Review

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The Role of Hypothalamic Phospholipid Liposomes in the Supportive Therapy of Some Manifestations of Long Covid: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Brain Fog

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Posted Date: 4 July 2023

doi: 10.20944/preprints202307.0005.v1

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The Role of Hypothalamic Phospholipid Liposomes in the Supportive Therapy of Some Manifestations of Long Covid: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Brain Fog

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Abstract: Long Covid is a heterogeneous clinical condition in which Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and brain fog stand out among the different clinical symptoms and syndromes. The cerebral metabolic alterations and neuroendocrine disorders seem to constitute an important part of Long Covid. Given the substantial lack of drugs and effective therapeutic strategies, hypothalamic phospholipid liposomes which have been on the market for several years as adjuvant therapy of cerebral metabolic alterations resulting from neuroendocrine disorders, can be taken into consideration in an overall therapeutic strategy that aims to control the Long Covid associated symptoms and syndromes. Their pharmacological mechanisms and clinical effects strongly support their usefulness in Long Covid. Our initial clinical experience corroborates this rationale. Further research is imperative in order to obtain robust clinical evidence.

Keywords: Long Covid; Covid-19; post-COVID syndrome; neuroendocrine disorders; chronic fatigue; brain fog; phospholipids; phospholipid liposome; phosphatidylserine

1. Introduction

The Covid-19 pandemic caused in Italy, by April 2023, over 25 million of documented infection cases and about 190,000 deaths. Beyond the devastating impact on hospital services which, in the first pandemic phase (2020-2021), were engaged almost exclusively in dealing with COVID-19, and a serious delay in taking care of other pathologies, despite having now the epidemic wave under control, thanks to vaccines and wise behavior, a new pathological entity has emerged that seems to be a direct consequence of the SARS-CoV-2 infection: the Long COVID [1–3].

2. Definition of Long Covid

Many definitions have been adopted to describe this complex of symptoms and syndromes that may follows the COVID-19 infection (1-2). The term "**post-COVID conditions**" has been adopted by CDC and refers to a wide range of sequelae that compromise the physical and mental health of some patients and that occur four or more weeks after SARS-CoV-2 infection. Post-COVID conditions are referred to by a wide range of names, including: *Long COVID, Post-acute COVID-19, Long-term effects of COVID, Post-acute COVID syndrome, chronic COVID, long-lasting COVID, Late sequelae, Post-acute sequelae of SARS-COV-2 infection (PASC).*

The CDC indicates that post-COVID conditions are present if recovery does not occur within 4 weeks after the acute phase, although many patients may continue to improve within 12 weeks. Although some patients can still recover after 12 weeks, the disease becomes more likely to be persistent. The CDC uses the 4-week period to define post-COVID conditions and emphasizes the importance of initial clinical evaluation and supportive care during the initial 4-12 weeks after acute COVID-19.

Several patterns of onset for post-COVID conditions have been identified that further exemplify their heterogeneity, including:

 doi:10.20944/preprints202307.0005.v1

- **persistent symptoms and conditions** that begin at the time of acute COVID-19 illness
- **signs, symptoms or conditions of new onset** following asymptomatic illness or a period of improvement or remission of acute symptoms
- **evolution of symptoms and conditions** which include some persistent symptoms (e.g., shortness of breath) with **the addition of new** symptoms (e.g., cognitive difficulties)
- worsening of pre-existing symptoms or conditions

Some manifestations may share similarities with other post-infectious syndromes: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia (FM), post-treatment Lyme diseases syndrome (PTLDS), postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia - mast cell activation syndrome (MCAS). Some of these conditions have also been described in patients with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), two other life-threatening diseases resulting from coronavirus infections.

A wide range of other symptoms, new or already present, can occur in people who have suffered from SARS-CoV-2 acute disease of varying degrees, including mild asymptomatic form. These symptoms may overlap with multiple organ complications or the effects of treatment or hospitalization. This category is heterogeneous and may include patients who have clinically important symptoms (e.g., difficulty thinking or concentrating, post-exertion malaise etc.) that may be persistent or intermittent post-acute SARS-CoV-2 infection.

