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Długoterminowe powikłania infekcji COVID-19 u osób w podeszłym wieku – przegląd piśmiennictwa. Część II. Specyficzne objawy narządowe

Long-term complications of the COVID-19 infection in the elderly – the literature review. Part II. Organ-specific sequelae

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

Streszczenie

Jest to druga część pracy omawiającej długoterminowe powikłania infekcji COVID-19 w populacji geriatrycznej. Przed lekturą, ku lepszemu zrozumieniu tematu, autorzy zachęcają do zapoznania się z poprzednią częścią, w której opisano patofizjologię choroby, objawy ogólne, potencjalne strategie diagnostyczno-terapeutyczne oraz podsumowano przeprowadzone dotychczas badania kliniczne wśród osób starszych. Druga część poświęcona jest szczegółowemu omówieniu powikłań specyficznych narządowo w nowej jednostce klinicznej zwanej „long COVID" lub „post-acute sequelae of SARS-CoV-2 (PASC)", obejmującej objawy utrzymujące się tygodniami po zakończonym zakażeniu. Opisujemy, między innymi, komplikacje płucne, sercowo-naczyniowe, immunologiczne, dysfunkcję autonomicznego układu nerwowego. Omawiamy mechanizmy zjawisk, wynikające z tego zagrożenia kliniczne i ich znaczenie u osób w podeszłym wieku. *Geriatria 2022;16:141-148. doi: 10.53139/G.20221621*

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

Abstract

This is the second part of the review detailing long-term complications of COVID-19 disease in the geriatric population. Before reading, for better understanding, the authors recommend taking a thorough look at the previous paper, where pathophysiology, general symptoms, and potential diagnostic and therapeutic strategies are discussed along with a review of the current studies on the elderly. In this part, we present organ-specific sequela in a new clinical entity called „long COVID" lub „post-acute sequelae of SARS-CoV-2 (PASC)". It includes various symptoms persisting weeks after the infection withdrew. Pulmonary, cardiovascular, immunological, and autonomic dysfunction sequela are characterized. We describe the mechanisms, subsequent clinical risks, and their consequences in older adults. *Geriatria 2022;16:141-148. doi: 10.53139/G.20221621*

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

Introduction

COVID-19 disease, caused by SARS-CoV-2 infection, is characterized by a highly contagious hyperacute inflammatory state, primarily associated with severe pneumonia, resulting in significant morbidity and mortality worldwide. In March 2020 WHO declared it a world pandemic and its consequences are being faced around the globe until now.

The disease's course is unpredictable and may provoke symptoms from all human body systems. In the majority, the infection lasts around 10 days and withdraws spontaneously. Noteworthy, emerging data suggest that in some patients the symptoms persist weeks after the infection is gone or new complications appear. COVID-19 survivors frequently complain about fatigue, weakness, cough, continuous dyspnea, etc. [1]. This phenomenon, described as a "long COVID" or "post-COVID-19 syndrome" or "post-acute sequelae of SARS-CoV-2 (PASC)", is a collective term for all post-infectious, ongoing manifestations, attrib-

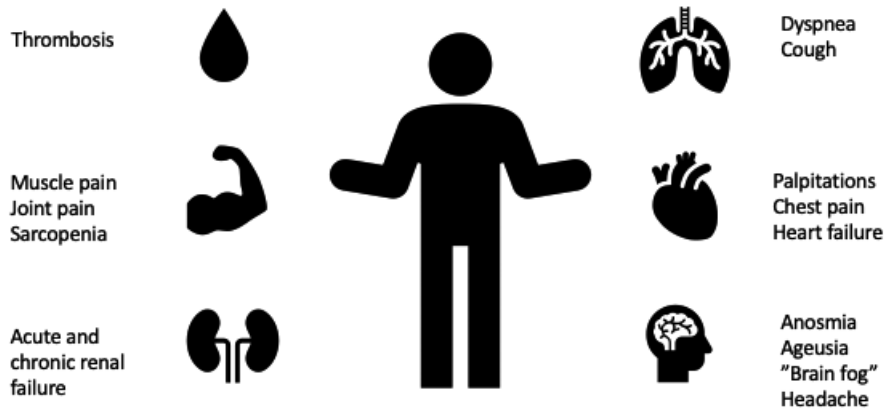

Figure 1. Organ-specific symptoms in long COVID-19 syndrome

uted to various organs (figure 1) and affecting patients' everyday routine.

