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Długoterminowe powikłania infekcji COVID-19 u osób w podeszłym wieku – przegląd piśmiennictwa. Część I. Patofizjologia, objawy ogólne

Long-term complications of the COVID-19 infection in the elderly – the literature review. Part I. Pathophysiology, systemic sequelae

Justyna Rohun, Ludmiła Daniłowicz-Szymanowicz
II Klinika Kardiologii i Elektroterapii Serca, Gdański Uniwersytet Medyczny

Streszczenie

Wybuch pandemii COVID-19 niezaprzeczalnie zmienił świat. Jak do tej pory potwierdzono ponad 555 milionów zakażeń, w tym ponad 6 milionów zgonów. Choroba nierzadko charakteryzuje się ciężkim przebiegiem i może powodować objawy związane z uszkodzeniem każdego układu. Niewątpliwie jednak najbardziej rozpowszechniona jest postać płucna. U części chorych rekonwalescencja jest procesem długotrwałym i skomplikowanym. Zdarza się, że nawet po łagodnej infekcji objawy nie ustępują całkowicie lub pojawiają się nowe. W literaturze zjawisko to zostało opisane jednostką zwaną „long COVID" lub post-acute sequelae of SARS-CoV-2 (PASC). Obejmuje ona zbiór różnych powikłań trwających tygodniami po zakończonym zakażeniu. Niniejsza praca ma na celu prezentację choroby COVID-19 oraz jest długotrwałych następstw ze szczególnym uwzględnieniem ludzi starszych. W pierwszej części dokonano opisu patofizjologii, objawów oraz możliwych strategii diagnostyczno-terapeutycznych. *Geriatria 2022;16:134-140. doi: 10.53139/G.20221620*

Słowa kluczowe: post-acute sequelae of SARS-CoV-2 (PASC), long covid, ludzie starsi

Abstract

The outbreak of the COVID-19 pandemic has undeniably changed the world. Until now, the reports indicate more than 555 million confirmed cases and over 6 million deaths. The inflammation frequently has a hyper-acute course and may include symptoms from all human body systems. However, the most severe form is the pulmonary one. There is a group of patients whose convalescence becomes complicated and entails much time. Even after a mild infection the symptoms may not withdraw entirely or new complications appear. A phenomenon called ‚long COVID syndrome' or post-acute sequelae of SARS-CoV-2 (PASC) has been described in the literature. It embraces a variety of signs persisting weeks after the infection is over. This review provides the most recent information about the COVID-19 disease and post-COVID syndrome, notably in the geriatric population. In the first part, we detail the pathophysiology, describe the symptoms, and discuss the possible diagnostic and therapeutic strategies. *Geriatria 2022;16:134-140. doi: 10.53139/G.20221620*

Keywords: post-acute sequelae of SARS-CoV-2 (PASC), long covid, elderly

Introduction

The outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019 is declared the world's biggest pandemic since the one of influenza A H1N1 in 2009. To date, as of 10 July 2022, World Health Organization (WHO) reported more than 555 million confirmed cases of COVID-19 disease and over 6 million deaths [1]. The highest prevalence was observed among elderly people.

The disease itself is characterized by significant heterogeneity. Over time, the clinical picture of COVID-19 has been changing. SARS-CoV-2 due to its viral nature tends to undergo mutations, which results in the appearance of different viral strains. So far, WHO declared five variants, which are Alpha,

first detected in the United Kingdom (UK), Beta – in South Africa, Gamma – in Brazil, Delta – in India, and Omicron with origin in South Africa as well. All the subtypes are characterized by different levels of transmissibility, severity, and mortality. Moreover, differences in the age range of patients and the severity of the illness can be noted. The first wave of the pandemic, affecting mostly older adults, was characterized by severe pneumonia with a high mortality rate and other symptoms related to the respiratory system, while over time, in the second wave patients were younger and presented new symptoms more frequently i.e. renal and gastrointestinal. The third wave was unique, as even though the already available vaccination process was the priority in the majority of the countries, the highly contagious delta variant was dominating and the infection chain did not stop.