3. Prevalence of Long Covid

The prevalence of post-COVID conditions is difficult to estimate, with wide range of variations (5-30%). There are several reasons for this: the diversity of symptoms or conditions studied, the time criteria used (from three weeks to many months after SARS-CoV-2 infection), the population studied (outpatient vs. hospitalized patients), how symptoms and conditions are evaluated (e.g., self-reporting vs. electronic health record database). Nearly 1 out of 5 U.S. adults (18-19%) who reported having had COVID-19, complain of symptoms of Long COVID, defined as symptoms lasting 3 months or more that were not present before having COVID-19; Nearly 1 out of 13 of U.S. adults (8%) of those with or without a previous diagnosis of COVID-19 currently have post-COVID conditions. Women are more likely than men to suffer from post-COVID conditions. Bisexual and transgender adults are more likely to have post-COVID conditions than adults of other sexual orientations and gender identities. Adults with disabilities are more likely to report post-COVID conditions than those without disabilities. Post-COVID conditions may be associated with a reduced ability to perform daily activities. The CDC estimated that in November 2021 at least 3-5 million of the U.S. adult population lived with post-COVID conditions that lasted for at least 1 month and limited their daily activities [4–9].

4. Clinical Symptoms & Syndromes

The Long Covid manifestations encomprise a long list of symptoms referred to different apparatus (Table 1).

It can be difficult to distinguish the symptoms of post-COVID conditions from those that have other causes. It is always necessary to consider alternative diagnoses in order to avoid even serious diagnostic errors. This is the case of dyspnea and chest pain, as well as in the case of neurological disorders.

Table 1. Post Covid syndromes and their clinical manifestations (adapted from [10]).

Post COVID syndrome	Clinical manifestations	Comment
Post COVID fatigue syndrome	Profound fatigue, post-exertion malaise and/or poor resistance	Rule out causes like anemia, electrolyte imbalance, hypothyroidism,

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Post COVID cardio-respiratory Syndrome	Cough, dyspnea or increased fatigue, low grade fever, chest pain, orthostatic hypotension, palpitations and tachycardia	Sudden worsening of dyspnea: Consider tension pneumothorax, pulmonary embolism, coronary artery disease or heart failure
Post COVID neuro-psychiatric Syndrome	Headaches, anosmia or dysgeusia, cognitive impairment or "brain fog", depression and other mood changes, paresthesias, insomnia and other sleep difficulties, dizziness	If acute onset neurological symptoms also consider vasculitis, thrombosis or demyelination. Properly evaluate post-covid psychological problems.
Post COVID gastro-intestinal Syndrome	Abdominal discomfort, diarrhea, constipation, vomiting	GI symptoms can be a sequalae of the disease or therapy-related side effects
Post COVID hepato-biliary Syndrome	Nausea, jaundice, Liver Function Tests alterations	Drugs used in the treatment of COVID-19 can cause hepatic impairment.
Post COVID musculo-skeletal Syndrome	Arthralgia, myalgia, muscle weakness	Causes include: Covid-19 disease, prolonged ICU care, neurological problems, myopathy or electrolyte imbalance. Usually subside during follow up. Inflammatory arthralgia has to be differentiated from other causes like Systemic Lupus Erithematosus, Rheumatoid Arthritis.
Post COVID thromboembolic Syndrome	Depending upon the vascular territory of involvement dyspnea in Pulmonary Embolism, chest pain in Coronay Artery Disease and limb weakness and neurological deficit in stroke	Early diagnosis and treatment is lifesaving. Follow the standard treatment protocol.
Post COVID multisystem inflammatory syndrome/post COVID autoimmune syndrome	Fever, gastrointestinal symptoms, rash, chest pain, Palpitations	Elevated levels of markers of inflammation.
Post COVID genito-urinary Symptoms	Proteinuria, hematuria, development of kidney injury, menstrual cycle irregularities, erectile dysfunction	
Post COVID dermatological Syndrome	Vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (COVID toe)	

Patients with post-COVID conditions may also share some of the typical symptoms of the following syndromes:

1. Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS)
2. Fibromyalgia (FM)
3. Post-treatment syndrome of Lyme disease (PTLDS)
4. Postural orthostatic tachycardia syndrome (POTS)
5. Mast cell activation syndrome (MCAS)

4.1. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

This condition has been already described as a consequence of viral infections, (eg after infectious mononucleosis, especially in patients who present the prolonged persistence of anti-EBV IgM); considered by many a pathological condition with a strong neuropsychiatric component, it is one of the prevalent and most disabling syndromes in the post-COVID period [11–14].

