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THE LONG COVID PHENOMENON: A LITERATURE REVIEW OF THE CLINICAL AND PHYSIOPATHOLOGICAL IMPLICATIONS OF POST COVID SYNDROME

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Abstract: Goal: To explore the relationship between the SARS-CoV-2 virus and Post-COVID Syndrome. Review and synthesize the available scientific evidence, investigating relevant studies that suggest an association between the virus and the development of the syndrome. **Methods:** This is a narrative literature review. Searches were carried out in the PubMed database, using the descriptors: "Long COVID" AND "pathophysiology" OR "diagnosis" OR "Treatment" OR "management". 5558 articles were found, of which 31 were used as a data source. **Discussion:** Studies point to a strong relationship between SARS-CoV-2 infections and the development of Long COVID, manifested by the persistence of symptoms such as fatigue (37%), mental confusion (32%), memory-related problems (28%), attention disorders (22%), myalgia (28%), anosmia (12%) and headache (15%). **Final considerations:** Rehabilitation and specific treatment are necessary according to the individual's needs, and a comprehensive, patient-centered multidisciplinary assessment is essential in order to identify the signs and symptoms that must be treated early. Furthermore, as important as post-COVID rehabilitation is the prevention of this syndrome, which undoubtedly involves preventing the SARS-CoV-2 infection itself, for which there are vaccines as primary prevention methods, as well as hygiene measures. guys.
Keywords: SARS-CoV-2, Post-COVID Syndrome, Long Covid-19.

INTRODUCTION

Post-COVID-19 Syndrome, also known as Long COVID-19, emerges as a multifaceted medical condition, manifesting itself through a diverse spectrum of symptoms that encompass multiple systems of the human body (ORONSKY B. et al.,2023). The persistence of these symptoms can vary in

terms of intensity, from mild manifestations to chronic complications, including pulmonary, cardiac and vascular fibrosis (YING D. U. et al., 2022). The heterogeneity of post-COVID-19 sequelae is evident considerably among patients, still lacking a consensual characterization. Commonly reported symptoms include fatigue, dyspnea, myalgia, mood changes, alopecia, and anosmia (ORONSKY B. et al.,2023).

Understanding the pathophysiological mechanisms underlying COVID-19 and Post-COVID-19 Syndrome remains partial, given the recent emergence of this pathology and the resulting unknowns that surround it. The clinical management of Long COVID-19 represents a challenge, with the therapeutic approach predominantly oriented towards symptomatic relief (LAI C.C. et al., 2022). Research into the applicability of antiretrovirals is ongoing and, to date, a definitive recommendation for their use has not been established.

There is a greater predisposition to contagion in males and older people. However, Post-COVID-19 Syndrome demonstrates a notable prevalence in young women, adding complexity to the analysis of this condition (NAJAFI M. B.; JAVANMARD S. H., 2023).

The present review aims to provide a comprehensive analysis of the clinical and pathophysiological implications associated with Long COVID-19. This objective unfolds into secondary goals, including: quantifying the prevalence of Long COVID-19; the identification of the predominant and most debilitating symptoms; the exploration of the pathophysiological mechanisms involved; assessing the impact of this syndrome on patients' quality of life; and a critical analysis of current and emerging therapeutic strategies. This way, this review aspires to contribute to the elucidation and effective management of Post-COVID-19 Syndrome, filling gaps in current scientific knowledge.

METHODOLOGY

This is a narrative bibliographic review developed in accordance with the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome, used to prepare the research through its guiding question: "What are the clinical implications and pathophysiological aspects of post-COVID syndrome in patients who have recovered from an acute SARS-CoV-2 infection, and how do these implications affect the quality of life and long-term prognosis of affected patients?" In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients who have recovered from an acute SARS-CoV-2 infection and present persistent symptoms or new symptoms after recovery, the variables include the clinical manifestations and pathophysiological mechanisms associated with post-COVID syndrome and the outcome encompasses the assessment of quality of life and long-term prognosis of patients affected by this syndrome.

