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Long Covid — Pathophysiology and Treatment

Długi Covid — patofizjologia i leczenie

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Abstract

A large number of patients who have recovered from the acute phase of COVID 2019 (COVID-19), caused by the new "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), have a host of long-term symptoms. Around 10% of suffer from long-term symptoms beyond three weeks, and a smaller proportion for months. Among them, more than half suffer from fatigue. In the above article fatigue in post-infections syndromes is described. In addition, selected hypothesis on pathophysiology of long Covid and current guidelines on approach in rehabilitation are discussed. Long Covid has a rich symptomatology with a chronic fatigue as one of many symptoms that patients might suffer from. Therefore, rehabilitation programme should be conducted in an interdisciplinary approach to aim to improve function of many body systems. Self-support should be advised, however, ideally patients should be supported throughout rehabilitation process. Further studies on natural course of long Covid and underlying pathological mechanism would be helpful in development of pharmacological and non-pharmacological long Covid treatments. If the symptomatology of long Covid patients would be as heterogenous as in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients, then development of individual approach in rehabilitation might be necessary to obtain high efficacy and low adverse effects rate. **(JNNN 2021;10(2):77–81)**
Key Words: chronic COVID, post-acute sequelae of SARS-CoV2, post-COVID

Streszczenie

Duża liczba pacjentów, którzy wyzdrowieli z ostrej fazy COVID 2019 (COVID-19), wywołanej przez nowy „drugi koronawirus ciężkiego ostrego zespołu oddechowego" (SARS-CoV-2), ma wiele długotrwałych objawów. Około 10% cierpi z powodu długotrwałych objawów powyżej trzech tygodni, a mniejsza część przez kilka miesięcy. Wśród nich ponad połowa cierpi na zmęczenie. W powyższym artykule opisano zmęczenie w zespołach poinfekcyjnych. Ponadto omówiono wybrane hipotezy dotyczące patofizjologii długiego Covida oraz aktualne wytyczne dotyczące podejścia w rehabilitacji. Długi Covid ma bogatą symptomatologię z chronicznym zmęczeniem jako jednym z wielu objawów, na które mogą cierpieć pacjenci. Dlatego program rehabilitacji powinien być prowadzony w podejściu interdyscyplinarnym, aby dążyć do poprawy funkcjonowania wielu układów organizmu. Należy doradzić samopomoc, jednak jeżeli istnieje taka możliwość, to pacjenci powinni być wspierani przez cały proces rehabilitacji. Dalsze badania nad naturalnym przebiegiem długiego Covida i leżącym u jego podstaw mechanizmem patologicznym byłyby pomocne w opracowaniu farmakologicznego i niefarmakologicznego leczenia długiego Covida. Jeśli symptomatologia pacjentów z długim Covid byłaby tak samo niejednorodna jak u pacjentów z Myalgic encephalomyelitis/zespołem przewlekłego zmęczenia (ME/ZPZ), to opracowanie indywidualnego podejścia w rehabilitacji może być konieczne dla uzyskania wysokiej skuteczności i niskiego wskaźnika skutków ubocznych. **(PNN 2021;10(2):77–81)**
Słowa kluczowe: przewlekły COVID-19, następstwa po ostrej fazie SARS-CoV2, post-COVID-19

Introduction

Long Covid

Fatigue is one of the most common complaints in both the general population and patients suffering from chronic conditions [1]. Fatigue tends to diminish after rest or treatment; however, persistent chronic fatigue, particularly when lacking a identified cause, substantially impairs health-related quality of life [2].