In this review, we would like to discuss the specific post-COVID sequelae in pulmonary, cardiovascular, nervous, hematological, immune, and renal systems. We systematically searched the literature to provide the most recent information on the prevalence, symptoms, and potential diagnostic and therapeutic strategies, notably in the geriatric population.

Methods

We systematically searched PubMed for the literature, clinical trials, and databases published in English from 2020 to July 2022 with the search terms „long COVID" ‚post-COVID-19" „PASC" combined with "pulmonary", "cardiovascular", "immune", "renal", "autonomic", "nervous", "hematological". Mostly cross-sectional studies, retrospective cohort studies, and case reports were found. The final list of references was chosen subjectively for its applicability to the theme.

Pulmonary complications

The initial, most frequent manifestation of acute COVID-19 is pneumonia. It may have a mild course or progress into severe inflammation resulting in adult respiratory distress syndrome (ARDS), requiring ventilation support. As described in part I of this review, the prevalence and mortality rates are notably high in older adults. They are reported to have an outstandingly unfavorable outcome, probably due to underlying co-morbidities or weak self-protection awareness. Around 10% of frail patients with coexisting diseases develop a severe course of infection with dyspnea and hypoxemia, while 5% developed a critical condition with respiratory failure [2].

ARDS is a clinical entity characterized by severe hypoxemia, pulmonary edema, and, consequently, pulmonary fibrosis. In response to the mechanical ventilation, there is a release of pro-inflammatory cytokines, which interrupt the cellular barrier and lead to non-cardiogenic pulmonary edema, respiratory failure, and, in a further stage, irreversible fibrosis. The geriatric population, as susceptible to an acute COVID-19 course and its complications, is prone to develop ARDS and post-covid idiopathic pulmonary fibrosis (IPF), further on. IPF is a progressive, interstitial lung disease where an excessive extracellular matrix is deposited within the lung parenchyma causing subsequent destruction of physiological pulmonary structure and leading to pulmonary failure. Emerging evidence suggests a rising incidence of IPF as a COVID-19 complication, especially in the elderly. The most recent meta-analysis estimate that about 44.9% of COVID-19 survivors develop pulmonary fibrosis [1]. The group at the highest risk are the older adults, notably those admitted to ICU and requiring ventilation support. Subjectively patients experience persistent fatigue (80%), myalgia (58.3%), dyspnea (50%) or chest pain (30.5%).

For early detection, the current British Thoracic Society (BTS) guidelines suggest performing chest X-Ray (CXR) on COVID-19 survivors. A follow-up imaging should be done at 4-6 weeks after the discharge for the patients suffering from severe pneumonia, and at 12 weeks for the others. The protocol includes other

studies, such as high resolution computed tomography, pulmonary function test, 6-minute walk test, echocardiography, or sputum for microbiology, in case of inconclusive results [3].

The specific treatment remains a future direction. Some physicians use corticosteroids to improve lung function. Two approved anti-fibrotic drugs (nintedanib and pirfenidone) are being compared for their efficacy and safety in pulmonary fibrosis in an ongoing trial (Pirfenidone vs. Nintedanib for Fibrotic Lung Disease After Coronavirus Disease-19 Pneumonia (PINCER)), [4]. but further research is required. However, experts suggest starting the therapy early to prevent lung function decline. Last-line management for the end-stage disease includes lung transplantation.

