post-COVID-19 weariness.

1.2. Factors Contributing to Post-Covid-19 Fatigue

1.2.1. Central Factors

The current understanding is not definitive on whether COVID-19 can directly invade the central nervous system (CNS). However, it is believed that other similar coronaviruses can enter the CNS through the bloodstream and nerve cells, suggesting that invasion into the CNS by the virus might be a potential factor in post-COVID-19 fatigue. Important factors such as neurotransmitter levels (e.g., dopamine and serotonin), neuronal excitability, inflammation, demyelination (which can affect the conduction of nerve impulses), and other factors are considered significant contributors to fatigue in individuals with COVID-19 [15].

Recent neuroimaging studies have supplied insights into the underlying causes of fatigue in COVID-19 patients. Delorme et al. [16] conducted a study using 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) to examine cerebral glucose metabolism in COVID-19 patients experiencing fatigue. The results revealed hypermetabolism in the cerebellum and hypometabolism in the frontal region, both of which may contribute to feelings of exhaustion. It has been consistently saw that cerebral hypometabolism is associated with fatigue in individuals with various neurological conditions [17]. It is possible that other symptoms, such as depression, might underlie the cerebral hypometabolism observed in COVID-19 patients with fatigue.

In a study conducted by Guedj et al. [18] using FDG-PET, significant cerebral hypometabolism was seen in COVID-19 patients. Further investigations were considered necessary to establish the relationship between hypometabolism and potential long-term effects, such as fatigue. Additionally, prolonged periods of inactivity have become more common due to lockdowns implemented worldwide. These extended periods of physical inactivity may lead to reduced excitability of motor neurons through inhibition. When combined with the reduced motor unit conduction velocity caused by COVID-19, as proved by nerve conduction studies and quantitative electromyography [19], this can contribute to feelings of fatigue.

1.2.2. Psychological Factors

For many patients, tension, anxiety, despair, and dread are all common conditions that can coexist with COVID-19-related fatigue. Numerous pandemic control strategies, including isolation, social exclusion, and quarantining, have been successful in reducing virus spread, but they may unintentionally make recovering COVID-19 patients feel more exhausted. Post-traumatic stress symptoms, anxiety, bewilderment, despair, and wrath are some of these detrimental psychological effects. It is believed that they may significantly contribute to fatigue when combined [20]. Furthermore, it is crucial to identify COVID-19 tiredness from possibly comparable symptoms including sadness, somnolence, and apathy in both clinical and research contexts. Although these symptoms and weariness may interact clinically, they are separate occurrences. From a research standpoint, using measurements of mood and sleepiness as variables can help find COVID-19 tiredness from related disorders. Just two examples of the key molecules involved in psychological weariness are serotonin and dopamine. The olfactory bulb in the forebrain, which is vital for motivation, pleasure, and action and is rich in the neurotransmitter dopamine, may provide COVID-19 with access to the brain. Dopamine and serotonin aren't the only neurotransmitters that COVID-19 may affect; acetylcholine, the primary neurotransmitter responsible for [21]

1.2.3. Peripheral Factors

Various external factors can contribute to post-COVID-19 fatigue. The virus can infect different types of tissues, including skeletal muscle. This can result in symptoms like pain, muscle weakness, and an increased risk of injuries in individuals with COVID-19. As a result, it is plausible to suggest that COVID-19 could directly affect skeletal muscle and potentially lead to fatigue. Ferrandi et al. [22] propose that susceptibility to COVID-19 in different types of skeletal muscle cells may be linked to the angiotensin-converting enzyme 2 (ACE2) pathway. COVID-19 can activate leukocytes present in the lungs, resulting in the release of cytokines, including interleukin-6 (IL-6). Elevated levels of IL-6 can disrupt the metabolic balance in muscles, potentially leading to muscle loss. Consequently, Ferrandi et al. suggest that COVID-19 might affect skeletal muscle through direct infection of ACE2-rich cell types within the muscles or indirectly via the systemic release of cytokines, which disturbs muscle homeostasis. It is important to note that individuals at a higher risk for COVID-19, such as older adults and those with dystrophies, often experience skeletal muscle myopathies. In the case of older individuals, fatigue may be further worsened due to the natural decline in muscle