Around 10% of patients who have recovered from the acute phase of COVID 2019 (COVID-19), caused by the new "severe acute respiratory syndrome coronavirus 2" (-CoV-2), have a host of long-term symptoms beyond three weeks, and a smaller proportion for months [3]. 'Post-acute COVID' is defined by symptoms lasting 3 weeks after COVID-19 infection [3], while 'Chronic COVID' is defined by symptoms persistence more than 12 weeks [4]. Nomenclature seems to different between authors, with terms used as long COVID, post-COVID, or post-acute sequelae of SARS-CoV2 (PASC) [5]. In the above paper, term long COVID would be used to describe symptoms persistence after acute phase of COVID 19. Among them, a large percentage of people (53.1%) perceive fatigue [6]. Fatigue is defined as a debilitating, lasting feeling of physical and mental fatigue or exhaustion characterized by a lack of energy, muscle weakness, slowness of reaction, sleepiness, and a deficit in concentration [7,8]. The Centers for Disease Control and Prevention (CDC) observed nearly 300 PCR-positive SARS-CoV-2 people for several weeks. Three weeks after the positive test, nearly half of the patients still had symptoms such as fatigue and cough — especially the elderly or those with chronic diseases [9]. Italian researchers studied 143 confirmed COVID-19 patients after the most severe symptoms subsided. Sixty days after onset, more than half of patients still had multiple bothersome symptoms and 41% reported a deterioration in quality of life [6]. Irish researchers studied 128 patients with PCR-documented SARS-CoV-2 infection and found that, on average 10 weeks after the onset of COVID-19 symptoms, 52% reported persistent fatigue and 31% did not return to work. Surprisingly, post-COVID fatigue has not been associated with acute disease severity, or with routine laboratory markers of inflammation, pro-inflammatory molecules and cell turnover [10].

Fatigue in Post-infectious Fatigue Syndromes

Scientific literature is rich of descriptions of infectious disorders triggering chronic fatigue. Post-infectious fatigue syndromes follow acute infections with several different types of infectious agents: viruses such as the SARS coronavirus [11], Epstein-Barr virus [12–14], Ross River virus [14], enteroviruses [15], human herpes virus-6 [16], Ebola virus [17], West Nile virus [18], dengue virus [19] and parvovirus [20]; bacteria such as Borrelia burgdorferi [21], Coxiella burnetii [22] and mycoplasma pneumoniae [23]; and parasites such as Giardia lamblia [24]. The acute symptoms of these diseases and the organ damage they cause can vary widely. However, the persistent chronic fatigue that follows every illness appears to be quite similar [25].

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic illness without completely known aetiology or cure. Some Authors suggest that in many cases ME/CFS might be triggered by a pathogen [25]. A parallel between chronic fatigue after acute phase of COVID disease and fatigue perceived by ME/CFS patients was suggested [25,26].

Pathophysiology of Long COVID

Currently, there is no clear data on natural course of COVID 19 and pathophysiology mechanism leading to long COVID. Some researchers proposed "cytokine storm" as a factor experienced during course of COVID and explaining prolonged fatigue [26]. Authors have suggested that the same cytokines that have been implicated in pathophysiology of ME/CFS might be also relevant to long COVID-19. Based on previous studies, Islam et al. suggested Interleukin-2, granulocyte-colony stimulating factor, and interferon-γ inducible protein 10 [26]. British Society for Immunology have proposed three hypotheses: persistent virus in immune-privileged sites, aberrant immune response, or autoimmunity [27]. However, further research should be conducted to possibly confirm these hypotheses.

There seems to be no clear relationship between severity of acute phase of COVID-19 and development of long COVID [28,29]. Results of study on 4,182 cases of COVID-19 showed that experiencing more than five symptoms during the first week of illness was related to development of long COVID [30]. In addition, presence of headache during acute phase was related to post-COVID fatigue [29]. Sykes et al. Followed up 134 COVID patients for a median of 113 days after discharge [28]. Eighty-six percent of patients reported at least one residual symptom at follow-up, however none had persistent radiographic abnormalities. Females were consisted of a group with higher risk with persistent symptoms including fatigue, myalgia and anxiety [28].

Dani et al. describe autonomic dysfunction in patients with long COVID [31]. In contrary, Townsend et al. showed that 20 long COVID patients with fatigue had no dysfunction in autonomic nervous system. Presumably, as in ME/CFS, high heterogeneity of patients might be expected group [32]. Ortelli et al. showed noted apathy,

neuromuscular and cognitive fatigue and executive dysfunction in a sample of post-COVID-19 patients [33].

