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Review

The autonomic aspects of the post-COVID19 syndrome

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ABSTRACT

The SARS-CoV-2 outbreak, responsible for the widespread COVID-19, led to one of the most rogue pandemics in modern time, yet the major effects of the pandemic may still be ahead of us. SARS-CoV-2 had been found to possess autoimmune properties. Close to 20 distinct autoantibodies which target GPCR of the nervous system and renin-angiotensin system-related molecules were found significantly associated with the clinical severity of COVID-19. The new on-set of more than 10 various autoimmune disorders were documented as well. Additionally, clinical presentations of persisted symptoms were triggered in numerous recently recovered COVID-19 patients, which led to the formulation of the novel term "post-COVID19 syndrome". Manifestations related to post-COVID-19 syndrome exist among approximately 50–80% of symptomatic COVID-19 patients who recovered, and among patients reported more than 50 different long-term effects of the SARS-CoV-2 infection. Many of the common symptoms of the post-COVID19 syndrome are not explained by the virus-related injury alone. Similarly to chronic fatigue syndrome and fibromyalgia, autoimmune-mediated autonomic nervous system dysfunction may play a significant part in the pathogenesis of such symptoms, including chronic fatigue, cognitive impairment, mood related disorders, and numerous more. Importantly, therapeutic options such as immunomodulatory and immunosuppressive therapy may favor some post-COVID19 patients, while plasmapheresis and IVIG could be considered in severe cases. Nevertheless, as physical exercise has been found to stabilize the autonomic nervous system, exercise therapy might be a safer and more effective remedy for the post-COVID19 syndrome.

1. The acute phase of COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, responsible for the widespread coronavirus disease of 2019 (COVID-19), led to one of the most rogue pandemics in modern time. This novel disease had caused morbidity and mortality at an unanticipated measure on a global scale. Nowadays, COVID-19 is perhaps most known for its acute phase, commonly presented with fever, respiratory tract symptoms [1] and, in some patients, extra-respiratory manifestations [2]. Although most individuals infected by SARS-CoV-2 are asymptomatic or present merely mild symptoms [3,4], severally-ill patients have extremely high mortality rates and overwhelm local health authorities [5]. The high inflammatory state was frequently referred to as "cytokine storm syndrome" (SCC) to describe a vicious cycle of the hyperstimulated immune system [6], leading to an uncontrolled inflammatory response. This disorder was recognized in the 'graft versus host disease' and was later adopted for the severe inflammatory state of extensive viral and bacterial infections [7]. The SCC involves numerous circulating cytokines and chemokines such as IL-1α, IL-1β, IL-2, IL-7, IL-6, IL-8, IL-10, tumor necrosis factor, interferon γ and high concentrations of ferritin, C-reactive protein can be detected [5,8–11]. SCC had been associated with extremely high mortality due to the extreme hyperstimulation of the immune system, leading to severe self-damage of tissue, often in the form of acute respiratory distress syndrome (ARSD)

Abbreviations: SARS-CoV-2, Syndrome coronavirus 2; COVID-19, Coronavirus disease of 2019; SCC, Cytokine storm syndrome; ARSD, Acute respiratory distress syndrome; aPL, Antiphospholipid antibodies; anti-TPO, Anti-thyroid peroxidase; WHO, World Health Organization; GPCRs, G-coupled receptors; CFS, Chronic fatigue syndrome; POTS, Postural orthostatic tachycardia syndrome; IVIG, Intravenous immunoglobulin.

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and multiple organ failure [12]. The state of hyperstimulation of the immune system that occurs in severely ill patients contributes to the wide range of autoimmune manifestations [6,13]. Autoimmunity in such patients is believed to be contributed to dysregulation of immunological components and loss of self and non-self description in individuals with a genetic predisposition. An additional mechanism that is not less important is molecular mimicry between viral components and human peptides, which had been described relating to the spike protein of SARS-CoV-2 [8,14,15].

In order to have a deep understanding of the post-COVID19 syndrome, the fundamental properties that initiate at the acute COVID-19 phase are established. For that matter, close to 20 distinct functionally active autoantibodies which target GPCR of the nervous system and renin-angiotensin system-related molecules that are all significantly associated with the clinical severity of COVID-19. The new on-set of more than 10 various autoimmune disorders were documented as well. Some of the frequently found manifestations include the presents of antiphospholipid antibodies (aPL); according to aPL data in COVID-19 patients from different cohorts, the positive rate of aPL and its subtypes are considerably high, although broad: ranging from 24.2% to 57.1%, significantly higher than ill non-COVID patients [16]. In contrast, the prevalence of aPL in the general population is much lower, estimated as 50 (95% CI 42–58) per 100,000 population [17].