function associated with age [23]. Although there is currently limited evidence supporting the direct impact of COVID-19 on adipose tissue, it is plausible that the virus could target adipose tissue due to the presence of ACE2 in adipocytes. Adipose tissue is commonly targeted by various viruses. Li et al. found a correlation between reduced insulin sensitivity and lower levels of ACE2, which could have significant implications. COVID-19 patients often experience hyperglycemia, and poorly managed glucose metabolism can worsen the severity and mortality in individuals with diabetes who also have COVID-19. Fatigue is a common symptom in both diabetes and COVID-19, so individuals with both conditions may have an increased likelihood of experiencing fatigue [24].

2. Assessment Of Post-Covid Fatigue

After recovering from COVID-19, individuals may experience a variety of symptoms, including respiratory symptoms such as shortness of breath, chest pain, and cough, which have been sporadically associated with post-viral fatigue. The exact cause of these respiratory symptoms is currently unknown, underscoring the importance of a thorough evaluation by a respiratory physician to decide their nature and figure out the best course of action [25]. When dealing with post-viral fatigue, exhaustive investigations are typically not needed. The National Institute for Health and Care Excellence (NICE) in the UK suggests that routine hematology and biochemistry tests, including full blood counts, urea and electrolytes, thyroid function tests, liver function tests, bone profiles, erythrocyte sedimentation rates, and vitamin B12 assessments, are generally sufficient for evaluating cases of ME/CFS (myalgia encephalomyelitis/chronic fatigue syndrome). Similarly, for most cases of post-COVID fatigue, if no specific warning signs showing an underlying medical condition are present, it is proper to use the same approach of routine laboratory tests [26]. It is essential to assess the nature and pattern of fatigue. A key feature of the condition is exercise intolerance, where both mental and physical exertion lead to incapacitating fatigue that cannot be relieved by rest or sleep [27]. Post-exertional malaise, a common symptom, is often accompanied by other immunological symptoms such as persistent sore throat or swollen lymph nodes. The syndrome is characterized by broad physical pain and recurring headaches in addition to cognitive impairment and unrefreshing sleep [28]. Dysautonomia and orthostatic intolerance are often linked to severe cases; as a result, these regions should be investigated, and a suitable therapy strategy should be created. Since post-viral fatigue is significantly correlated with both depression and anxiety, mood assessment is necessary [29]. Evaluation of the patients' coping mechanisms is also necessary. These coping mechanisms may be beneficial and should be supported, but other techniques may be maladaptive and require opposition.

2.1. Approach To Management

Since there are no well-designed randomized controlled trials for post-viral fatigue, it is challenging to develop a management approach that is totally evidence-based. Since post-viral fatigue is regarded as a subacute type of chronic fatigue syndrome (ME/CFS), it stands to reason that the same management techniques used to treat ME/CFS might also be used to treat post-viral fatigue. Any episode of post-viral tiredness lasting longer than six months may be referred to as having ME/CFS [30]. The core ideas of a biopsychosocial philosophy should be included into the conventional management method. The foundation upon which management is constructed is an understanding, sympathetic, and empathetic team that is supportive and confirms the patient's suffering.

Educating patients about the nature and characteristics of the disease is an important aspect of their care. This includes explaining the role of factors that contribute to the illness, such as predisposing factors, precipitating factors, and perpetuating factors. By providing this contextual information, patients can shift their perspective from a conventional medical model to a more comprehensive understanding of the condition as a

complex issue that requires multiple interventions to make a meaningful difference. Additionally, it is essential to involve the patient in their own care and treatment. In terms of managing the condition, there are various strategies aimed at improving sleep quality and setting up a baseline for activities, which can be beneficial for patients [31].