The searches were carried out by searching the PubMed Central (PMC) database. The search terms were used in combination with the Boolean term "AND" and "OR": "COVID-19 Long"; "Pathophysiology"; "Diagnosis"; "Treatment"; "Management". From this search, 5558 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese or Spanish published between 2022 and 2023 and that addressed the themes proposed for this research, review and meta-analysis studies, observational studies and made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. A total of 31

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articles were selected to compose the present study.

DISCUSSION

Post-COVID-19 Syndrome occurs in around 10% of patients affected by the SARS-CoV-2 virus. This condition is characterized by the persistence of more than 200 distinct symptoms, which affect a variety of organ systems (DAVIS H. E. et al., 2023). Currently, there is a divergence regarding the exact definition of the symptoms that make up this syndrome, however, long-lasting heterogeneous symptoms are observed that have a negative impact on multiple organs (DEPACE N. L.; COLOMBO J., 2022). Risk factors identified for the development of this disease include female sex, advancing age, high body mass index, insulin resistance, diabetes mellitus and history of previous hospitalization for Covid (LENG A. et al., 2023) (DEPACE N. L.; COLOMBO J., 2022) (PATEL M.A. et al., 2022).

There is still no definitive hypothesis explaining its pathophysiology, but some suggest the persistence of the SARS-CoV-2 virus in tissues, immunological dysregulation, pathological reactivation or development of autoimmune diseases. Davis H.E. et al. (2023) point out that T cells can undergo changes, such as exhaustion and reduction, with a decrease in CD4+ and CD8+ that can last for up to 13 months, along with changes in PD1 proteins. Such immunological changes can increase autoantibodies to ACE2, increasing the chance of reinfection and influencing the severity of the disease.

According to the clinical trial conducted by Al-Hakeim H. K. et al. (2023), the majority of affected individuals present one or more physical and mental symptoms. The most prevalent symptoms within three months of infection include fatigue (37%), mental confusion (32%), memory problems (28%), attention disorders (22%), myalgia (28%), anosmia (12%), dysgeusia (10%) and headache (15%) (LENG A. et al., 2023). Motor disorders and ataxia represent less frequent symptoms. Symptoms such as fatigue, chest pain, dyspnea and difficulty concentrating persist for more than three months in some patients and, in extreme cases, can last for more than a year (LENG A. et al., 2023) (NATARAJAN A. et al., 2023). There may also be an increase in peripheral insulin resistance and a decrease in insulin production by pancreatic beta cells (BATIHA G.E. et al., 2022).

In the clinical trial carried out by Al-Hakeim H. K. et al. (2023), using properly diagnosed patients, it was discovered that long COVID-19 is associated with a decrease in antioxidants and the stabilization of inflammatory processes, which decreases O2 saturation and increases oxidative stress and body temperature. Long COVID-19 is characterized by two or more physical and/or mental symptoms, such as dyspnea, fatigue, post-traumatic stress, concentration and memory problems, including anxiety and depression. Among those infected, 74%-87% may present somatic symptoms and generalized muscle pain (AL-HAKEIM H.K. et al., 2023).

According to Natarajan A. et al. (2023), long COVID-19 presents multiple symptoms, without determined patterns, similar to some viral diseases. Their meta-analysis study highlights the relationship between the most prevalent symptoms and the impacted systems: in the neurological system, the main symptoms are headache, anosmia and cognitive impairment; in the cardiopulmonary system, chest pain, dry cough, dyspnea and palpitations are more frequent; in the gastroenteric system, abdominal pain and diarrhea are common, while in mental health, depression and anxiety are the most frequent findings, in line with the studies presented by

Al-Hakeim H. K. et al. (2023).