Development of some autoantibodies seems to be acquired in the acute phase of COVID-19. At the same time, many autoimmune manifestations presented by COVID-19 patients were developed weeks or months after their recovery [8,18]. For instance, among 159 acute COVID-19 patients, anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin were present in 20% and 11%, respectively. Follow-up (after approximately three months) was done for 127 patients. 7 (5.5%) patients which were initially negative anti-TPO were later found positive, whereas only one patient, originally positive for anti-TPO, was found negative in the follow-up [18]. The same group also found 20.1% (41/204) with "long COVID-19", defined as the presence or persistence of symptoms upon follow-up [18]. These results are worrisome because they may indicate the development of autoimmunity in COVID-19 patients in the long term. Importantly, additional autoantibodies share a similar long-term development and persistency [19].

Autoantibodies are essential laboratory findings because some of them can represent a pre-clinical phase of autoimmunity, while others have well-known pathogenetic outcomes. Moreover, new onset of autoimmune manifestations and diseases were also developed following an acute phase of COVID-19 [8]. Furthermore, new-onset of immune-mediated neuropathies, such as Guillain-Barré syndrome, Miller Fisher syndrome, and myasthenia gravis were recognized as well [20–23]. Some of the autoimmunity following COVID-19 were organ/system specific, such as numerous cases of Kawasaki-like disease secondary to COVID-19 cases [24], immune-mediated neuropathies, and immune thrombocytopenic purpura [25], while others were systemic diseases [8].

Some immune-mediated disease flares and new-onset disease following COVID-19 vaccination were documented [26]. These manifestations could be related to the vaccination and are important recognition, yet should not use to create fear of vaccination, mainly because the COVID-19 is associated with much higher risks [26,27].

2. Introduction to post-COVID19 syndrome

In this review, we discuss the most current and vital discoveries that have been made, which have revealed the syndrome as a multi-organ disease with a broad spectrum of symptoms. Additionally, we will review the possible mechanisms that might play a crucial role in developing the chronic post-COVID19 syndrome and which treatments might be suitable for these patients. Nonetheless, and maybe most importantly, is our discussion on how individuals can prevent such chronic syndrome. It should be raised that the possible ability of SARS-CoV-2 to trigger autoimmunity in the acute disease may contribute to the development of the chronic symptoms of the post-COVID19 syndrome in multiple mechanisms, which will be further discussed.

Recent studies have focused on analyzing the clinical presentation and epidemiology of such symptoms, leading to meaningful conclusions that formulated the novel term "post-COVID19 syndrome", "post-acute COVID19 syndrome", "Persistent COVID-19 Symptoms", "long COVID-19", etc. In October 2021, the World Health Organization (WHO) had released a formal clinical definition for the post-COVID19 syndrome, which includes: "*Illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within three months from the onset of COVID-19, with symptoms and effects that last for at least two months*" [28]. Importantly, for these symptoms to be diagnosed as a post-COVID19 syndrome, they should not be explained by an alternative disorder.

Significant amount of time has passed since the pandemic outbreak, and many recovered patients are experiencing non-specific symptoms that substantially impact the everyday functioning of COVID-19 recovered individuals. These symptoms are correlated with the timing of the SARS-CoV-2 infection, do not have an alternative cause, and last for at least two months. The common morbidity of such symptoms includes substantial neurological and psychiatric (e.g., cognitive dysfunction, chronic fatigue, shortness of breath, sleep disturbances, anosmia, and paranesthesia) [29,30]. Other symptoms, also included in the post-COVID19 syndrome manifestations, are likely connected to the organ-specific injury due to the viral damage and inflammation, such as pulmonary fibrosis, cardiomyopathy, and thromboembolic events [29]. Notably, the morbidity of the post-COVID19 syndrome was found to be most significant, yet not limited to, the more severe COVID-19 patients [30].

Many local health authorities worldwide are currently struggling to cope with the active COVID-19 patients, yet there is no doubt that future healthcare systems will be obligated to address the post-COVID19 syndrome.

3. Clinical presentation and epidemiology of post-COVID-19 syndrome

Considerable time has passed since the pandemic's outbreak, and many recovered patients were found to suffer from vague symptoms connected to the SARS-CoV-2 infection. The understanding of such symptoms is crucial for identifying the underlying mechanism.