Long COVID Therapy

Currently, there is no proven treatment for long COVID. Daynes applied on 30 patients with long COVID six weeks rehabilitation programme with two supervised sessions per week. The programme consisted was multimodal (aerobic and strength training as well as education and pacing). Patients aerobic capacity has improved and no serious adverse events recorded [34]. However, it should be underlined that physical exercise programme in ME/CFS might be deleterious to some patients. Fifty one percent of dropout rate was noted due to post-exertional malaise (PEM) perceived by CFS patients undergoing physical activity programme based on aerobic physical activity [35]. CFS patients with higher severity of disturbance in autonomic control over blood vessels, worse cognitive function and the lower the maximal Heart Rate during physical exercise had lower chance of completion of programme based on physical activity [35]. Therefore, If above described suggestions on parallels between pathophysiology of ME/CFS and long COVID would be confirmed in further researches, then reactions of long COVID patients on rehabilitation based on physical activity programmes should be closely monitored due to risk of PEM occurrence.

NICE guidelines in terms of planning care suggest self-management for patients with long COVID [36]. In addition, option for supported self-management might be considered by patients. One of the management pathways is suggested to be chosen. First is to ask for support from integrated and coordinated community, primary care, mental health support and rehabilitation. Second option is the referral to an integrated multidisciplinary assessment service. Third option is the referral to specialist care for specific complications [36]. In terms of patients management, self-management and supported self-management is suggested. It should consists of give advice and information on self-management with initial patients assessment included. Necessity of setting of realistic goals was underlined. Patients should be educated on current knowledge on effects of non-pharmacological supportive therapy, as diet supplements protocols. Support of patients in coming back to daily life tasks from before COVID infection should be taken [36]. According to NICE guidelines, rehabilitation should be multimodal, adequate to multifaceted nature of long COVID symptoms, including physical, psychological and psychiatric aspects. Patients should be supported throughout rehabilitation process and encouraged to track their symptoms and progress [36].

Interestingly, results of a yet not peer-reviewed small study [37]. suggested that AstraZeneca and Pfizer-BioNTech vaccines were related with overall improvements in symptoms in long COVID patients. However, this finding should be replicated in further studies on bigger sample sizes.

Conclusions

Management of long COVID sufferers might become a new priority of medical community around the world when pandemic would become better controlled. Around half of Long COVID patients suffer from fatigue. Importantly, symptomatology of Long COVID seems to of rich. Further studies on natural course of long COVID and underlying pathological mechanism would be helpful in development of pharmacological and non-pharmacological long COVID treatments. In addition, it should be decided if long COVID should be unified with ME/CFS diagnosis. It could have potentially important implications for approach to rehabilitation of the above mentioned patients. Anyway, precise medicine approach is advised because of heterogeneity of symptoms in both patients groups and adverse reactions to physical exercise in a group of ME/CFS patients with severe PEM.

Implications for Nursing Practice

Long COVID has a rich symptomatology with a chronic fatigue as one of many symptoms that patients might suffer from. Therefore, as NICE guidelines suggest, rehabilitation programme should be conducted in an interdisciplinary approach to ideally aim to improve function of many body systems. Self-support should be advised. However, patients should be supported throughout rehabilitation process. Goals taken by patients should be realistic [35].

It is advised for all types of clinicians to follow the recent literature on efficacy and adverse effects in literature on rehabilitation programmes applied in long COVID patients. Currently, further research is needed to undercover long COVID-19 pathophysiology and to establish specifics of rehabilitation programme (duration of programme, type, intensity and frequency of sessions) [38]. If the symptomatology of long COVID patients would be as heterogenous as in ME/CFS patients [31], then development of individual approach in rehabilitation might be necessary to obtain high efficacy and low adverse effects rate.

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