These symptoms occur due to increased inflammation in conjunction with a state of hypercoagulability, affecting all organic systems of the body and generating symptoms in multiple organs (DEPACE N. L.; COLOMBO J., 2022). As cited by Low R. N. et al. (2023), this process intensifies coagulation through the release of pro-inflammatory cytokines associated with endothelial injury, increasing the propensity for thrombosis. The gastrointestinal tract is affected in approximately 84% of patients, due to prolonged intestinal inflammation associated with dysbiosis, which can affect organs such as the liver, brain and lungs, through complex regulatory axes. Visual complications originate from the production of inflammatory cytokines by mast cells, resulting in conjunctival hyperemia and chemosis (BATIHA G.E. et al., 2022) (LOW R. N. et al., 2023). Additionally, the inflammatory process affects multiple peripheral nerves and cranial nerves, generating neuroinflammation that culminates in neurocognitive impairment (CASTANARES-ZAPATERO D. et al., 2023) (LOW R. N. et al., 2023).

Cytokine Release Syndrome (CRS) presents 4 degrees of manifestation, which according to the COVID-19 infection, and can manifest itself in all degrees in the body, with 4 being the most serious, which continues with dyspnea and the need for mechanical ventilation.

The product of the cytokine cascade results from an autoimmune inflammatory reaction, being the most harmful of the damages caused directly by SARS-CoV-2.

Pre-existing comorbidities, such as obesity, diabetes mellitus, systemic arterial hypertension, or even aging, favor higher levels of circulating cytokines, resulting in a worse prognosis (LAY Y. J. et al., 2023).

Initially, a dysregulated immune response occurs, with polarization between a reparative or anti-inflammatory Macrophagic (M2) state and a pro-inflammatory Macrophagic (M1) state, favoring the release of pro-inflammatory cytokines. Thus, Resident Brain Macrophage Activation Syndrome occurs, as when responding to different environments, they acquire different functional phenotypes, similar to what occurs in lupus erythematosus and juvenile rheumatoid arthritis, for example.

Associated with the decrease in the function of Natural Killer (NK) cells and cytolytic CD8 T cells, this process prolongs and amplifies the inflammatory response, which can lead to potentially fatal inflammation. However, with aging, chronic infection or stress, these resident brain macrophages can become dysfunctional so that they become hyper-reactive to signals from the peripheral immune system, producing an exaggerated and prolonged central cytokine response. This set of macrophages, known as microglia, becomes resistant to normal regulation, unable to revert to a quiescent state after the resolution of inflammation, implicating the pathophysiology of numerous neurodegenerative disorders (LAY Y. J. et al., 2023).

Many neurological symptoms of long COVID, such as fatigue, malaise, fever, dyspnea, "brain fog" (changes in neurotransmission that lead to depression, anxiety, mental slowness, difficulty concentrating, memory loss, dizziness and imbalance), are mediated by the Central Nervous System (CNS), explaining the persistent and recurrent course of these symptoms. This process occurs due to two pathways: the first through neuroinflammation, triggered by direct infection of the CNS or signals from the peripheral immune system, and the second due to the modulation of CNS function by a persistently activated peripheral immune system (LAY Y. J. et al., 2023). The virus can be transported throughout the body in

different ways, and when transport occurs along the cranial and peripheral motor, sensory or autonomic nerves, when it enters the nerve endings it is actively transported within the neurons to the brain, finally crossing the barrier blood-brain disease resulting in neuroinvasion, which triggers neuroinflammation, a chronic immune response in the brain that involves long-term activation of microglia, local release of inflammatory cytokines and resulting oxidative stress, altering CNS function and producing symptoms of Long COVID-19. The cytokines released peripherally will act in the brain through two communication routes: the first via the neural route, carried out by the primary afferent neurons that innervate the infected region, and the second is via the humoral route, in which the peripheral cytokines stimulate the immune cells of the brain to produce pro-inflammatory cytokines (LAY Y. J. et al., 2023).

The systemic consequences of COVID-19 Longa include neuropsychological, neuro-sensory, gastrointestinal, cardiac, rheumatological and platelet changes. Cytokines affect the synthesis, secretion and reuptake of several central neurotransmitters, such as norepinephrine, dopamine, glutamate, serotonin, GABA and acetylcholine, as well as the expression of several neuropeptides in different regions of the brain.