Numerous patients are experiencing chronic symptoms following the eradication of SARS-CoV-2, while only a minority of the infected completely recover with no symptoms left [31–33]. A wide variety of chronic/late symptoms were described following the coronavirus infection, including pulmonary (dyspnea, cough, pulmonary fibrosis), cardiovascular (chest pain, palpitations, stress cardiomyopathy, myocarditis), hematologic (thromboembolic events), neuropsychiatric (headache, chronic fatigue, depression, anxiety, sleep disturbances, cognitive imbalance anosmia, paranesthesia), renal (renal failure), dermatologic and endocrine (diabetic ketoacidosis, Hashimoto's thyroiditis, Graves' disease) sequelae [29] (Table 1).

Recent studies indicate that manifestations related to post-COVID-19 syndrome exist among approximately 50–80% of symptomatic COVID-19 patients who recovered (Fig. 1) [31–33]. A German study, focusing on cardiovascular injury, had found that 78% of recently recovered COVID-19 patients had a persisting symptom; the most prevalent abnormality was myocardial inflammation (60%) [31]. An Italian study that assessed patients after a mean of 60.3 days from the onset of the first COVID-19 symptom found only 18 (12.6%) completely free of any COVID-19–related symptom, while 32% had 1 or 2 symptoms and 55% had three or more; worsened quality of life was observed among 44% of patients [32]. Finally, a study that analyzed 355 symptomatic COVID-19 patients had found that 46% developed post-COVID-19 symptoms, with post-viral fatigue being the most prevalent symptom in 70% of cases

Table 1
Description of the common symptoms of the post COVID19 syndrome, classified by systems involved.

Clinical Presentation of Post-Covid19
General symptoms
Chronic Fatigue
General pain
Intermittent fever
Red eyes
Hair loss
Excessive sweat
Neuropsychiatric
Headache
Depression
Anxiety
Sleep disturbances
Cognitive imbalance
Dysautonomia
Anosmia/hyposmia
PTSD
Stroke
Cardiovascular
Chest pain
Palpitations
Stress cardiomyopathy
Myocarditis
Post-Orthostatic tachycardia syndrome
Respiratory
Cough
Dyspnoea
Pulmonary fibrosis
Pulmonary dysfunction
Renal
Renal failure
Gastrointestinal
Anorexia
Digestive disorders
Endocrinal
Hashimoto's thyroiditis
Grave's disease
Diabetic Ketoacidosis
Rheumatologic
Joint pain
Fibromyalgia
Dermatologic
Non-specific rash
Hematologic
Thromboembolic events

[33]. The frequency of post-COVID19 syndrome in asymptomatic patients is still uncertain.

An extensive systematic review and meta-analysis performed by a Mexican group compiled more than 50 possible long-term effects of the coronavirus infection [29]. A "long-term symptom" was considered as any symptom that persisted for more than two weeks after the disease onset and was not completely reversible. From all the COVID-19 patients included in their data, 80% presented with at least one long-term complaint. The most common symptom was fatigue (58%) [29]. Regarding persistent respiratory-related consequences of SARS-CoV-2 infection, the most were dyspnea and cough, yet more severe sequelae such as pulmonary fibrosis and dysfunction were also reported [29]. Similar results were found in cohort studies from Italy, England, and China [32,34,35].

Headache is also on the top of the chronic COVID-19 complaints list [36,37], and according to the mentioned meta-analysis, it is present in near 45% of those patients [29]. Other neuropsychiatric symptoms are also frequently reported, such as anosmia (21%), attention disorder (27%) and depression (12%), and anxiety (13%). Depression, anxiety, fogginess, and post-trauma-stress-disorder (PTSD) were previously correlated with COVID-19 in other studies [35,38].

At least one of the following non-specific symptoms was described in 10–20% of the patients: hair loss, joint pain, excessive sweat, digestive disorders, general pain, intermittent fever, and red eyes [29,39]. Less common but more severe manifestations, such as strokes and renal failure, were also described [29,39].

Regarding epidemiology, some studies have shown a predominance of post-COVID19 syndrome among Black, Asian and other minority ethnicities when compared with Caucasians [40,41]. In contrast, others found conflicting results, showing a higher prevalence among white people [42,43]. The syndrome is more common among patients older than 40, and there is no consensus whether females or males are more susceptible [42,43].