An increasing number of reports describe the persistent cough as a frequent post-COVID sequela [5]. UK Office for National Statistics COVID-19 Infection Survey reported it as the second most common symptom after the infection (11.4%), preceded by fatigue [6]. There is a paucity of longitudinal studies on the general population, but the estimated prevalence was 7-10% [5]. So far, little is known and the mechanism remains unclear. The neuroinflammatory and neuroimmune process of vagal sensory neurons by the SARS-CoV-2 was hypothesized, but for better understanding more evidence should be established. Along with the other post-COVID syndrome symptoms, it may depicture a central sensitization process, however, the differential diagnosis is crucial. In clinical management, it is essential to exclude any pathologies damaging the lung parenchyma so that patients benefit from the therapy, possibly with neuromodulators or anti-inflammatory drugs.

A new-onset or persistent dyspnea in COVID-19 survivors should always prompt the physician to further diagnosis, as pulmonary embolism, along with other thromboembolic events, is frequent in both COVID-19 infection and long COVID syndrome. The complication is reported to occur more commonly in patients with higher (III and IV) NYHA class [7]. and other comorbidities, most of which are the elderly people. Moreover, the risks were increasing over time. In the first week after the infection, the incidence rate ratio was 36.17%, and 46.40% during the second week [8]. As a hematological sequela, the mechanism, incidence, and symptoms are detailed more profoundly in an appropriate chapter of the review.

Among others, less common complications, cavitary lesions, small airway disease, and the development of pulmonary hypertension are also mentioned to occur [5].

In the long-haulers follow-up, clinical, physiological, and radiological monitoring is recommended in terms of pulmonary sequelae. Despite the irreversibility of the condition and lack of specific treatment, with a prompt diagnosis and rehabilitation, the patient's general well-being and life quality can improve.

Cardiovascular complications

Even though there are many reports of cardiovascular involvement in the acute phase of COVID-19, only a few studies were conducted to analyze the post-COVID symptoms within this system. Previous cardiovascular diseases (CVD), frequent in elderly people, are reported to expose the patients to a severe COVID-19 course and negatively affect the prognosis [2]. On the other hand, the infection can also exacerbate the antecedent myocardial dysfunction.

The risk factor for the post-covid sequelae may be the initial COVID-19 infection severity. The incidence of cardiac complications, such as arrhythmia or cardiac arrests, was higher in the patients admitted to the Intensive Care Unit (ICU), among whose the majority were the elderly [9]. Nevertheless, even a mild, asymptomatic infection can result in myocarditis after recovery even in the absence of laboratory markers of left ventricular dysfunction. In the cohort study of COVID-19 survivors in Germany, cardiovascular magnetic resonance (CMR) revealed heart involvement in 78% of patients and 60% of them had ongoing inflammation regardless of any other conditions [10]. Another cross-sectional study conducted on healthcare workers revealed a 26% incidence of myocarditis and CMR abnormalities were seen in 75% [11].

The condition's pathophysiology does not remain clear and is yet to be investigated. Some authors suggest that the SARS-CoV-2 directly invades cardiomyocytes by ACE2 causing cell death, complement activation, hypercoagulation, and, as in the lung tissue, subsequent fibrosis. Another theory implies the effect of systemic inflammation on the heart. Regardless, all result in endothelial damage and subsequent myocardial injury presenting clinically as myocarditis, heart failure, or cardiogenic shock.

Authors of one cohort study categorized the cardiovascular post-COVID sequelae into ischemic

and non-ischemic heart disease, dysrhythmias, and others (i.e. myocarditis, pericarditis) and claimed the 12-month risk of its development as substantial [9]. The exact extent of cardiovascular involvement in post-COVID-19 varies and the data is missing. In one cohort study, the incidence of any cardiovascular outcome was estimated at 45.29% [12]. A recent study of 124 elderly COVID-19 patients demonstrated that 32 had cardiovascular complications (26%) with new-onset atrial fibrillation (AF) as the most common [13]. Also, one retrospective analysis of 808 inpatients aged >60 years demonstrated a 21.8% incidence of AF. Age correlated with a higher CHA2DS2-VASc score and a likelihood to present comorbidities [14]. Nonetheless, for more credible data more tailored studies need to be conducted.