To address negative beliefs, CBT starts by supporting the patient's suffering and then challenges the belief logically. A common example of such an emotional reaction to illness is catastrophizing, which is when a person believes that a set of unfavorable long-term symptoms must inevitably show a serious illness. The CBT approach can use the standard investigations and the fact that many patients experience the same symptoms as strong arguments that the symptoms, while unpleasant, are extremely unlikely to point to a hidden illness separate from the diagnosed condition. It may be simpler to change unpleasant habits than it is to alter one's ideas. It is simpler to recommend that a patient quit going to the gym altogether than to ask her to lessen her worry. Almost all patients use boom-and-bust behavior as their primary maladaptive strategy. It takes a variety of tactics to stop this practice because it always makes you feel more exhausted. It is crucial to inform patients early on about the management's aims. The aim is to keep the patient's energy level initially to lessen the impact of the post-exertional symptoms and achieve a stable baseline; after that, a progressive increase in energy is encouraged. This is because no clinical intervention can give patients more energy.

2.2. Management of Associated Symptoms

Post-viral fatigue and ME/CFS are often characterized by a range of symptoms including physical discomfort, recurrent headaches, general malaise, cognitive decline, unrefreshing sleep, frequent sore throats, and lymphadenopathy. These symptoms are closely associated with the post-exertional phase of the boom-and-bust cycle. The presence of these unusual and diverse symptoms often causes patients to become anxious and perceive them as indicators of a serious underlying condition [32]. It is important to conduct a thorough analysis of the type and pattern of these symptoms to cut the possibility of other diseases that may respond to specific interventions. It is not uncommon for one or more of these associated symptoms to be secondary to an unrelated pathology, so a comprehensive evaluation is necessary [32].

Common post-exercise symptoms in individuals with post-viral fatigue and ME/CFS include physical discomfort, fatigue, headaches, and cognitive difficulties. It is important to effectively communicate the concept of post-exertional symptoms to patients. On days when a patient pushes themselves too hard, there is an energy deficit in the body. To help patients understand this abstract concept, a common analogy is using a bank account in the red. The presence of unpleasant symptoms is a protective mechanism that discourages the patient from exerting themselves beyond their available energy resources. When the body is running on empty, these symptoms act as a warning system. By reframing bodily symptoms as an alarm system, patients can shift their perspective from perceiving a symptom as a sign of a new pathology or something to be suppressed at all costs, to viewing it as an indicator of progress in their journey towards managing their illness.

2.2.1. Physical Pain

When assessing pain in cases of post-viral fatigue or ME/CFS, it is helpful to follow the traditional approach of asking patients about the nature, severity, location, radiation, and factors that make it better or worse. In these conditions, pain is often muscular rather than primarily found in the joints. In the early stages, pain is typically not very severe and may be all-encompassing or migratory in nature. One important question to ask is how much pain the patient experiences on good and bad days. A common pattern is the absence or mildness of pain on good days, which worsens on bad days. Patients should be encouraged to view pain as an alarm system, as mentioned earlier, and to aim for its complete elimination by avoiding boom and bust behavior. However, if necessary, basic pain relievers can be used. In cases where the pain is clearly muscular or neuropathic,

conventional treatments for neuropathic pain can be considered. This may involve the use of GABA agonists, tricyclic antidepressants, or serotonin and noradrenaline re-uptake inhibitors (SNRIs) [33].

2.2.2. Recurrent Headaches

Nearly 80% of ME/CFS patients experience acute or recurrent migraines [34]. In post-viral exhaustion, headache or migraine incidence is unknown. The management strategy should adhere to set up best practices while trying to control triggering factors with or without pharmaceutical management. Despite its frequent side effects, which can resemble the primary symptoms of CFS/ME such as fatigue and pins and needles, topiramate has recently shown to be well tolerated in CFS/ME patients. [35]

2.2.3. Unrefreshing Sleep

This symptom is present in all ME/CFS patients and may be accompanied by hypersomnia or insomnia. Although it is often resistant to treatment, advice on good sleep hygiene can be quite beneficial. Avoid using sedatives and sleeping pills as they rarely result in better sleep.