4. Post-COVID19 syndrome and autonomic nervous system dysfunction

In the past two decades, researching the role of autoimmunity in developing some autonomic nervous system dysfunction disorders has been considerably accelerating. Autoantibodies against G-coupled receptors (GPCRs) are in the spotlight, including adrenergic, muscarinic, endothelin, and angiotensin receptors [44,45]. These autoantibodies are suspected of playing an active role in many autoimmune disorders [44,45]. For example, the involvement of β2-AR signaling was reported in the pathogenesis and progress of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and myasthenia gravis. In addition, autoantibodies against muscarinic acetylcholine receptor M3 have been found to affect the progression of Sjogren's syndrome [45,46]. SARS-CoV-2 may contribute greatly to triggering autoimmune manifestations, including the development of various autoantibodies [8,25,27,47], thus some believe specific autoantibodies lead to autonomic nervous system dysfunction, which could explain many of the post-COVID19 syndrome manifestations.

Functionally active autoantibodies against different GPCRs, which are known to disturb the balance of neuronal and vascular activity, were found present in post-COVID-19 syndrome patients [48]. In that study, 31 post-COVID19 patients were included; all reported having between 2 and 7 different functionally active autoantibodies targeting GPCRs, that acted as receptor agonists, such as β2-adrenoceptor, α1-adrenoceptor, and Angiotensin II receptor type 1 receptor [48]. These autoantibodies, found before the infection, might explain the triggering of neurological and cardiovascular symptoms of the post-COVID-19 syndrome [48]. Further investigation of autoimmunity against the autonomic nervous system is carousal to extend the knowledge of this mechanism that may be the root of post-COVID19 syndrome's symptoms.

Our group had found close to 20 distinct autoantibodies which target GPCR of the nervous system and renin-angiotensin system-related molecules that are all significantly associated with the clinical severity of COVID-19 (Otavio Cabral-Marquesa, Gilad Halpertd, Lena F. Schimkea, et al.; nature communications in press) (Fig. 1). Further investigation of autoimmunity against the autonomic nervous system is carousal to extend the knowledge of this mechanism that may be the root of post-COVID19 syndrome's symptoms.

The post-COVID19 syndrome phenomenon, which the WHO had well defined, seems to involve many different organs and leads to a broad spectrum of symptoms that are difficult to attribute to a single mechanism, virus- or immune-mediated. Nevertheless, the clinical presentation of the post-COVID19 syndrome can help us better evaluate the most reasonable underlying pathophysiologic process worth exploring. In this context, many had identified overwhelming similarities between manifestations related to post-COVID19 syndrome and other disorders, such as chronic fatigue syndrome (CFS) [49], fibromyalgia [50–52], postural orthostatic tachycardia syndrome (POTS), [53], and manifestations associated with silicone breast implants [45]. The typical presentation of the post-COVID19 syndrome, CFS, and fibromyalgia includes chronic fatigue and widespread pain accompanied by cognitive disorders that reduce the quality of life [29,54–58] (Table 2). Interestingly, these conditions are suspected of having an underlying autoimmune