The disease's course is unpredictable. The manifestations may involve the immune system, metabolism, pulmonary system, neuropsychiatric manifestations, etc. It may occur as a mild inflammation or severe respiratory failure requiring ventilatory support. The individual outcome can be determined by many factors i.e. age, medical pre-infection status, comorbidities, vaccination status, and virus strain. The wide range of prevalence and mortality rates around the globe suggests the importance of government policy or hospital care level, additionally.

COVID-19 in general occurs mostly in adults over 40 with the same prevalence in both females and males. Nevertheless, the elderly are reported to be affected at a disproportionally high rate [2]. Moreover, many studies show that in approximately half of the affected older adults the illness is severe and 10% of them die [3]. According to the reports, infection in this group very often progresses rapidly to a life-threatening condition [2,3].

In the majority of the patients, the symptomatic period is one or two weeks. However, emerging data suggest that many COVID-19 patients complain of persistent symptoms when the disease has gone [4]. As with the disease itself, the post-inflammatory interval may also include a broad spectrum of symptoms. A phenomenon under the name of "post-COVID-19 syndrome" or "long COVID" or "post-acute sequelae of SARS-CoV-2 (PASC)" was described in the literature. The term embraces manifestations lasting over 3–4 weeks after the inflammation and includes numerous systems of the human body. These after-effects impact mortality, and morbidity and influence further prognosis, especially in older adults.

In this paper, we briefly summarize post-COVID syndrome mechanisms and manifestations, notably in a geriatric population.

Methods

We systematically searched PubMed for the literature, clinical trials, and databases from 2020 to July 2022. The keywords were ‚post covid', ‚long covid' ‚PASC' ‚covid complications'. Mostly cross-sectional studies, retrospective cohort studies and case reports were found. There is a lack of explicit reports so the subject requires further, more detailed studies.

Pathophysiology of COVID-19 disease and long COVID syndrome

The underlying pathophysiology is complicated and there is still a shortage of knowledge in this field. The virus spreads among nasal and oral droplets and, at a molecular level, enters the cell by the angiotensin-converting enzyme receptor 2 (ACE2) in the way of endocytosis. Consequently, cells with the expression of this receptor on its surface are considered a target for the virus, i.e. endothelium, glial cells, and neurons. Once inside the cell, its reproductive cycle begins.

The mechanisms of progression of COVID-19 are complex. Severe immune dysregulation with a cytokine storm seems to play a key role. The inflammation pattern is characterized by the release of increased levels of tumor necrosis factor (TNF)-α, interleukin (IL) – 1β, 6, 10, which is progressive and leads to critical immune dysfunction. Moreover, the hypercoagulative state is observed in COVID-19 patients. Activation of the coagulant cascade with disequilibrium of the fibrinolysis result in multiplication of D-Dimer levels, creation of microthrombi, and, often, disseminated intravascular coagulation (DIC). As type II alveolar epithelial cells are known to express ACE2 on a considerable scale, the pulmonary lining suffers the most acute lesion and severe pulmonary failure can be observed. Additionally, the virus is described to provoke oxidative stress, accelerate the aging of cells, have an impact on mitochondrial dysfunction, and provoke local hypoxia.

Nevertheless, for a more profound understanding of the mechanisms, explicit studies are required, especially in terms of the long COVID syndrome. Most of the recently conducted ones aim to explore

the infection mechanisms, paying less attention to the post-COVID period. The implication of genetics of the host, primary viral lesions, modification in the immune system after the disease, and patient's comorbidities are supposed [4]. This may explain the higher prevalence in older adults, whose immune system is undergoing the natural process of immunosenescence, and other immunosuppressive coexisting conditions, such as diabetes mellitus, are more numerous. There are theories highlighting the role of overexpression of transforming growth factor beta (TGF-β), a multifunctional molecule with an anti-inflammatory and immunosuppressive effect, which, as a counter-balance in response to primary inflammation, causes immunosuppression and, further, fibrosis of the organs [5]. But, as there is a paucity of data, the theme is still being only hypothesized.