Recently, it was demonstrated that IL-6 mediates the neuropsychiatric symptoms of COVID-19, and that, associated with post-exertional malaise or worsening of post-exertional symptoms, symptoms worsen or recur after physical or mental activity, this being one of the most notable and demoralizing symptoms of Long COVID-19, reported by most patients, usually triggered by social, psychological or mental stress. Within this process, the access of the virus to the brain stem and olfactory cortex occurs through the travel of the virus through multiple peripheral and cranial nerves, which also explains the channeling of the virus within the nervous and sensory system, leading to symptoms of forgetfulness, decreased of smell, conjunctival chemosis, among others (LAY Y. J. et al., 2023). Furthermore, various brain damages can occur, such as encephalitis, Guillian Barré Syndrome and cognitive-mental disorders (ESPÍN E. et al., 2023), which can also be called Myalgic Encephalomyelitis or Chronic Fatigue Syndrome (BATIHA G. E-S., et al., 2022), due to persistent inflammation of neural tissue, resulting in sensory dysautonomia that leads to neurocognitive impairment (ESPÍN E. et al., 2023). This dysautonomia is the result of systemic fatigue developed from the constant exposure of autoantibodies against adrenergic and muscarinic receptors. This production of autoantibodies can also lead to endocrinopathies, as autoantibodies can harm gangliosides, 5-hydroxytryptamine and phospholipids (BATIHA G. E-S. et al., 2022).

Consequently, in addition to the neurological symptoms of Long COVID-19, there are many reports from patients about gastrointestinal symptoms, which occur due to the deregulatory action of cytokines on the intestinal microbiota, altering the microbiome and leading to dysbiosis, resulting in changes in intestinal permeability. which allow bacteria to enter the bloodstream from the weakened intestinal wall. Furthermore, psychiatric symptoms, neurodegenerative diseases and even cognition can be affected by the microbiota-gut-brain axis, so that persistent inflammation can cause the gut microbiota to communicate with the brain and thus alter cytokines. the maintenance of the blood-brain barrier (LAY Y. J. et al., 2023).

Regarding rheumatological changes, the SAR-CoV-2 virus, when it activates Toll-like receptors and the complement system, leads to inflammation and the formation

of autoantibodies, generating molecular mimicry and viral persistence through polyclonal activation, resulting in pain and joint stiffness, both resulting from immune-mediated injury (LAY Y. J. et al., 2023).

In short, the COVID-19 virus has the ability to bind to platelet receptors, resulting in hyperactivation and greater platelet aggregation. Furthermore, the spike protein present in the virus promotes the release of clotting factors which, associated with intense disseminated inflammation, increase endothelial injury and thrombus formation (LAY Y. J. et al., 2023).

These thrombi can reach the cerebral microvasculature, generating local microthromboses in the brain tissue, a phenomenon that can be exacerbated not only by hypercoagulation, but also by mitochondrial insufficiency, leading to the neurological symptoms already mentioned (ESPÍN E. et al., 2023). Associated with these thrombovascular phenomena, cardiac activity can also be affected in the long term, including conditions such as fibrosis or heart failure, sinus tachycardia and postural orthostatic tachycardia syndrome (POTS) (BATIHA G. E-S. et al., 2022). Microvascular disorders can also lead to myocardial inflammation, affecting myocardial contractility and vascularization, due to damage to cardiomyocytes (ESPÍN E. et al., 2023).

The consequences on the respiratory system are attributed not only to COVID-19 infection in lung tissue, but also to the inflammatory cascade of cytokines, which results in reduced endothelial integrity and rupture of pulmonary vessels and alveoli. This process triggers the release of pro-inflammatory cytokines and infiltration of immune cells, predominant in the exudative phase of COVID-19, while in the fibroproliferative phase there is greater deposition of collagen and fibronectin in the alveolar space (BATIHA G. E-S. et al., 2022). In the long term, intense exposure to supplemental oxygen during the acute phase of the disease, in severe cases, can lead to pulmonary fibrosis, due to excess oxygen that favors an increase in oxidative stress, maintaining the inflammatory state and facilitating the activation of pathways fibrotic (ESPÍN E. et al., 2023). According to Castanares-Zapatero D. et al. (2023), the epidemiology of COVID-19 Longa reveals a greater occurrence in female patients, with an older age group and a higher body mass index.