2.2.4. Anxiety And Depression

Individuals with ME/CFS tend to experience higher levels of anxiety than depression. These patients often show characteristics of being highly driven individuals with a strong work ethic and a sense of altruism. However, their inability to meet their own high standards of performance, taking care of others, or keeping their personal environment at their usual level of perfection can lead to feelings of loss of control and low self-esteem. Untreated anxiety disorders can present significant obstacles to a patient's recovery. It is important to address and manage anxiety symptoms as part of the treatment plan for ME/CFS patients. Different anxiety disorders can range in intensity, including conditions such as recurrent panic attacks, post-traumatic stress disorder (especially in individuals who have been hospitalized), and obsessive-compulsive disorder accompanied by repetitive behaviors. These anxiety syndromes can manifest as minor health anxiety or fall within a spectrum of severity. The primary treatment choice for anxiety and depression is cognitive-behavioral therapy (CBT), although there are situations where medication management may be necessary. It is important for the treating physician to emphasize that mood disorders play a significant role in perpetuating ME/CFS. In the first stages of treatment, reducing activities and abandoning enjoyable pursuits can lead to an increase in depression. This can occur when patients must let go of goals that bring them a sense of accomplishment and pride. On the other hand, anxiety can deplete energy and affect the patient's ability to challenge unhelpful beliefs. If verbal therapy alone proves ineffective in managing mood disorders, the consideration of pharmacological medication may be necessary [32]. This study aimed to evaluate the physical and mental fatigue in patients recovered from COVID-19 and to study whether the severity can predict the possibility of developing Post COVID-19 fatigue for long time.

3. Patient And Methods

3.1. Study Design and Settings

This study is a clinical retrospective study conducted in Post Covid-19 fatigue syndrome in Iraq Baghdad, in 22 February 2022 .

3.2. Study Population

The population of the study was about the patients who recovered from Covid-19 and may developed post Covid-19 fatigue syndrome.

3.3. Data Collection

The data was collected by a questionnaire in google forms. The following information was checked by every participant.

3.4. Demographic characteristics of the patients

Age and gender, Co.morbid disease, time of infection, number of infection, neverity of infection and symptoms of patients, vaccinated people and type of vaccine, therapy protocol of patients infected with Covid-19, the incidence of post Covid-19 fatigue syndrome, duration, and patient syndromes, therapy protocol used to treat fatigue syndrome and the response to treatment.

4. Results

This study included 74 patients recovered from COVID-19 with mean age of 25.6 years; 4% of patients were in age group less than 20 years, 82.4% of them were in age group 20-30 years, 6.7% of them were in age group 30-40 years, 6.7%of them were in age group above 40 years . Female patients were more than male patients with female ratio of 60.81 % to male ratio of 39.18%, all these findings wereshown in table 1.

Table 1: Demographic characteristics of the patients.

Age		No. of patients %
<20 years	3	4.054054054
20-30 years	61	82.43243243
30-40 years	5	6.756756757
>40 years	5	6.756756757
Total	74	100
Gender		
Male	29	39.18918919
Female	45	60.81081081
Total	74	100

The number of infections of these patients were ranged between 74.32% for patients who infected for one time, 20.27% for patients who infected twice and 5.4% for patients who infected for more than two times. All these findings were shown in the table 2.

Table 2: number of infections for the patients in this study.

Number of infections		No. of patients %
One time	55	74.32432432
Two time	15	20.27027027
More than two	4	5.405405405
Total	74	100

The vaccination rate was between 87.83% for patients who took the vaccine and 12.16 for the patients who did not get vaccinated yet. these findings were shownin table 3.

Table 3: counting for vaccinated patients in this study.