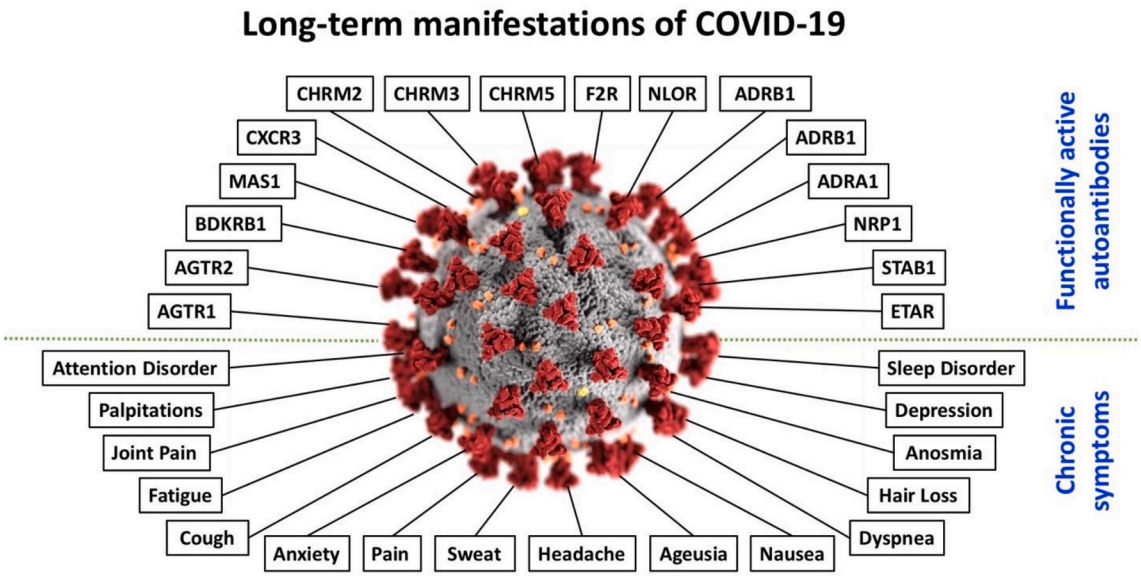

Fig. 1. In the center appears the SARS-CoV-2. Around it, at the upper part of the figure, appear some of the functionally active autoantibodies linked to COVID-19. At the bottom part of the figure appear some of the chronic symptoms associated with COVID-19.
AGTR1: Angiotensin II Receptor Type 1; AGTR2: Angiotensin II Receptor Type 2; BDKRB1: Bradykinin Receptor B1; MAS1: MAS1 Proto-Oncogene; CXCR3: C-X-C Motif Chemokine Receptor 3; CHRM2: Cholinergic Receptor Muscarinic 2; CHRM3: Cholinergic Receptor Muscarinic 3; CHRM5: Cholinergic Receptor Muscarinic 5; F2R: Coagulation Factor II Thrombin Receptor; NOR: nociception-like opioid receptor; ADRB1: Adrenergic receptor beta-1; ADRB2: Adrenergic receptor beta-2; ADRA1: Adrenoceptor Alpha 1A; NRP1: Neuropilin 1; STAB1: Stabilin 1; ETA: Selective endothelin-A.

Table 2
The most common symptoms of Post-COVID19 syndrome, Fibromyalgia, and Chronic Fatigue Syndrome / Myalgic encephalomyelitis [29,54–58].

Post-COVID19 syndrome	Fibromyalgia	Chronic Fatigue Syndrome /Myalgic encephalomyelitis
Fatigue	**Fatigue**	**Fatigue**
Headache and Joint pain	**Chronic widespread pain**	**Chronic widespread pain**
Hair loss	**Unrefreshing sleep**	**Unrefreshing sleep**
Cognitive impairment	**Fogginess ("fibrofog")**	**Impaired memory**
Dyspnea-related	**Physical exhaustion**	**Impaired concentration**
Mood related disorders	**Cognitive impairment**	**Post-exertional malaise**
Ageusia and anosmia		
Sweat		

dysautonomic-related disorder [59–61]. Furthermore, CFS and fibromyalgia are also associated with various viral infections [62–64].

Importantly, alongside the presence of functionally active autoantibodies against the autonomic nervous system components, dysfunction of the system was also found in patients with the post-COVID19 syndrome [48,65]. For example, a series of individuals with post-COVID-19 symptoms had resulted in orthostatic intolerance syndromes, possibly related to a virus- or immune-mediated disruption of the autonomic nervous system [65].

Many post-COVID-19 patients describe a clinical condition similar to the CFS: overwhelming and incapacitating fatigue, sleep disorders, cognition impairments, different kinds of autonomic dysfunction, which are exacerbated in exercises [29,35,66]. CFS causes disturbances of the central nervous system and immune regulation, leading to debilitating disorders with an autoimmune etiology [67]. The triggering of the disease, like many autoimmune diseases, it is believed to be activated by some specific viral pathogens, such as EBV [67,68]. In addition, CFS has been shown to be associated with higher serum levels of autoantibodies against the autonomic receptors, such as beta-adrenergic and muscarinic receptors [69]. The same autoantibodies were previously related to other autonomic syndromes, such as POTS and small-fiber neuropathy [70–72]. Interestingly, those autonomic dysfunctions are some of the non-specific symptoms described in the post-COVID19 symptomatic patients [53,73,74].