Some conditions, like heart failure (HF), seem to be likely to occur as a long-COVID syndrome manifestation but there are no reports of the onset of *de novo* HF. However, in the literature, cases of chronic HF clinical deterioration after the recovery of COVID-19 were detailed [15].

Occasionally pulmonary embolism, stress cardiomyopathy, and arterial thromboses were described. [12,15,16].

Diagnosing the myocardial damage includes laboratory findings (elevated cardiac enzymes) electrocardiocardiographic changes (ST-segment and T wave alterations), and echocardiographic abnormalities. Emerging data highlight the importance of CMR as it provides a detailed image of a disease's course and extent of cardiac involvement. Moreover, it can help to classify the severity of the symptoms [10,11]. There is a need for more evidence as no designed studies were conducted so far. A potential role of cardiac positron emission tomography (PET) replacing CMR to detect subacute or chronic inflammatory changes was also suggested.

Autonomic dysfunction

According to the current evidence, the long COVID syndrome involves symptoms of autonomic nervous system deregulation. The first hypothesis was presented in 2003 during the SARS outbreak when 50% of recovered patients were documented with autonomic dysfunction. Some authors link the condition with postural orthostatic tachycardia syndrome (POTS), as symptoms in PASC-associated dysautonomia may include those of orthostatic intolerance. In 2021 the American Autonomic Society (AAS) stated that the PASC may overlap with POTS [17].

Although the incidence of PASC-dysautonomia is most prominent in females with a median age of 50, the first cases of autonomic nervous system deregulation in COVID-19 were described in the elderly. It always should be kept in the physician's mind during the differential diagnosis and follow-ups as the incidence is rising.

The mechanisms associated with PASC-associated dysautonomia are complex. The major role is contributed to the autoimmunity reactions. Like in POTS, the virus triggers the immune system by either cytokine-storm inflammation or autoantibodies creation targeting directly against the autonomic system. Hypovolemia decreasing the blood volume and increasing heart rate, extracardiac postganglionic SNS neuron destruction, and alterations of brainstem medullary centers by direct invasion were also proposed.

The first signs of autonomic imbalance may appear during the acute phase of illness or complicate the convalescence occurring as a long-COVID sequela. Reports show that in PASC-associated dysautonomia, patients experience syncopes, dizziness, headache, tachycardia, fatigue, or somatic anxiety. Palpitations prevalence range varied in different countries and was up to 80% of survivors [18].

Management of POTS-related syndrome in long COVID seems challenging due to the heterogeneity of the clinical presentations. Treatment of symptomatic PASC-dysautonomia may be either pharmacological or non-pharmacological, but the tailored, specific therapy is to be investigated. The non-pharmacological methods, such as proper education and measures against orthostatic intolerance (physical reconditioning, adequate water and salt intake, proper sleeping position, physical maneuvers), are the first-line treatment. Pharmacological measures should be reserved for the second-line therapy as a complementary method. The management should be individualized considering the patient's clinical profile. Drugs include volume expanders, antiarrhythmics, vasoconstrictors, sympatholytics, and, occasionally, IVIG for patients presenting an autoimmune profile.

Nervous system disturbances

Even though COVID-19 was considered initially a severe pulmonary infection, it presents with an increasing number of neurologic manifestations that

may persist, especially in older people. Researches prove that the SARS-CoV-2 virus is able to enter the central nervous system (CNS) either by olfactory bulb through glial cells, causing inflammation, or through invasion of the endothelial cells (a hematogenous mechanism). However, the exact mechanisms are yet to be established. Some authors suggest the role of the immune system i.e. in post-COVID Guillain–Barré syndrome (GBS). It presents as a sensorimotor dysfunction with ascending weakness, loss of tendon reflexes, and sensory deficits. After intravenous immunoglobulins (IVIG) administration clinical improvement was observed [19]. Likewise, in the new emerging entity called "Post Covid-19 Neurological Syndrome (PCNS)" the altered immunological response background has been suggested. Signs include myopathy in the form of prolonged muscle weakness. Little is known and the disease is described to be a new neurologic challenge [20].