Diagnosis of ME/CFS requires the concomitant presence of the following three symptoms:

1. Substantial reduction or alteration of employment, educational, social, or personal capacities that persists for more than 6 months and is accompanied by asthenia, often profound, of new or recent

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onset (not pre-existing), is not the result of continuous excessive effort, and is not effectively alleviated by rest

2. Post-exertion malaise* and

3. Non-restorative sleep*

The concomitant presence of at least one of the following two disorders is also required:

1. Cognitive impairment* or

2. Orthostatic intolerance

** The frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not suffer from these disorders at least half the time, with moderate, substantial, or severe intensity.*

The possible mechanisms that cause post-covid-19 fatigue encomprise a wide range of central, peripheral and psychological factors. Chronic inflammation in the brain, as well as in the neuromuscular junctions, can result in chronic fatigue. Damage and atrophy of fibers in skeletal muscle sarcolemma, can play a decisive role in chronic fatigue, along with psychological and social factors (Figure 1).

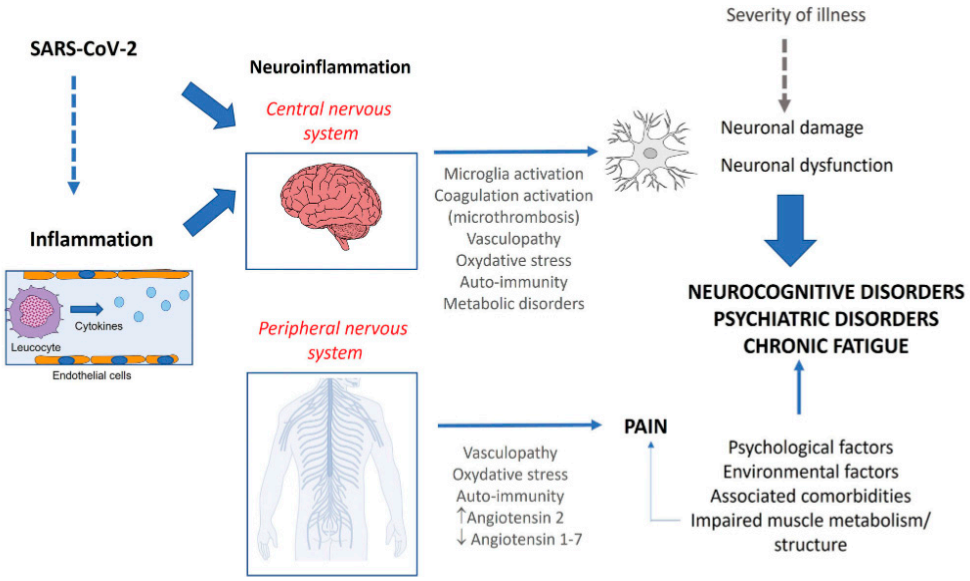

Figure 1. Putative pathophysiological mechanisms involved in Long Covid [15].

4.2. Cognitive disorders

Several underlying mechanisms of the neurological disorders of Long COVID with cognitive and mental impairment are hypothesized: hypometabolic activity in various brain areas, a reduced inhibitory activity of GABA, but also neuroinflammatory phenomenons with cerebral microstructural modifications and vascular disorders. In the CNS, the long-term immune response activates glial cells that chronically damage neurons. The hyperinflammatory and hypercoagulability state increases the risk of thrombotic events. Damage and dysregulation of the blood-brain barrier results in permeability alteration, which allows blood-derived substances and leukocytes to infiltrate the cerebral parenchyma. Chronic inflammation in the brainstem can cause autonomic dysfunction. The effects of Long Covid in the brain may lead to cognitive hesitation (Figure 1)

One of the hypotheses that is proposed to explain the multiple neuro-cognitive symptoms of Long Covid is the existence of demyelination phenomena generated by the concomitant action of viral replication, alterations of cerebral microcirculation and activation of microglia T cells (Figure 2) [16].