Vaccinated		No. of patients %
Yes	65	87.83783784
No	9	12.16216216
Total	74	100

The severity of infection in these patients before recovering from COVID-19 was between mild , moderate and severe . Most of them were in moderate cases. The rate was 32.43 for mild cases, 62.16 % for moderate cases and 5.4 % for severe cases. These findings were shown in table 4.

Table 4: severity of infection.

Severity of infection		No. of patients %
Mild	24	32.43243243
Moderate	46	62.16216216
Sever	4	5.405405405
Total	74	100

The symptoms of COVID-19 of these patients were in range between 37.8 % for GIT symptoms, 32.4 % for RESP (respiration rate) symptom, 54.1 % for anosmia (loss of smell) symptom , 52.7 % for ageusia (loss of taste) symptom , 8.1 % for decreasing in SPO2 and need of O2 symptom and 83.8 % for patients who suffers from fever symptom. These findings were shown in table 5.

Table 5: symptoms of COVID-19 for the patients in this study.

Symptoms of COVID		No. of patients %
GIT	28	37.80%
RESP	24	32.40%
anosmia	40	54.10%
ageusia	39	52.70%
Decrease of SPO_2	6	8.10%
Need of O_2	6	8.10%
Fever	62	83.80%

The patients who suffered from post COVID-19 fatigue syndrome experienced symptoms ranged in 59.7 % for malaise symptom, 41.7 % for hair loss, 25 % cognition impairment, 50 % loss of appetite and 18.1 % had no symptoms of fatigue. These findings were shown in table 6.

Table 6: symptoms of post COVID-19 fatigue syndrome that the patients suffered from.

Symptoms of Fatigue syndrome		No. of patients %
Malaise	43	59.70%
Hair loss	30	41.70%
Cognition impairment	18	25%
Loss of apetite	36	50%

None	13	18.10%

Therapy protocol of patients infected with Covid-19 according to what thepatients said was:

supportive therapy analgesics and antipyretic (ex: paracetamol, aspirin sachets).

supplementary vitamins (ex: vitamin c, vitamin d, zinc, multi vitamins) cough preparations (ex: acetyl cystine sachets) antibiotics (ex: azithromycin, Ceftriaxone, Levofloxacin, Amoxicillin Clavulanic acid), dexamethasone, lozenges, montelukast, antihistamines. Therapy protocol that used to treat post COVID-19 fatigue syndrome accordingto what the patients said was: analgesics + caffeine for malaise, multi vitamins (ex: vitamin d, vitamin c, Biotin) for malaise and hair loss .and according to the patients they said they Has a good response for thetherapy.

5. Discussion

While the leading symptoms during coronavirus disease 2019 (COVID-19) are show and most patients fully recover, a significant fraction of patientsnow increasingly experience post Covid-19 fatigue syndrome. The Present study showed that 82% of participated patients experience fatigue syndrome. Findings of our study showed us that most of patients who had COVID-19 got to experience fatigue syndrome regardless of its severity. Most patients of this study faced a fatigue syndrome with duration of not morethan 30 days, very small number of patients experienced a long-term fatigue syndrome and some of them still facing it until now. The lack of patients with co-Morbid disease in contrast with COVID-19 in this study we could not decide if there is a relation between co-Morbid disease and fatigue syndrome. We found that people who have been vaccinated had a less duration time of symptoms of those who did not get vaccinated, but both (vaccinated, not vaccinated) got some post COVID-19 fatigue symptoms.

6. Conclusions

The incidence rate of post covid-19 fatigue syndrome was 82% which considered as high rate of incidence compared to the number of patients who participated in this study , and this means that we need more and more studies in the future to find out more accurate information about the causes of post COVID-19 fatigue syndrome and to make specific therapy protocol about the syndrome.

7. Limitation of the study

Short study duration, small number of sources that have useful information, lack of patient’s compliance, lack of face-to-face communication with participating patients.

8. Recommendations

we encourage people to get vaccinated and to not be afraid of getting sick with this disease because getting sick make people feel stronger afterward and this did not come randomly but from our own experience.

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