The exact incidence of post-COVID neurological sequelae remains unknown. Retrospective analysis of 1760 COVID patients shows that 38.7% suffered cerebrovascular disease, 35.8% - altered mental status, and 22.6% - had peripheral nervous system diseases [21]. Another study demonstrates that 28% and 34% of the patients suffered anosmia or ageusia, respectively, after the recovery [22]. Also, sleep disorders, headache, or subjective cognitive impairment ("brain fog") were observed. Thus, the clinical picture of long covid may resemble other diseases like myalgic encephalomyelitis or chronic fatigue syndrome, which postpone the proper diagnosis and deteriorate the patient's life quality.

Hematological complications

COVID-19 is likely to provoke thromboembolic complications, both venous and arterial. Deregulation of coagulation processes (imbalance of pro- and anticoagulation factors) results in the creation of microthrombi, thrombocytopenia, and, often, DIC. Almost 58% of the COVID-19 deaths were due to pulmonary embolism or venous thrombosis, and 70% were due to DIC [23]. Inflammation, hypoxia, and immobilization, all observed in critically ill (i.e. ICU) patients, of which the majority were older people, contribute to the thrombotic risk and coagulopathy development. According to one study, 31% incidence of thrombotic complications was reported in ICU patients at the median age of 64 [24].

The underlying mechanism of the thrombotic complications in post-COVID is a persistent vascular injury that activates the coagulant cascade and abovementioned micro thrombosis, which lead to functional impairment of numerous organs and systems of the human body. The formatted micro clots in the post-COVID period are described to be anomalous and resistant to fibrinolysis [25]. This phenomenon is described as a thrombotic sequela. Thus, the long COVID syndrome may present with a cerebral vascular accident (CVA), myocardial infarction (MI) or pulmonary embolism, alterations of behavior and emotion, and many more. Late-onset thrombocytopenia, autoimmune thrombocytopenic purpura (ITP), and hemorrhagic incidents were rarely described.

As a laboratory index increased D-dimers were observed in almost all of the patients after the discharge and their level corresponded with the severity of the disease, unfavorable prognosis, and higher mortality rate. It was more common in patients aged over 50 years [26].

According to reports, even though there is no effective treatment for long COVID, clotting pathologies may benefit from early anticoagulation therapy. Thrombosis, caused by systemic inflammation, is considered to play a key role in the pathophysiology of long COVID. Thus, early prophylactic can reduce the thrombotic consequences and improve the outcomes [27].

Immune system deregulation

As already described in the first part of the review, inflammation resulting in cytokine storm is supposed to be the principal mechanism of the acute phase of COVID-19. It leads to systemic impairment and consequent acute organ dysfunction. Otherwise, in post-COVID, the emerging data highlights the role of autoantibodies, the rogue antibodies, that surge during or after the infection, attack immune system elements, and, accumulated in large amounts, lead to persistent damage [28]. The mechanisms of its formation include the hyperstimulation of the immune system by SARS-CoV-2 and the molecular mimicry phenomenon, which is homology between the elements of the human body elements and the virus'. Also, the use of immunosuppressive drugs may play a role.

In a six-month follow-up, seven out of the 17 autoantibodies tested were elevated in inpatient or outpatient SARS-CoV-2 patients. The found molecules

were the ones related to connective tissue diseases, i.e. autoantibodies against anti-alanyl-transfer ribonucleic acid (tRNA) synthetase (PL-12), Ku, anti-topoisomerase (Scl-70), β-2-glycoprotein, proteinase 3, ribonucleoprotein (RNP)/anti-Smith (Sm), and sjögren syndrome type B (SSB/La) [29]. Another study reports the development of over 15 separate types of autoantibodies along with above 10 distinct autoimmune diseases in COVID-19 survivors [30]. Autoantibodies against molecules of the immune system, including interferon responses, leukocyte trafficking, and lymphocyte function were found as well.