The neuroradiological findings are however modest and sporadic, because a very limited number of studies have used highly sensitive techniques for myelin quantification.

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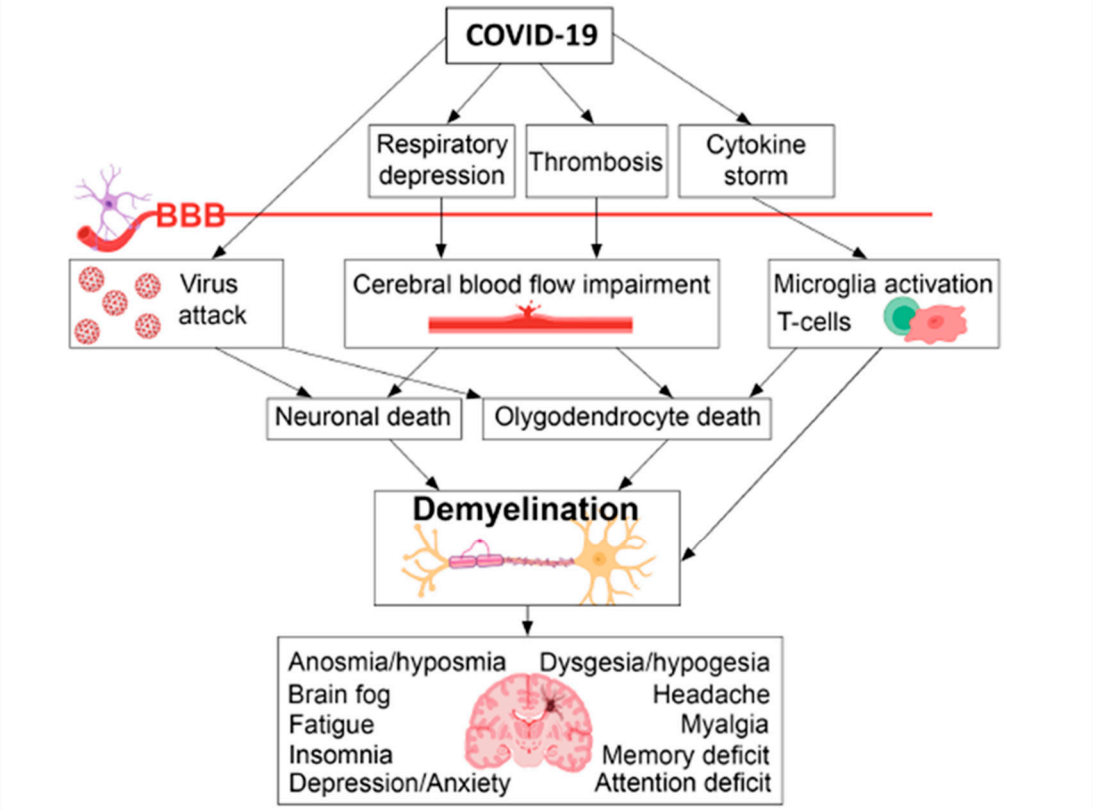

Figure 2. A schematic repreThe relationships between COVID-19, demyelination and neuropsychiatric sequalae [16].

Further hypothesis that received attention because might offer either a comprehensive pathophysiological understanding of the mechanism underlying several manifestations of Long Covid or some therapeutic perspective, refers to the generation of amyloid fibrin micro-clots in the vascular system [17]. This hypothesis, supported by an elegant although isolated scientific report, has however generated the uncontrolled use of expensive treatments whose real effectiveness is at least doubtful: blood washing and triple anticoagulation therapy. Many patients turn to private facilities in Europe to undergo apheresis procedures, spending a lot of money for a procedure without clear evidence of efficacy [18].

The National Institute of Health (NIH) has committed more than 1 USD billion to post-COVID-19 research, and the WHO is coordinating global efforts. The challenges to understand and treat postinfectious complications of SRS-CoV-2 will be daunting, but never have such resources been allocated. Understanding the basis of postinfectious sequelae will gamer greater legitimacy and spur the prospect of successful treatments [8].