It is important to highlight that patients with neurological and cardiovascular sequelae have demonstrated an increased risk of mortality (LENG A. et al., 2023). Documented sequelae include myocarditis, pericarditis, angina, and arrhythmias. Considering that symptoms can fluctuate, increase or recur over time, there is a continued negative impact on various organs and systems of the body (DEPACE N. L.; COLOMBO J., 2022).

Diagnosis of Long COVID-19 is challenging due to its heterogeneous nature and lack of specific tests. Studies point to a range of persistent symptoms, including fatigue, breathing problems, joint pain and cognitive difficulties. Diagnosis is based on the patient's medical history, duration of symptoms, and exclusion of other medical conditions. Some differential forms are being tested, such as the study of microclots, corneal biomicroscopy to identify small fiber neuropathies and magnetic resonance imaging to detect lung abnormalities (DAVIS H. E. et al., 2023).

The main blood biomarkers indicative of angiogenesis in Long COVID-19 are Angiopoietin-1 (ANG-1) and Selectin-P (P-SEL). ANG–1 is an angiopoietin, that is, a secreted glycoprotein ligand that causes the phosphorylation of the TIE2 tyrosine kinase, expressed only in pericytes and vascular endothelial cells. This marker is significantly elevated in female patients. On the other hand,

P-SEL is a type 1 transmembrane glycoprotein expressed on platelets and endothelial cells; when the endothelium is activated during infection, P-SEL facilitates platelet aggregation (CASTANARES-ZAPATERO D. et al., 2023).

The identification of specific biomarkers, such as changes in mitochondrial function discussed by Chen et al. (2023), may also provide a more objective approach in the future. Several studies in the archive indicate that mitochondrial dysfunction may be a key component in the pathogenesis of Long COVID-19. Changes in mitochondria, which are crucial for cellular energy production, may be related to symptoms such as fatigue and muscle weakness. Biomarkers of mitochondrial dysfunction therefore emerge as potential candidates for the diagnosis and monitoring of Long COVID-19, enabling a more targeted approach to treatment. Research into Long COVID-19 is still in its early stages, and diagnosis remains a challenge. Studies suggest that a multidisciplinary approach, which includes assessment of clinical symptoms, laboratory testing, and assessment of biomarkers such as mitochondrial dysfunction, may be necessary. Recognizing specific symptom patterns and correlating them with underlying physiological changes, as indicated in the articles, will be essential to advance the diagnosis and treatment of Long COVID-19.

Treatment of COVID-19 Longa involves managing a variety of post-viral symptoms. Current approaches include rehabilitation therapies and psychological support. Sebők & Gyires (2023) mention that the use of anti-inflammatories and regulation of the immune system may be emerging strategies. Chen et al. (2023) also suggests that treatments focused on protecting and recovering mitochondrial function may be a promising approach.

Melatonin emerges as a promising alternative in the treatment of Long COVID-19, particularly in cases with symptoms of chronic fatigue and cognitive disorders, such as "brain fog", which encompass failures in attention, short-term memory, working memory, learning and speed of processing. The administration of this hormone aims to minimize bodily damage through its immunomodulatory action, antioxidant activity via glutathione synthesis, and anti-inflammatory effect by suppressing inflammatory cytokines and increasing anti-inflammatory cytokines, in addition to its regulatory function of the circadian cycle (CARDINALI D. P. et al., 2022).

Another therapeutic modality, specifically for chronic fatigue and post-Covid fibromyalgia, is hyperbaric oxygen therapy (HBOT). This approach is based on the hypothesis that chronic inflammation is one of the underlying mechanisms of Long COVID-19, with the administration of 100% oxygen under high pressure in a hyperbaric chamber exerting anti-inflammatory effects, reducing oxidative stress and improving endothelial function (KJELLBERG A. et al., 2022).

A double-blind randomized clinical trial with 26 patients with Long COVID-19, a history of SARS-CoV-2 pneumonia and symptoms of fatigue and exercise intolerance, demonstrated significant improvements in respiratory function after a home-based inspiratory muscle training (IMT) program), suggesting that it is a promising intervention to restore exercise capacity and improve quality of life post-Covid (PALAU P. et al., 2022).