SARS-CoV-2 seems to provoke profound, persisting abnormalities in numerous immune cells. In the follow-ups, some immune cells, like T cells, were still showing anomalies while others, like B cells, recovered, but the function of both was still altered. Consequently, the long-term immunity may be affected and these changes may promote other systemic consequences in the long COVID syndrome [31].

Immunosenescence is a gradual dysfunction of the immune system that advances with age. The process includes remodeling of lymphoid organs and impairment of the number and function of immune cells, which lead to the development of infections, autoimmune diseases, and malignant tumors. SARS-CoV-2 is believed to aggravate the immunosenescence and, subsequently, put the elderly at the highest risk of developing the post-COVID sequela.

Renal complications

COVID-19 is likely to provoke renal complications because of the high expression of ACE2 in the kidneys. The prevalence rate of acute kidney injury (AKI) ranges by country (from 0.5% in China to 80% in France) and severity of illness (10% among the admitted patients, 26-45% in the ICU subgroup) [32]. ARDS, need for mechanical ventilation and severe course were associated with lower chances of AKI recovery. The population of elderly people admitted to hospital with COVID-19 had a higher incidence of AKI, as reduced baseline kidney function reduction is considered a risk factor for the development of renal insufficiency [33]. Among survivors, less than 1% were reported with AKI and 1.4% continued with the diagnosis on the follow-up date [34]. At 12-month follow-up, 26% of the COVID-19-positive patients had an incident or progression of kidney failure. Thus, AKI coexisting with COVID-19 is considered a negative prognostic factor with lower recovery and higher mortality [35]. 60% of the discharged patients restored renal function [34]. Kidney involvement may persist for many months with a subclinical course and lead to progressive kidney failure or deteriorate the pre-infectious chronic kidney disease (CKD). Current evidence highlights the importance of vaccination in elderly people with co-existing kidney disease, as it is a unique strategy to avoid further renal complications [36].

Musculoskeletal complications

Musculoskeletal pain is one of the most common symptoms in both acute COVID-19 infection and long COVID syndrome. SARS-CoV-2 by provoking high-catabolism status exerts changes in the amount, structure, and function of skeletal muscles. Further on, the bed regimen, reduction of physical activity, and decreased alimentation may lead to sarcopenia and impact the physical deterioration and patients' prognosis. Reports show that the survivors frequently suffer from myalgias, joint pain, fatigue, and exercise intolerance. Advanced age, along with smoking, were considered risk factors for arthralgia in one retrospective cohort study [36]. The prevalence of arthritis was 37%.

For now, there is a paucity of data describing the exact mechanism and incidence. One prospective, longitudinal study is designed to explore the etiology, mechanism, and evolution of muscle pain in long COVID. The estimated completion date is December 2024 [37]. Current evidence show increased levels of inflammatory markers (CRP, ESR), suggesting a hyper--inflammatory background [37,38]. Noteworthy, viral, i.e. respiratory tract or gastrointestinal (GI), infections are a common cause of new-onset rheumatoid arthritis. A growing body of evidence reports COVID-19 to cause post-infectious new-onset inflammatory arthritis [39]. Also increased interleukin 6 (IL-6) levels, commonly linked with pulmonary lesions in post-COVID, have been proposed to have a predictive role in the prevalence of arthritis [40]. Notwithstanding, more designed studies are required for better understanding.

Conclusions

COVID-19 has an unpredictable course and the survivors are facing its consequences weeks after the disease is gone. The long COVID syndrome is a new clinical entity and embraces the post-infectious complications within all human body systems. Pulmonary,

cardiovascular, nervous, renal, musculoskeletal, etc. sequela are commonly reported, especially in older adults, as a highly predisposed population.

The mechanisms are complicated and still need to be investigated in a more profound manner for a better understanding of the clinical picture. Likewise, specific diagnostic and treatment protocols are missing. All of the above make the diagnostic process complicated and increase the risk of misdiagnoses. With an increasing number of long-haulers, it should always be kept in physician's mind and prompt further investigation.

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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