In the meantime, dealing with a substantial lack of drugs and effective therapeutic strategies, it is necessary to try to help any single patient, also considering the potential role of preparations that have been on the market for several years, with an excellent safety profile, which can be taken into consideration in an overall therapeutic strategy that aims to control the Long Covid associated symptoms and syndromes.

5. The potential role of hypothalamic phospholipid liposomes in Long Covid

In COVID-19, important variations in sphingolipids and glycero-phospholipids have been described: the increase in the blood level of specific compound seems to be correlated with a greater or lesser severity of the disease. In particular, elevated levels of phosphatidilcoline (PC) correlate with a less severe form of COVID-19 and this could be useful both as a prognostic marker and as a potential therapeutic intervention [19]. Furthermore, alterations of phospholipid metabolism as well as phospholipid composition of cellular structures (such as the mitochondria of microglia), have also

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been reported in the literature [20,21]. On the other hand, various complex mechanisms underly the pathophysiology of Long Covid including cerebral metabolism alterations and neuroendocrine disorders. Indeed, recent findings that SARS-CoV-2 spike protein can bind to receptors of the neuroendocrine system shed light on the neuroendocrine involvement in Covid-19 [22]. Additionally, the levels of copeptin, a neuroendocrine biomarker of the stress response by Hypothalamic-Pituitary axis, correlate with Covid-19 severity [23]. Covid-19 infection alters the hypothalamic-pituitary-adrenal (HPA) axis due to direct viral infection of hypothalamic structures or the effect of pro-inflammatory cytokines [24,25]. Finally, among the heterogenous clinical manifestations of Long Covid, ME/CFS is a syndrome characterized by the presence of neuroendocrine disorders as part of its pathophysiological and clinical features [26,27].

In this view, taking into account the alterations of the phospholipid metabolism, as well as the importance of the neuroendocrine disorders in the pathophysiology and the clinical manifestations of Long Covid, a medicine containing a mixture of hypothalamic phospholipids (Liposom Forte®) indicated as "adjuvant therapy of cerebral metabolic alterations resulting from neuroendocrine disorders" elicits particular interest. Liposom Forte® is a mixture of hypothalamic phospholipids in the form of liposomes. It is extracted from porcine brain and its major components are phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylserine (PS), representing all together about 90% of the total phospholipids of the mixture [28]. Hypothalamic phospholipid liposomes reach the central nervous system where they exert different effects by influencing the physico-chemical and structural properties of the neural membrane, as well as by affecting its function and that of the related cellular structures [28,29]. Liposom Forte® has shown an excellent safety profile during its long-time presence on the market. Its mechanism of action, as well as the clinical evidence on its efficacy, offer a strong rationale on the use of hypothalamic phospholipid liposomes in Long Covid.

5.1. Pathophysiological mechanisms in Long-Covid and the pharmacology of hypothalamic phospholipid liposomes

There are many mechanisms by which hypothalamic phospholipid liposomes could benefit patients with Long Covid, especially those affected by ME/CFS and brain fog. We explore here the pathophysiological mechanism of Long Covid that may be the target of some of the pharmacological effects of hypothalamic phospholipid liposomes (Table 2).

5.1.1. The monoaminergic hypothesis

Monoaminergic neurotransmission alterations have been proposed as a potential pathophysiological mechanism for the neuropsychiatric manifestations of Long Covid [30]. This is suggested by a significant link between Angiotensin I Converting Enzyme 2 (ACE2, encoding the main receptor to SARS-CoV-2) and Dopa Decarboxylase (DDC, encoding the enzyme that catalyzes the biosynthesis of dopamine, noradrenaline and serotonin). Indeed, the gene exhibiting the most statistically significant coexpression link with ACE2 is DDC [30]. The co-expression and co-regulation of ACE2 and DDC is corroborated by findings such as high ACE2 expression in dopaminergic neurons and its reduction in Parkinson's disease (characterized by dopamine deficiency) [31], the increase in brain dopamine content following infusion of angiotensin 1-7 in the hypothalamus of rats [32], as well as dramatically low serotonin levels in the blood and the brain of ACE2 knockout mice [33]. SARS-CoV-2 is a neuroinvasive and neurotropic virus able to infect neural cells through binding of the ACE2 receptor [34]. Given that upon infection, SARS-CoV-2 down-regulates ACE2 [35], the defective expression of ACE2 might be paralleled by a DDC dysfunction, with consequent potentially altered neurotransmitters' levels in the brain [30]. This mechanism could explain some of Long Covid's neuropsychiatric manifestations such as anxiety, depression and chronic fatigue [36]. Indeed, the alterations in dopamine and serotonin homeostasis are deeply involved in the development of fatigue [37].