Histamine receptor blockers (H1 and H2), according to a cohort study with 14 patients, were effective in treating some symptoms associated with Long COVID-19, especially those linked to hyperinflammation mediated by mast cell activation (MCA). The 20-day treatment provided considerable

improvements in symptoms such as fatigue, brain fog, tachycardia and abdominal disorders, compared to the control group (SALVUCCI F. et al., 2020).

Rehabilitation for patients with this pathology focuses on improving quality of life and functionality, ranging from physical therapy to nutritional and psychological support. Long COVID-19 manifests itself through varied and persistent symptoms that affect different systems of the body. In general, these symptoms impact the patient's functionality in the physical, psychological and/or social spheres. This way, rehabilitation becomes crucial to improving the individual's quality of life. For rehabilitation to be successful, it is essential to carry out a comprehensive, patient-centered multidisciplinary assessment, with the aim of identifying both the symptoms truly related to post-Covid, and the warning signs that require early intervention to prevent complications. After this assessment, we proceed to planning the rehabilitation strategy appropriate to the patient's clinical situation (CHUANG H.J. et al., 2023).

Previous research has identified that, among the various symptoms associated with Long COVID-19, those that require rehabilitation include: fatigue, exacerbation of post-exertional symptoms, dyspnea, exercise intolerance, orthostatic intolerance, cognitive impairment, anxiety, depression, sleep disorders and arthralgia.

For each of these clinical conditions, the rehabilitation plan can range from changes in diet and behavior—such as adequate fluid intake, salt, avoiding large meals, using compression stockings and avoiding hot environments for patients with orthostatic intolerance—, to therapies psychological and pharmacological, such as in cases of depression, anxiety and cognitive impairment. However, there is a consensus that, regardless of the symptom, the practice of physical exercise, whether aerobic or resistance, is recommended, having demonstrated significant results in groups that participated in effectiveness studies (CHUANG H.J. et al., 2023).

Prevention of COVID-19, including its sequelae, remains centered on vaccination, wearing masks and maintaining good general health. Research by Sebők & Gyires (2023) highlights the importance of prevention, while Chen et al. (2023) suggest that understanding the mitochondrial pathogenesis of Long COVID-19 may open avenues for new preventive strategies. Additionally, studies indicate that the combination of melatonin can enhance protection, due to its cytoprotective, neuroprotective, immunoregulatory and antioxidant properties, which are mediated by the induction of glutathione synthesis. Much research conducted during the pandemic has corroborated the effectiveness of melatonin; however, as it is a non-patentable and low-cost compound, it has not attracted significant interest from the pharmaceutical industry (CARDINALI D.P. et al., 2022).

FINAL CONSIDERATIONS

This study provided an in-depth analysis of long COVID, a complex and debilitating syndrome that results from a chronic inflammatory and autoimmune reaction triggered by the SARS-CoV-2 virus. It is crucial to recognize the variety of persistent symptoms, which can involve more than 200 different manifestations, including everything from chronic asthenia to cognitive and cardiovascular problems. Understanding the underlying pathophysiological mechanisms is essential to advance the treatment and management of this condition. The central role of the inflammatory cytokine cascade in the development of long COVID was highlighted. Furthermore, the study highlighted the

importance of blood biomarkers such as ANG-1 and P-SEL in identifying angiogenic and endothelial processes in the syndrome, essential for early diagnosis and the development of appropriate treatment strategies. Post-COVID syndrome has a profound impact on patients' quality of life, which reinforces the need for multidisciplinary support and rehabilitation approaches. This study highlights the complexity of post-COVID syndrome and its diverse clinical repercussions, highlighting the importance of an effective and personalized therapeutic plan that addresses the particularities of each individual. Finally, the continuous need to expand and update studies on long COVID is highlighted.

This is vital to provide a better quality of life and minimize the risk of complications in patients infected with SARS-CoV-2, highlighting the importance of continued research and innovative therapeutic approaches.

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