Post-COVID Syndrome manifestations

Post-COVID syndrome presents with a broad spectrum of complications and varies from patient to patient. It can include about 200 different and overlapping symptoms i.e. persistent fatigue, chest and muscle pain, headache, shortness of breath, anosmia, muscle weakness, fever, cognitive dysfunction, tachycardia, and intestinal disorders. Moreover, the prevalence may evolve over time and present diversity in different countries. Comorbidities, disease severity, and sex modified the prevalence as well.

Tianqi Yang et al. in their most recent meta-analysis including 72 studies identified a total of 167 post-COVID sequelae in hospitalized survivors up to 1 year of follow-up [6]. The most common were fatigue (27.5%, range 1.5-84.9%), somnipathy (20.1%, range 1.2-64.8%), anxiety (18%, range 0.6-47.8%), dyspnea (15.5%, range 0.8-58.4%), post-traumatic stress disorder (PTSD) (14.6%, range 1.2-32%) reported over 3-13.2 months after the hospital discharge. Apart from fatigue and somnipathy, which persisted after > 9 months, the other symptoms withdrew.

According to another meta-analysis by Salim Alkodaymi M et al. prevalence of symptoms is significantly heterogeneous and changed over time [7]. The report includes all COVID-19 survivors, both hospitalized and non-hospitalized. After 3- to <6 months of follow-up the most common symptoms were fatigue, dyspnea, sleep disorder, and difficulty concentrating (32%, 25%, 24%, and 22%, respectively). After 6- to <9month follow-up patients reported effort intolerance, fatigue, sleep disorder, and dyspnea (45%, 36%, 29%, and 25%, respectively). Fatigue (37%) and dyspnea (21%) dominated at 9 to <12months. Finally, the symptoms, which persisted at > 12 months after the disease, were fatigue, dyspnea, sleep disorder, and myalgia (41%, 31%, 30%, and 22%, respectively).

In table I we collected so-far available studies with a special insight into the geriatric population, dated from 2020 to 2022, reporting the most common signs in older adults. Mainly cross-sectional studies and retrospective cohort studies were found. As may be observed, in the majority systemic (fatigue, malaise) and pulmonary (dyspnea) complications are the most frequent. Below we would like to discuss the most common manifestations grouped by human body systems.

Chronic fatigue

Persistent fatigue was reported as the most frequent post-COVID symptom in the majority of the studies (table I). The relevance of the problem is highlighted by the fact that WHO classified post-viral fatigue syndrome in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [24]. The phenomenon is complex

Table I. Studies reporting post-COVID-19 sequelae observed in geriatric population with a brief information regarding the main symptoms/ Tabela 1. Badania dotyczące długoterminowych powikłań po infekcji COVID-19 w populacji geriatrycznej z krótką prezentacją najważniejszych objawów

Study reference	Type of study	Study location	Sample size	Age (SD)	Symptoms (% of patients/risk difference regarding comparison group that did not have covid-19)
Cohen K, et al, 2022 [8]	Retrospective cohort study	USA	87337	≥ 65	1. Respiratory failure (7.55) 2. Fatigue (5.66) 3. Hypertension (4.43)
Yoonjung K, et al, 2021 [9]	Cross sectional	Kyungpook, Korea	5252	16-70	1. Fatigue (26.2%) 2. Concentration difficulty (25.1%) 3. Amnesia (24.3%)