On the other hand, there is extensive preclinical and clinical evidence that hypothalamic phospholipid liposomes increase monoaminergic neurotransmission, as shown by the activation of

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tyrosine hydroxylase (the rate limiting-enzyme in the synthetic pathway of dopamine and other catecholamines); the increase in monoamines turnover and release; the stimulation of the dopamine-dependent adenylyl cyclase and the increase in dopamine metabolite levels in human cerebrospinal fluid (CSF); the decrease of prolactin secretion, through a dopamine agonist activity (being dopamine the main inhibitor of the prolactin synthesis and release) and finally, the modification of the receptor adaptation of central aminergic neurons to chronic treatment with antidepressants [28,29,38–41]. The monoaminergic effect of hypothalamic phospholipid liposomes renders them highly relevant for the treatment of fatigue, where a dopaminergic effect is particularly needed, as well as for the treatment of other Covid-19 neuropsychiatric sequalae, such as anxiety and depression.

5.1.2. Neuroinflammation, demyelination and impaired neurogenesis

Other pathophysiological mechanisms potentially of great importance in Long Covid, such as neuroinflammation, demyelination and impaired neurogenesis, have also been corroborated from animal model and human studies [15,16,42,43]. Even in mild Covid-19 infection, the inflammatory response caused by the respiratory Covid-19 induces neuroinflammation through CSF cytokine elevation and microglial reactivity [15,44]. Interleukins with anti-neurogenic effects such as IL-1β and IL-6 are particularly elevated in the brain of Covid-19 subjects, which leads to neuronal damage and impaired neurogenesis in structures such as hippocampus, explaining learning, memory and executive dysfunctions [42]. Neuroinflammation, probably in combination with other factors such as direct effect of the virus on oligodendrocytes and cerebrovascular disorders, causes persistent loss of oligodendrocytes and demyelination [44,45]. Numerous reviews, theoretical and experimental studies convincingly indicate that demyelination may underlie many neuropsychiatric sequalae of COVID-19 [16].

Hypothalamic phospholipid liposomes exert e neurotrophic effect by improving the membrane structure and function, increasing endogenous phospholipid synthesis, and promoting dendritogenesis, as demonstrated by increased dendritic spines' density [28,29]. Animal models support the antagonizing effect of phospholipids on demyelination with data suggesting that phosphatidylcholine and phosphatidylethanolamine ameliorate myelination deficit [46], while phosphatidylserine prevents autoimmune demyelination [47]. Furthermore, recent preclinical studies have shown that hypothalamic phospholipid liposomes have a positive effect on hippocampal neurogenesis and an antagonizing effect on neuroinflammation [29]. Chronic treatment with hypothalamic phospholipid liposomes has been shown to reverse and prevent the reduction of neurogenesis induced by chronic stress in the dentate gyrus of the hippocampus in a study on rats [29]. Meanwhile, in a model of neuro-inflammation induced by lipopolysaccharide (LPS) injection, the marked increase of proinflammatory cytokine release elicited by LPS (IL-1β, IL-6, TNF-α) in different brain areas was antagonized by hypothalamic phospholipid liposomes administration in a dose-dependent manner [28]. The effects on neuroplasticity and on the cytokines involved in Covid-19 induced neuroinflammation, further strengthen hypothalamic phospholipid liposomes' relevance in the treatment of Long Covid.