The similarity between fibromyalgia and the post-COVID19 syndrome was demonstrated by a study that included a sample of 616 COVID-19 recovered patients. All the participants filled a web-based survey 6 ± 3 months after the COVID-19 diagnosis had found that 189 (30.7%) satisfied the American College of Rheumatology criteria for fibromyalgia (56.6% women). A further multivariate logistic regression model had shown that male gender and obesity were the strongest predictors of being classified as having post-COVID19 fibromyalgia (both $p < 0.0001$) [50]. A recent study demonstrated the pathogenicity of fibromyalgia patients' IgG [75]. The researchers treated mice with IgG from fibromyalgia patients, which led to the increased sensitivity to noxious mechanical and cold stimulation and nociceptive fibers in skin-nerve preparations compared with control [75]. These findings support the belief that fibromyalgia has an autoimmune basis, and therapy that reduces patient IgG concentrations could benefit fibromyalgia [75]. It should be emphasized that there is substantial controversy relating to the etiology and pathophysiology of fibromyalgia. Many clinicians still label the signs and symptoms of fibromyalgia patients as merely psychological while not acknowledging this disorder as an 'organic' disease, despite strong evidence [76]. The post-COVID19 symptoms, similar to fibromyalgia, are not clearly understood thus might be disregarded by many healthcare professionals if not raised to their awareness.

5. Therapeutic options for post-COVID-19 patients

Numerous patients are at need for medical solution for new onset of symptoms following the COVID-19 recovery, in order to improve their quality of life [32]. In assessing the most beneficial therapy from post-COVID19 syndrome patients, the most probable underlying mechanism should be targeted. As SARS-CoV-2 contributes to

hyperstimulation of the immune system in the acute phase and may lead to the development of functional autoantibodies against the autonomic nervous system in the chronic phase, immunomodulatory therapy could be beneficial for post-COVID19 patients. Steroids could be considered the first line of treatment for the hyperstimulation phase of the disease [77], while other immunosuppressive treatments could be prescribed for persistent use [78]. In severe cases, plasmapheresis and intravenous immunoglobulin (IVIg) could be considered [79]. In addition, it was suggested that therapies that reduce autoantibodies levels, such as rituximab and extracorporeal apheresis, could help ease the post-COVID19 symptoms [49]. Those possibly beneficial therapeutic options should be carefully assessed in clinical in well-organized clinical trials due to the significant potential adverse effects and their high cost.

Physical exercise was found to be significantly beneficial in CFS and fibromyalgia patients [80–82]. Thus, exercise therapy might be a safer and more effective remedy in post-COVID19 syndrome in comparison to the potent immunomodulatory and immunosuppressive treatments. Exercise therapy, particularly graded aerobic and strength training, had been found to produce considerable improvements in pain, increase physical function and improve quality of life [80,83]. In controlled randomized trials, possible adverse effects of exercise, such as pain, fatigue, and musculoskeletal problems, had not been consistently reported. Therefore, a prescribed graded exercise is considered safe for these patients [80,82].

Although not much research had been done on the connection between the autonomic nervous system and autoimmune diseases, it is known that cardiovascular autonomic dysfunction is common in autoimmune disorders, specifically rheumatic diseases; systemic lupus erythematosus rheumatoid arthritis scleroderma and primary Sjögren's syndrome have an association with autonomic nervous system dysfunction, with or without cardiological [84].

The mechanism as which therapeutic physical exercise stabilizes the autonomic nervous system and restores its normal function remains unclear. Yet some findings suggest that exercise therapy can improve the outcome of patients with autonomic nervous dysfunction by increasing vagal modulation, mainly demonstrated on patients and animal models with chronic cardiac disease [85]. Further research is necessary in order to assess the benefit of physical exercise, as a therapy, in autoimmune disorders.

6. Conclusion

It is of great importance to recognize the autoimmune manifestations of COVID-19 and post-COVID19 syndrome in order to properly cope with their outcomes in the ongoing pandemic and the long-term post-pandemic period, giving the possible autoimmune-mediated underlying mechanisms. The key to managing post-COVID19 syndrome might be concealed in our knowledge of similar presentations, such as CFS and fibromyalgia. As SARS-CoV-2 contributes to hyperstimulation of the immune system in the acute phase and may lead to the development of functional autoantibodies against the autonomic nervous system in the chronic phase, some medication strategies may be beneficial. Therapeutic options such as immunomodulatory and immunosuppressive therapy could be favorable for some post-COVID19 patients, while plasmapheresis and IVIG could be considered in severe cases. Nevertheless, due to the potential adverse effects of the available therapeutic options, exercise therapy might be a safer and more effective therapeutic option in post-COVID19 syndrome. Yet, currently, further research is still necessary in order to assess the optimal treatment for the diverse symptoms and severity of the post-COVID19 syndrome.

Declaration of Competing Interest

None.

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