Davis HE, et al, 2021 [10]	Cross sectional	Worldwide (online) - 41.2% was from USA	3762	18-80+	1. Fatigue (80%) 2. Cognitive dysfunction (58.4%) 3. Headache (53.6%)
Fang X, et al, 2022 [11]	Prospective cohort study	Wuhan, China	1233	≥ 60	1. Fatigue (32.4%) 2. Sweating (20.0%) 3. Chest tightness (15.8%)
Shang YF, et al, 2021 [12]	Retrospective cohort study	Wuhan, China	1174	20-97	1. Fatigue (25.3%) 2. Sleep disorder (23.2%) 3. Shortness of breath (20.4%)
Bell ML, et al, 2021 [13]	Prospective cohort study	Arizona, USA	543	12-82	1. Fatigue (37.5%) 2. Shortness of breath (37.5%) 3. Brain fog (30.8%) 4. Psychiatric (anxiety, stress) (30.8%)
Mandal S, et al, 2021 [14]	Cross sectional	London, UK	384	44-76	1. Fatigue (69%) 2. Breathlessness (53%) 3. Cough (34%)
Moreno-Perez O, et al, 2021 [15]	Prospective cohort study	Alicante, Spain	277	53-72	1. Fatigue (34.8%) 2. Dyspnea (34.4%) 3. Anosmia-dysgeusia (21.4%)
Petersen MS, et al, 2021 [16]	Cross sectional	Faroe Islands	187	0-67+	1. Fatigue (30%) 2. Anosmia-ageusia (15- 25%) 3. Arthralgia (11%)
Jacobs LG, et al, 2020 [17]	Prospective cohort study	New Jersey, USA	183	25-85	1. Fatigue (55%) 2. Dyspnea (45.3%) 3. Muscular pain (51%)
Carfi A, et al, 2020 [18]	Cross sectional	Rome, Italy	143	19-84	1. Fatigue (53.1%) 2. Dyspnea (43.4%) 3. Joint pain (27.3%)
Landi F, et al, 2021 [19]	Retrospective cohort study	Rome, Italy	137	19-89	1. Fatigue (51%) 2. Dyspnea (44%) 3. Cough (17%)
Aly MAEG, et al, 2021 [20]	Cross sectional	Egypt	115	73.18 (6.42)	1. Fatigue (57.4%) 2. Stress (56.5%) 3. Sadness (47.8%)
Halpin SJ, et al, 2021 [21]	Cross sectional	Leeds, UK	100	20-93	1. Fatigue (60.3-72%) 2. Beathlessness (42.6-65.6%) 3. Psychological distress (23.5-46.9%)
Salmon-Ceron D, et al, 2021 [22]	Cross sectional	Paris, France	70	23-75	1. Neurological (neuro-cognitive,headache,sensory disturbance) (77.1%) 2. General (fatigue, asthenia) (72.9%) 3. Cardiothoracic (chest pain, palpitations, cough, dyspnea) (71.4%)
Daher A, et al, 2020 [23]	Prospective cohort study	Aachen, Germany	33	61-67	1. Fatigue, tiredness (45%) 2. Dyspnea (33%) 3. Cough (33%)

Abbreviations/skróty: COVID-19 Coronavirus Disease 2019, et al et alia/i inni, SD standard deviation/odchylenie standardize, UK United Kingdom/Zjednoczone Królestwo, USA United States of America/Stany Zjednoczone Ameryki, PTSD post-traumatic stress disorder/Zespół Stresu Pourazowego

and involves profound deregulation of the central nervous system (CNS), immune system, dysfunction of cellular energy metabolism and ion transport, and cardiovascular anomalies. Consequences are noted in physical and cognitive function abnormalities, which disable the ordinary daily activities of survivors. Even minimal activity causes sudden worsening of the general well-being and deteriorates the quality of life.

In a retrospective cohort study of 75 long-haulers, who complained about new-onset fatigue, muscle weakness, and/or dyspnea 2 months after hospital discharge, the blood serum profile revealed elevated ferritin and CRP levels along with a decrease in hemoglobin and albumin levels [25]. Such evidence reveals the metabolic alterations in post-COVID syndrome triggering the chronic inflammatory state.