5.1.3. Cerebral hypometabolism

Case-control, cohort and case studies using [18F] fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) suggest that cerebral metabolic alterations may be responsible for the neurocognitive findings in Long Covid [48–52]. Hypometabolism of different brain areas (especially of the frontal cortex) in Long Covid patients suffering from neurocognitive symptoms is the main finding of these studies [52]. Hypothalamic phospholipid liposomes activate cerebral metabolism by increasing brain glucose content and phospholipid synthesis [28]. In addition, they are specifically indicated as adjuvant treatment in cerebral metabolic alterations caused by neuroendocrine disorders [29].

5.1.4. Male fertility alterations

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Low serum testosterone levels have been encountered in as much as 30% of men up to 12 months after Covid-19 infection [53]. Low testosterone in combination with other alterations such as psychological stress, activation of Hypothalamic-Pituitary-Adrenal axis and low dopamine levels, may contribute to erectile dysfunction and loss of libido [24,54,55]. Indeed, in male athletes, phosphatidylserine (one of the main components of Liposom Forte®) has been shown to increase plasma levels of testosterone compared to placebo [56] as well as increase testosterone to cortisol ratio in an exercise-related context [57]. Furthermore, it has been hypothesized that phospholipids increase the capacity of high-density lipoproteins (HDL) to take up free cholesterol from the cytoplasm membrane of peripheral cells and to transport it in the esterified form to the steroid producing glands where it serves as a precursor to steroid hormones such as testosterone [58]. These effects, together with the normalizing effect on HPA axis and the dopaminergic effect of hypothalamic phospholipid liposomes [29], may account for their potential beneficial role in male sexual health alterations.

5.2. Clinical evidence on hypothalamic phospholipid liposomes and its implications for Long Covid

Although there are currently no published clinical studies on the efficacy of hypothalamic phospholipid liposomes in Long Covid, available evidence in other conditions supports their potential clinical relevance as a therapeutic option for Long Covid, in particular for symptoms such as anxiety and depression, chronic fatigue and brain fog, as well as potentially for orthostatic intolerance and male sexual health problems (Table 2).

Clinical evidence on the efficacy and safety of hypothalamic phospholipid liposomes (Liposom Forte®) has been generated in open studies with and without a control group, in active drug-controlled trials and in double-blind, randomized, placebo-controlled trials [28]. Hypothalamic phospholipid liposomes, as add-on treatment to antidepressant therapy, further improve depressive symptomatology while reducing antidepressant effect latency compared to antidepressant therapy alone [28,59–61]. In a double-blind, randomized, placebo-controlled trial hypothalamic phospholipid liposomes in monotherapy were active against mild anxiety and depressive symptoms in menopausal women [62].

Furthermore, hypothalamic phospholipid liposomes have shown efficacy against other clinical symptoms which are commonly encountered in Long Covid. They improve asthenia caused by menopause [62] or induced by a drug [61]. Additionally, hypothalamic phospholipid liposomes are effective against restlessness and dizziness [62]. Furthermore, hypothalamic phospholipid liposomes antagonized the hypotension and the reflex tachycardia caused by trazodone [61].

Taking into consideration that hypothalamic phospholipid liposomes contain different phospholipids, efforts have been made to identify the effect of the specific phospholipids in the mixture. Evidence during the initial phases of research seemed to suggest that phosphatidylserine might be the active ingredient of the mixture [63]. Phosphatidylserine is an essential component of the cerebral cortex and is associated with cognitive function [64]. In 2003, based on preliminary evidence, FDA authorized a Qualified Health Claim that phosphatidylserine may reduce the risk of dementia and cognitive dysfunction in the elderly [65]. In a more recent meta-analysis phosphatidylserine was shown to improve age-associated cognitive decline, especially memory, with no adverse effects [64]. Furthermore, phosphatidylserine has been shown to benefit the memory of a small group of patients with Alzheimer's disease [66]. These data suggest that phosphatidylserine may also display its clinical benefits against cognitive dysfunction caused by Long Covid, widely known as brain fog.

Finally, preliminary evidence from an open clinical study has demonstrated that phospholipids (mainly phosphatidylcholine) may be useful and well tolerated in the treatment of male sexual disorders such as erectile dysfunction and loss of libido [58].

Considering the clinical relevance of ME/CFS and brain fog and the substantial lack of specific pharmaco-therapy, before considering drugs of the class of selective serotonin reuptake inhibitors (SSRIs) that could generate benefit in selected patients with ME/CFS, it seems reliable to to try one or more cycles of therapy with hypothalamic phospholipid liposomes which, in our personal experience, showed to induce a significant improvement in the clinical conditions of the patient,

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with good tolerability. Low cost and the short duration of any therapeutic cycle (in our experience, 1 vial via IM injection, morning and evening for 10 days) are other favorable aspects of this therapeutic approach. Pharmacotherapy should be combined with behavioral therapy, reassuring the patient on the high probability to overcome the pathological status.

However, it is imperative to make any effort to collect more extensive and robust clinical data, observing a cohort of treated patients, evaluating them with a point-by-point questionnaire administered before and after therapy and using an adequate follow-up of at least 3-6 months. The urgency to find adequate responses for patients with the Long Covid syndrome must not exempt itself from adopting the research methods required by evidence-based medicine.

Table 2. Long Covid's pathophysiology and clinical manifestations matched to the relevant hypothalamic phospholipid liposomes' mechanism of action and clinical evidence (ACE2 - Angiotensin I Converting Enzyme 2; IL-1β – Interleukin 1β; IL-6 – Interleukin 6; TNF-α – Tumor Necrosis Factor α; PE – Phosphatidylethanolamine; PC – Phosphatidylcholine; PS – Phosphatidylserine).

Long Covid	Hypothalamic phospholipid liposomes
Pathophysiology	**Mechanism of action**
Hypometabolic activity in certain brain areas [52]	Activation of cerebral metabolism (i.e., increased brain glucose content and phospholipid synthesis) [28]
ACE2-Dopa Decarboxylase co-expression which leads to impaired monoaminergic neurotransmission [30]	Increased catecholamine turnover and release, stimulation of tyrosine hydroxylase and dopamine dependent adenylyl cyclase, modification of monoaminergic receptor adaptation [28,29]
Neuroinflammation from CSF cytokine elevation (e.g., IL-1β, IL-6) and microglial reactivity [15,42,44]	Antagonizing effect on proinflammatory cytokines (IL-1β, IL-6, TNF-α) in different brain areas [28]
Demyelination and impaired neurogenesis [16,42]	Neurotrophic effect, increase in neurogenesis and dendritogenesis, as well as antagonizing effect of PE, PC and PS on demyelination [29,46,47]
Low testosterone [53,55]	PS increases plasma levels of testosterone compared to placebo and the testosterone to cortisol ratio in an exercise-related context [56,57]
Clinical manifestations	**Clinical evidence**
Fatigue	Improvement of asthenia [61,62]
Brain fog	PS: • improves age-associated cognitive decline, especially memory, with no adverse effects [64] • may reduce the risk of dementia and cognitive dysfunction in the elderly [65] • improved the memory of a small group of patients with Alzheimer's disease [66]
Anxiety and depression	Improvement in the symptomatology of anxiety and depression as monotherapy or add-on to antidepressants [28,29]
Orthostatic intolerance	Antagonizing effect on hypotension and reflex tachycardia caused by trazodone [61]
Male sexual health problem	Phospholipids (PC in particular) improve erectile dysfunction and loss of libido [58]

5. Conclusions

Long Covid is a heterogeneous clinical condition in which ME/CFS and brain fog stand out among the different clinical symptoms and syndromes. The cerebral metabolic alterations and neuroendocrine disorders seem to constitute an important part of Long Covid. Given the substantial lack of drugs and effective therapeutic strategies, hypothalamic phospholipid liposomes which have been on the market for several years, as adjuvant therapy of cerebral metabolic alterations resulting from neuroendocrine disorders, can be taken into consideration in an overall therapeutic strategy that aims to control the Long Covid associated symptoms and syndromes. Their pharmacological mechanisms and clinical effects strongly support their usefulness in Long Covid. Our initial clinical experience corroborates this rationale. Further research is imperative in order to obtain robust clinical evidence.

Conflicts of Interest: The author declares no conflict of interest.

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