As the symptoms of PASC, with fatigue leading, may resemble a chronic fatigue syndrome (CSF), hypotheses linking these two entities were proposed. However, fatigue in PASC represents different features than the one in CSF. Over 50% of the patients did not meet the CSF diagnostic criteria [26]. Neither reduced heart rate variability nor impaired cerebral blood flow, found in CSF patients, were diagnosed in COVID-19 survivors [27]. Anyway emerging studies show that COVID-19 may increase the burden of post-viral CSF, so regular check-ups, especially in the elderly, are essential for prevention and symptom alleviation [28].

Considering fatigue as an energy imbalance and exhaustion of metabolic reserves, it goes along with the theory of frailty syndrome, commonly seen in older people. Consequently, in the future, an overlap of these two entities can cause a high prevalence of frailty in COVID-19 survivors.

Management of long COVID syndrome

Numerous experts discuss the topic of the timing of follow-up in COVID-19 survivors, the type of analysis to perform, or the therapies, [29-31]. but a consensus with clear recommendations has not been reached yet. The constantly increasing number of long haulers creates an urgent need for new, standardized guidelines for screening and testing. Due to the involvement of diverse systems of the human body, a multidisciplinary collaboration plays a key role and the individualization of the treatment strategy is essential. Regular check-ups, rehabilitation, adequate alimentation, and psychological support build a picture of the early, holistic management of the long-haulers. That may help to prevent or, at least, reduce the long-lasting effects. A basic follow-up may consist of some screening questionnaires (i.e. C19-YRS, Yorkshire Rehabilitation Screen) followed by further personalized investigations, such as imaging (chest x-ray (CXR), CMR) or laboratory tests (clotting profiles, C-reactive protein, d-dimer, renal function test). The Swiss COVID Study Group and Swiss Society for Pulmonology (SSP) formulated a 13-question survey for the diagnosis and treatment of pulmonary insufficiency [32]. This may contribute to the formation of more complex, multi-systemic protocols in the future.

Emerging evidence highlights the multiple benefits of exercise in reducing the long COVID effects, among them pain modulation, stress reduction, cardiovascular function improvement, aging retardation, brain plasticity modulation, and many others, which are being enumerated [33]. Noteworthy, the Geriatric Rehabilitation Special Interest Group of the European Geriatric Medicine Society (EuGMS) proposed guidance for geriatric rehabilitation for post-COVID patients [34]. The document consists of two parts- the general requirements and the specific procedures including patient selection, admission, treatment, discharge, follow-up, and monitoring. In the general part, the authors highlight the importance of the safety of both the patient and the care provider and discuss the optimal care organization. High-quality personal protective equipment (PPE) along with COVID-19 testing plays a key role. Patients being subjected to rehabilitation should not be contagious anymore. Optional equipment use is also discussed. However, the subject needs to be developed in a more profound manner, as studies prove rehabilitation to be superior to its lack considering muscle strength, dyspnea, and health-related quality of life (HRQOL) [35]. Further evidence is necessary to work on the individualization and effectiveness of the regimes. Shall we hope that the Researching COVID to Enhance Recovery (RECOVER) cohort studies [36]. and other emerging ones, that longitudinally evaluate COVID-19 consequences, will provide us with better knowledge of the PASC sequelae and complex, standardized guidelines will be formulated.

Conclusions

COVID-19 is an acute, hyper-inflammatory, multi--systemic disease and often patients are facing its consequences weeks or months after the infection is gone.

The long covid syndrome embraces not only respiratory symptoms but may appear within all human systems. The mechanisms are complicated and the entity of the clinical picture impacts mortality, and morbidity and influences further prognosis notably in older adults, as an especially predisposed population.

With the constantly increasing number of long-COVID patients, the theme needs to be investigated in a more detailed manner in the future. The paucity of tailored studies reporting the incidence, mechanisms, and symptoms is a future direction along with the standardized diagnostic and treatment guidelines which are yet to be established.

Conflict of interest
None

Correspondence address
Justyna Rohun
II Klinika Kardiologii i Elektroterapii Serca,
Gdański Uniwersytet Medyczny
Smoluchowskiego 17, 80-214 Gdańsk, Polska
☎ (+48 58) 584 47 60
justynarohun@gumed.edu.pl

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